JAMA | Original Investigation

Age-Adjusted D-Dimer Cutoff Levels to Rule Out Deep Vein Thrombosis

Grégoire Le Gal, MD, PhD; Helia Robert-Ebadi, MD; Venkatesh Thiruganasambandamoorthy, MBBS; Fares Moustafa, MD; Andrea Penaloza, MD, PhD; Judith Catella, MD; Marie Chevallier Grenot, MD; Shaun Visser, MD; Lucia Mazzolai, MD, PhD; Alain Plumacker, MD; Stefano Barco, MD, PhD; Eddy Lang, MD; Vicky Tagalakis, MD; Claire Deroche, MD; Meghan Garnett, MD; Jennifer Hulme, MD; Pierre-Marie Roy, MD; Alexandre Ghuysen, MD, PhD; Francis Couturaud, MD, PhD; Rolf Engelberger, MD; Dominique El Kouri, MD; Drahomir Aujesky, MD, PhD; Marc Righini, MD; for the ADJUST-DVT Investigators

IMPORTANCE The age-adjusted D-dimer cutoff (age × 10 µg/L in patients 50 years or older), safely increases the diagnostic yield of D-dimer in patients with suspected pulmonary embolism but has not been validated in patients with suspected leg deep vein thrombosis (DVT).

OBJECTIVE To prospectively validate whether using an age-adjusted D-dimer cutoff allows clinicians to safely rule out DVT.

DESIGN, SETTING, AND PATIENTS Multicenter, multinational prospective management outcome study conducted in 27 centers in Belgium, Canada, France, and Switzerland between January 2015 and October 2022 (last follow-up visit, January 30, 2023) and including outpatients presenting to the emergency department with suspected DVT.

INTERVENTIONS Patients were assessed by a sequential diagnostic strategy based on the assessment of clinical pretest probability by the Wells score, a highly sensitive D-dimer test, and leg compression ultrasonography. Patients in whom DVT was ruled out were followed up for a 3-month period.

MAIN OUTCOME AND MEASURE The primary outcome was the rate of adjudicated symptomatic venous thromboembolic events during follow-up in patients in whom DVT was ruled out based on a D-dimer value between the conventional cutoff of 500 µg/L and their age-adjusted cutoff.

RESULTS A total of 3205 patients were included. Median age was 59 years, and 1737 (54%) were female. DVT prevalence was 14%. Among the 2169 patients with a non-high or unlikely clinical probability, 531 (24.5% [95% CI, 22.7%-26.4%]) had a D-dimer level less than 500 µg/L, and 161 additional patients (7.4% [95% CI, 6.4%-8.6%]) had a D-dimer level between 500 µg/L and their age-adjusted cutoff. No failures were identified in patients with a D-dimer level 500 µg/L or greater but below the age-adjusted cutoff (0% [95% CI, 0%-2.3%]). Among patients 75 years or older, using the age-adjusted cutoff instead of the 500-µg/L cutoff increased the proportion of negative D-dimer from 33 of 379 (8.7% [95% CI, 6.3%-12.0%]) to 99 of 379 (26.1% [95% CI, 22.0%-30.8%]), without any false-negative test results.

CONCLUSIONS AND RELEVANCE The age-adjusted D-dimer cutoff may safely rule out DVT and was associated with a larger number of patients in whom DVT could be effectively ruled out.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02384135.

Editorial page 403

Supplemental content

CME Quiz at jamacmelookup.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The ADJUST-DVT Investigators appear in Supplement 3.

Corresponding Author: Marc Righini, MD, Division of Angiology and Hemostasis, Department of Medical Specialties, Geneva University Hospital and Faculty of Medicine, 4, rue Gabrielle-Perret-Gentil, CH-1211 Geneva 14, Switzerland (Marc.Righini@hcuge.ch).

JAMA. 2026;335(5):416-424. doi:10.1001/jama.2025.21561
Published online January 5, 2026.

Deep vein thrombosis (DVT) of the lower limbs is a common medical condition that represents a significant diagnostic challenge for clinicians. Rapid and accurate diagnosis is critical, because untreated DVT can lead to life-threatening complications such as pulmonary embolism. Traditional diagnostic strategies for DVT involve the use of clinical decision rules, such as the Wells score, D-dimer measurement, and imaging with lower limb venous compression ultrasonography.[1]

The D-dimer test, which measures fibrin degradation products, has become a widely used tool for excluding DVT in patients with low to intermediate or unlikely clinical probability. However, the specificity of the test decreases with age, leading to a reduced clinical usefulness in older adult patients.[2] Over the last decade, the safety of adjusting the D-dimer cutoff value based on a patient's age has been extensively studied in patients with suspected pulmonary embolism.[3,4] The use of the age-adjusted D-dimer cutoff for pulmonary embolism (defined as D-dimer level < patient's age × 10 in µg/L in patients aged ≥50 years) is now endorsed by major clinical practice guidelines.[5,6] However, whether this can be extrapolated to patients with suspected lower limb DVT remains to be established.

Retrospective data showed promising results: in studies of patients with suspected DVT in which all patients with a D-dimer level greater than 500 µg/L underwent compression ultrasonography, a low venous thromboembolism (VTE) rate at initial presentation or during follow-up was reported among those with a negative age-adjusted D-dimer level.[7-9] Therefore, the study hypothesis was that using the age-adjusted D-dimer cutoff would reduce the need for ultrasound imaging without compromising diagnostic safety.

To confirm this hypothesis, a large prospective international diagnostic management study was designed, using the age-adjusted D-dimer cutoff in combination with pretest probability assessment and compression ultrasonography in patients with suspected leg DVT.

Key Points

Question Does an age-adjusted D-dimer cutoff safely increase the proportion of patients in whom deep vein thrombosis (DVT) can be excluded?

Findings In this multinational prospective outcome study including 3205 outpatients presenting to the emergency department with suspected DVT, the age-adjusted D-dimer cutoff safely excluded DVT. Among patients with D-dimer level between 500 µg/L and their age-adjusted cutoff, none developed venous thromboembolism at 3 months. Use of the age-adjusted cutoff resulted in a 7.4% absolute increase in the proportion of patients in whom the diagnosis could be excluded.

Meaning An age-adjusted D-dimer cutoff may safely rule out DVT and increase diagnostic efficiency, reducing the need for unnecessary imaging.

Methods

Study Setting

The Age-Adjusted D-Dimer Cutoff Levels to Rule Out Deep Vein Thrombosis: a Prospective Outcome Study (ADJUST-DVT) was designed as a multicenter, multinational prospective diagnostic management outcome study, involving 27 hospitals in 4 countries (Belgium, Canada, France, and Switzerland). The ethics committees of all participating institutions approved the study, and all patients provided written informed consent before enrollment. A data and safety monitoring board oversaw study progress and participants' safety. The trial protocol is available in Supplement 1.

Patients

Patients who presented to the emergency department of the participating hospitals were eligible if they had a clinical suspicion of lower limb DVT. Patients were excluded if they were younger than 18 years, were pregnant, were already receiving anticoagulant therapy (eg, previous VTE, atrial fibrillation), had concomitant symptoms of pulmonary embolism, a life expectancy of less than 3 months, were unwilling or unable to provide informed consent, or were not available for follow-up.

Diagnostic Strategy

Clinical pretest probability was assessed using the 2-level or the 3-level Wells score for DVT (eTable in Supplement 2).[10] While Canadian centers used the 2-level Wells score, stratifying patients into unlikely or likely clinical probability categories, centers in Europe used the 3-level Wells version, stratifying patients into low, intermediate, or high clinical probability. The assessment of the Wells score was performed by emergency department physicians. Patients with a high or likely clinical probability directly proceeded to compression ultrasonography. In patients with a low/intermediate or unlikely pretest probability, a D-dimer test was performed. D-dimer result was interpreted according to the age-adjusted cutoff: in patients younger than 50 years, DVT was excluded in those with a D-dimer value below 500 µg/L. In patients 50 years or older, the D-dimer test was considered negative if the result was below their age multiplied by 10, in µg/L. Several quantitative high-sensitivity D-dimer assays were used: the VIDAS D-dimer exclusion test of first or second generation (bioMérieux), second-generation Tinaquant and Cobas h 232 and Cardiac Reader (Roche Diagnostics), Liatest D-dimer (Stago), D-dimer HS500 (IL Diagnostics), Innovance D-dimer and Immulite 2000 D-dimer (Siemens), AxSym D-dimer assay (Abbott), MDA auto D-dimer (Trinity Biotech), and Nycocard D-dimer (Nycomed Pharma).

No further testing was required in patients with a negative D-dimer test, and they were not prescribed anticoagulant therapy. Patients with a positive D-dimer test result underwent compression ultrasonography. Patients with a positive ultrasound result started anticoagulant therapy, while patients with a negative result were not prescribed anticoagulant treatment.

Follow-Up

All patients underwent follow-up for 3 months. Patients were instructed to seek urgent care in case of recurrent leg symptoms

Table 1. Characteristics of Included Patients

Characteristic	No. (%) (N = 3205)
Sex	
Female	1737 (54.2)
Male	1468 (45.8)
Age, median (IQR), y	59 (45-71)
BMI, median (IQR)[a]	28 (24-32)
Risk factors	
Personal history of VTE	543 (16.9)
Surgery within 1 mo	313 (9.8)
Long travel	308 (9.6)
Active malignancy	277 (8.6)
Bed rest	256 (8.0)
Oral contraceptives	168 (5.2)
Signs and symptoms	
Calf pain	1974 (61.6)
Pitting edema	1278 (39.9)
Increase in calf circumference >3 cm	845 (26.4)
Collateral veins (nonvaricose)	328 (10.2)
Alternative diagnosis at least as likely as DVT	1108 (34.6)
Pretest clinical probability	
Non-high/unlikely clinical probability	2169 (67.7)
High/likely clinical probability	1036 (32.3)

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; VTE, venous thromboembolism.

[a] Calculated as weight in kilograms divided by height in meters squared.

or new respiratory symptoms. At the end of follow-up, all patients included in the study were interviewed by telephone by a study coordinator using a structured script. Patients were asked to disclose all health-related events since their index visit: consultation with any physician, admission to hospital, change in medications, diagnostic testing, or hemorrhagic complication. The family physician was contacted whenever a possible VTE event was disclosed, and medical records were reviewed if a patient was readmitted to the hospital for any cause.

Outcomes

The primary outcome was the rate of adjudicated symptomatic VTE, comprising leg DVT and/or pulmonary embolism, during the 3-month follow-up period among patients with a D-dimer value between the conventional cutoff of 500 µg/L and their age-adjusted cutoff (failure rate).

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

We also analyzed the additional diagnostic yield of the age-adjusted D-dimer cutoff according to age groups (18-49, 50-64, 65-74, and ≥75 years).

Symptomatic VTE during follow-up was defined according to usual criteria: leg DVT was confirmed by an abnormal proximal compression ultrasonography result and pulmonary embolism by either a high-probability ventilation-perfusion scan or computed tomography pulmonary angiography showing segmental or more proximal intraluminal defects. Deaths were classified using the International Society on Thrombosis and Haemostasis (ISTH) definition for VTE-related death.[11] Only pulmonary embolism–related deaths, corresponding to the categories (A1-A2-A3) of the ISTH document, were included in the primary outcome. Other venous thromboses, such as cerebral, splanchnic, gonadal, or upper extremity vein thromboses, were not included in our primary outcome. All suspected VTE events and deaths were independently adjudicated by 2 blinded experts using the CanVECTOR Verdict web-based platform. Disagreements were resolved by a third adjudicator and, if needed, by a consensus meeting.

Statistical Analysis

Descriptive statistics included mean and standard deviations, or median with interquartile ranges for continuous variables, depending on their distribution, and proportions for categorical variables. We used the Wilson score method without continuity correction to compute 2-sided 95% CIs around estimated proportions. Sample size was estimated based on our previous retrospective validation dataset and pulmonary embolism management outcome study.[12,13] We aimed to include a sufficient number of patients to provide accurate estimates of our primary and secondary outcomes. To validate the safety of ruling out DVT on the basis of a D-dimer value between 500 µg/L and the age-adjusted cutoff, the upper limit of the 95% CI for the 3-month thromboembolic event rate needed to be below 3%. This failure rate corresponds to that observed after a negative phlebography[14] and is widely accepted as an acceptable failure rate to validate diagnostic strategies for VTE.[15,16] Achieving this would require no more than 2 events in 240 patients in this subgroup. In our prior pulmonary embolism validation cohort, approximately 10% of patients older than 50 years with an unlikely clinical probability had a D-dimer value between 500 µg/L and their age-adjusted cutoff. Therefore, we estimated that 2400 patients older than 50 years with an unlikely or non-high clinical probability of DVT were required. Considering that two-thirds of patients were expected to be older than 50, a total of 3200 patients with suspected DVT needed to be enrolled. Given the lack of a specific guideline for reporting prospective diagnostic management outcome studies, we adhered to a STARD guideline. Statistical analyses were performed using SPSS version 30.0 (IBM Statistics).

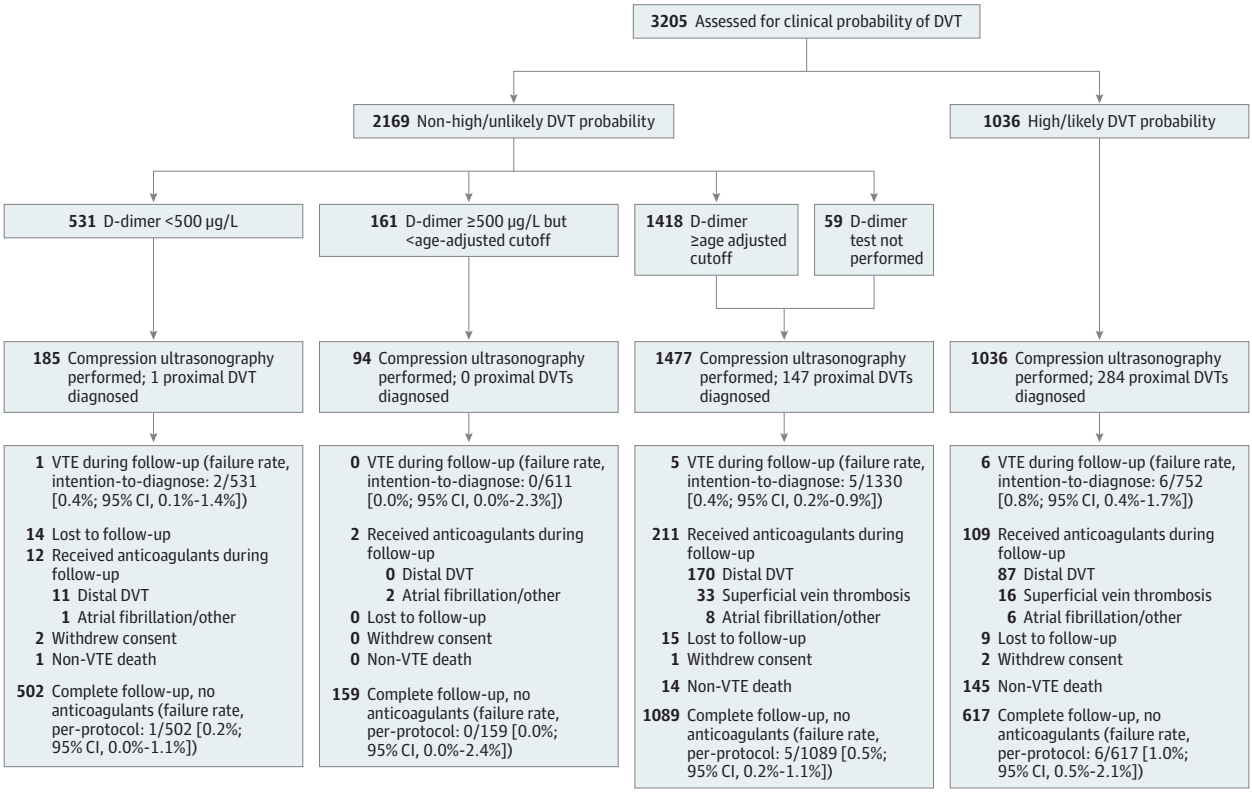
Results

Between January 15, 2015, and October 6, 2022, 3205 patients were enrolled. General characteristics are depicted in **Table 1**.

Diagnostic Workup

The study flow is summarized in **Figure 1**. A non-high or unlikely pretest probability was observed in 2169 patients (67.7%). Among these, 692 patients (31.9% [95% CI, 30.0%-33.9%]) had

Figure 1. Flow of Study of D-Dimer Cutoff Levels to Rule Out Deep Vein Thrombosis



Compression ultrasonography was repeated in case of an indeterminate result. Complete follow-up, no anticoagulants refers to the number of patients who were not prescribed anticoagulants, did not withdraw consent, were not lost to follow-up, and did not die during follow-up. DVT indicates deep vein thrombosis; VTE, venous thromboembolism.

a negative D-dimer result according to the age-adjusted cutoff: 531 (24.5% [95% CI, 22.7%-26.4%]) had a D-dimer level less than 500 µg/L, and 161 additional patients (7.4% [95% CI, 6.4%-8.6%]) had a D-dimer level between 500 µg/L and their age-adjusted cutoff. Therefore, use of the age-adjusted cutoff resulted in a 7.4% (95% CI, 6.4%-8.6%) absolute increase, or a 23.3% (95% CI, 20.3%-26.6%) relative increase, in the proportion of negative D-dimer results. **Figure 2** depicts the correlation between patients' age and D-dimer levels, in those with and without DVT, and illustrates the absence of DVT or pulmonary embolism in patients with D-dimer level between 500 µg/L and the age-adjusted cutoff.

The most commonly used assays were the VIDAS Exclusion D-dimer test (n = 749), the Innovance (n = 719), the D-dimer HS 500 (n = 342), and the Liatest (n = 205). Other assays were used in fewer than 50 patients each.

Further testing with compression ultrasonography was required in the 1418 patients with a D-dimer level above the age-adjusted cutoff, in the 59 patients in whom D-dimer testing was not performed (protocol deviations), and in the 1036 patients with a high or likely clinical probability of DVT. Moreover, despite a negative D-dimer test result, 185 patients with D-dimer level less than 500 µg/L and 94 patients with D-dimer level between 500 µg/L and the age-adjusted cutoff underwent compression ultrasonography. One patient with a D-dimer level less than 500 µg/L was diagnosed with a proximal DVT.

Overall, a proximal DVT was diagnosed in 432 of 3205 patients (13.5%): 148 of 2169 patients (6.8%) with non-high/unlikely clinical probability and 284 of 1036 patients (27.4%) with high/likely clinical probability.

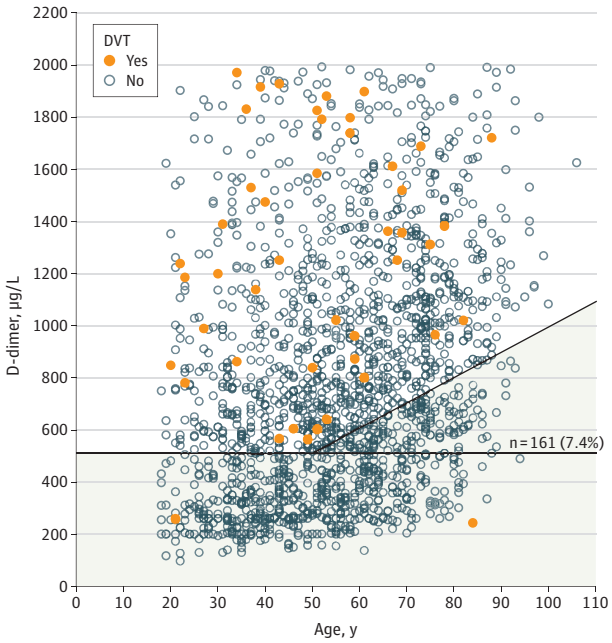
In addition, a DVT limited to distal veins was diagnosed in 11 of the 185 patients who had a D-dimer level less than 500 µg/L, in 0 of 94 patients with D-dimer level between 500 µg/L and the age-adjusted cutoff, in 170 patients of 1477 with a non-high/unlikely clinical probability and positive D-dimer results, and in 87 patients of 1036 patients with a high/likely clinical probability. The overall prevalence of distal and proximal DVT at index visit was 21.8% (700/3205).

Three-Month Follow-Up

Patients With a D-Dimer Level Less Than 500 µg/L

During the 3-month follow-up period, of the 531 patients with a D-dimer level less than 500 µg/L, 12 patients received anticoagulants during follow-up: 11 were treated for a distal DVT and 1 for another indication. Fourteen patients were lost to follow-up, and 2 withdrew consent. Among the 503 remaining patients, 1 died from a cause unrelated to venous thromboembolism, and 14 had suspected VTE during follow-up. Of these 14 events, 1 was adjudicated as having a confirmed

Figure 2. Scatterplot of D-Dimer Results vs Age in Non-High/Unlikely Clinical Probability Patients



Horizontal line indicates the conventional 500-µg/L cutoff value; diagonal line, the age-adjusted cutoff (age x 10, in µg/L, in patients aged ≥50 years). Patients with D-dimer values greater than 2000 µg/L were omitted for readability. DVT indicates deep vein thrombosis.

proximal DVT, contralateral to the initial suspicion. Thus, the 3-month risk of venous thromboembolism among patients with a D-dimer level less than 500 µg/L who completed the 3-month follow-up without anticoagulants was 1 in 502 (0.2% [95% CI, 0.0%-1.1%]) (per-protocol analysis). In the intention-to-diagnose analysis, the failure rate was 2 in 531 (0.4% (95% CI, 0.1%-1.4%]).

Patients With a D-Dimer Level Between 500 µg/L and Their Age-Adjusted Cutoff

Of the 161 patients with a D-dimer level between 500 µg/L and their age-adjusted cutoff, no patient was lost to follow-up and 2 patients received anticoagulant treatment for another indication than VTE. Of the remaining 159 patients, none died, and 5 underwent testing for suspected VTE during follow-up. None of these patients had an adjudicated confirmed VTE. Therefore, in the intention-to-diagnose analysis, the failure rate was 0 in 161 (0.0% [95% CI, 0.0%-2.3%]). The per-protocol analysis showed similar results (0/159; 0.0% [95% CI, 0.0%-2.4%]).

Patients With a D-Dimer Level Above the Age-Adjusted Cutoff

Of the 1477 patients with a D-dimer level above the age-adjusted cutoff or in whom D-dimer testing was not performed, a proximal DVT was diagnosed at initial testing in 147 patients. Of the remaining 1330 patients, 15 were lost to follow-up, 1 withdrew consent, and 211 were given anticoagulants (170 for distal DVT, 33 for superficial vein thrombosis, 8 for another indication). Of the remaining 1103 patients, 14 died from a cause other than VTE, and 47 presented a suspected VTE during follow-up. Five of these 47 suspected events were adjudicated as confirmed or possible events (pulmonary embolism, n = 4; DVT, n = 1). The 3-month risk of VTE among patients with a D-dimer level greater than their age-adjusted cutoff who completed the 3-month follow-up without anticoagulants was 5 in 1089 (0.5% [95% CI, 0.2%-1.1%]) (per-protocol analysis). In the intention-to-diagnose analysis, the failure rate was 5 in 1330 (0.4% [95% CI, 0.2%-0.9%]).

Patients With a High or Likely Clinical Probability

Of the 1036 patients with likely or high clinical probability, a proximal DVT was diagnosed at initial testing in 284. Among the 752 patients with no proximal DVT, 9 were lost to follow-up, 2 withdrew consent, and 109 were given anticoagulants (87 for distal DVT, 16 for superficial vein thrombosis, and 6 for another reason). Of the remaining 632 patients, 15 died of another cause than VTE, and 31 presented with a suspicion of a thromboembolic event. Six of these 31 suspected events were adjudicated as confirmed or possible VTE events (pulmonary embolism, n = 3; DVT, n = 3). The 3-month risk of VTE among patients with a high/likely pretest probability who completed the 3-month follow-up with no anticoagulants was 6 in 617 (1.0% [95% CI, 0.5%-2.1%]) (per-protocol analysis). In the intention-to-diagnose analysis, the failure rate was 6 in 752 (0.8% [95% CI, 0.4%-1.7%]). The overall failure rate was 13 in 2774 (0.5% [95% CI, 0.3%-0.8%]) in the intention-to-diagnose analysis and 12 in 2367 (0.5% [95% CI, 0.3%-0.9%]) in the per-protocol analysis.

Subgroup Analysis According to Patient Age Groups

Table 2 shows main study results stratified by age groups. The proportion of non-high/unlikely clinical probability patients with a D-dimer level below 500 µg/L was 59.6% in patients younger than 50 years but only 8.7% in patients older than 75 years. Using the age-adjusted cutoff led to an absolute increase in the proportion of patients with negative D-dimer result of 6.1% among those aged 50 to 64 years, 14.8% among those aged 65 to 74 years, and 17.4% among those 75 years or older. Overall, 597 (18.6%) patients were 75 years or older; of these, 379 (63.5%) had a non-high or unlikely pretest clinical probability. The proportion of patients with D-dimer level less than 500 µg/L was 33 of 379 (8.7%). Another 66 patients (17.4%) had a D-dimer level between the conventional cutoff and their age-adjusted cutoff. Therefore, the proportion of patients older than 75 years with a non-high or unlikely clinical probability and a negative D-dimer result using the age-adjusted cutoff was 99 of 379 (26.1%). Of those patients, 1 received anticoagulant therapy for an indication other than VTE. There were no patients lost-to follow up, no deaths, and none withdrew consent. One patient of 99 with a D-dimer less than 500 µg/L had a confirmed VTE (proximal DVT contralateral to the index initial suspicion) during follow-up (1.0% [95% CI, 0.2%-5.5%]).

Two- vs 3-Level Wells Score

Table 3 shows the breakdown of patients managed according to the 2-level vs the 3-level Wells score. More patients were

Table 2. Subgroup Analysis of the Primary Outcome According to Age

Age, y	No.	No. (%)			Absolute increase in the proportion of negative D-dimer (age-adjusted vs 500 µg/L), %	3-mo VTE rate, non-high/unlikely clinical probability and D-dimer < age-adjusted cutoff, No. (%) [95% CI]
		Non-high/ unlikely clinical probability	D-dimer <500 µg/L among non-high/ unlikely	D-dimer < age-adjusted among non-high/ unlikely		
18-49	1010	770 (76.2)	290 (59.6)	290 (59.6)	0	1 (0.3) [0.1-0.9]
50-64	1001	641 (64.0)	153 (23.9)	192 (30.0)	6.1	0 [0.0-2.0]
65-74	597	379 (63.5)	55 (14.5)	111 (29.3)	14.8	0 [0.0-3.4]
≥75	597	379 (63.5)	33 (8.7)	99 (26.1)	17.4	1 (1.0) [0.2-5.5]

Abbreviation: VTE, venous thromboembolism.

Table 3. Two- vs 3-Level Wells Score

Wells score	No. (%)	No. (%)		No./total (%)			3-mo VTE rate in patients with a negative age-adjusted D-dimer No./No. (%) [95% CI]
		Confirmed DVT	Non-high/ unlikely clinical probability	Negative D-dimer in patients with a non-high/unlikely probability	Non-high/ unlikely and negative D-dimer	Patients requiring compression ultrasonography	
In 2 categories (North America)	1181 (36.8)	180 (15.2)	561 (47.5)	209/561 (37.3)	209 (17.7)	972/1181 (82.3)	1/209 (0.5%) [0.1%-2.7%]
In 3 categories (Europe)	2024 (63.2)	252 (12.5)	1608 (79.4)	483/1608 (30.0)	483 (23.9)	1541/2024 (76.1)	1/483 (0.2%) [0.0%-1.2%]

Abbreviations: DVT, deep vein thrombosis; VTE, venous thromboembolism.

eligible for D-dimer testing when using the 3-level Wells score, but the chance of a negative result was lower. The failure rates were 1 in 209 (0.5% [95% CI, 0.1%-2.7%]) with the 2-level score and 1 in 483 (0.2% [95% CI, 0.0%-1.2%]) with the 3-level score.

Discussion

Among outpatients with suspected leg DVT, using the age-adjusted D-dimer cutoff (defined as D-dimer level < patient's age × 10 in µg/L in patients ≥50 years) allows to safely rule out DVT. The failure rate, as defined by the 3-month rate of symptomatic VTE, was low in patients with a negative age-adjusted D-dimer level (2/692; 0.3% [95% CI, 0.1%-1.1%]). There were no events among the 161 patients with a D-dimer level greater than 500 µg/L but below their age-adjusted D-dimer cutoff (0/161; 0.0% [95% CI, 0.0%-2.3%]).

These results are consistent with those from prospective trials evaluating the age-adjusted D-dimer testing in patients with suspected pulmonary embolism.[3,4] While several retrospective studies in patients with suspected DVT have supported the potential safety and clinical usefulness of the age-adjusted cutoff across various assays and settings,[17,18] a prospective outcome study, in which treatment of patients with suspected DVT would be managed without anticoagulants on the basis of a negative age-adjusted D-dimer test result has been lacking.

Using the age-adjusted D-dimer threshold significantly increases the number of patients 75 years or older who can safely avoid compression ultrasonography—from 5.5% using the conventional 500-µg/L cutoff to 16.6% using the age-adjusted threshold. Put differently, while only 1 in 18 older adults could be ruled out for DVT using the standard cutoff, this increased to 1 in 6 patients older than 75 years with the age-adjusted approach. This effectively restores the diagnostic yield of the D-dimer test in older adults to levels more comparable to those of the general population. In clinical practice, this has meaningful implications: enabling more patients to be discharged without imaging, reducing emergency department length of stay, and avoiding unnecessary empiric anticoagulation. Importantly, these advantages were not offset by any compromise in diagnostic safety.

Other efforts have been made to spare imaging in patients with suspected VTE, using clinical probability-adjusted D-dimer cutoffs. For instance, in patients with suspected pulmonary embolism, higher D-dimer thresholds (eg, 1000 µg/L) have been prospectively validated in patients with a low pretest probability.[19,20] However, similar efforts have been limited in the DVT setting. A prospective study, the 4D study,[21] applied a 1000-µg/L cutoff in patients with a low clinical probability of DVT and showed a 3-month VTE rate of 0.6% (95% CI, 0.3%-1.2%).

This study has several strengths. This was a large international collaboration. All suspected VTE events and deaths during follow-up were adjudicated by an independent committee blinded to patient's initial D-dimer result. Another strength is the choice of focusing on the subgroup of patients with a D-dimer level 500 µg/L or greater but below their age-adjusted cutoff as the primary outcome, which allowed assessing the safety in this specific subgroup of interest without diluting the result by considering the whole population of patients including those with a D-dimer level less than 500 µg/L. Beyond reducing unnecessary imaging and conserving health care resources, this study provides important prospective validation of the age-adjusted cutoff to safely rule out leg DVT and pulmonary embolism. Many centers have been hesitant to implement the age-adjusted cutoff in their emergency departments due to concerns about inconsistent cutoffs for DVT and pulmonary embolism. Acknowledging that other challenges to implementation may exist, including the lack of

standardization across institutions or medicolegal hesitations in deviating from the conventional 500 µg/L cutoff, this study supports the consistent use of the age-adjusted cutoff in patients with suspected pulmonary embolism and those with suspected leg DVT.

Limitations

Among study limitations, 11 different commercial D-dimer assays were used. Therefore, not all included patients had treatment managed using the exact same diagnostic tests. Acknowledging that standardization of D-dimer assays remains a challenge,[22] the study only used highly sensitive D-dimer assays, which have been reported to have comparable diagnostic performances.[3,23] Moreover, this could increase the generalizability of the findings to a wide number of settings. This may also be said about the assessment of clinical probability, which was performed by either the 2- or 3-level Wells score, without impacting the failure rate.

Second, this study was not designed as a randomized controlled study. Therefore, the 3-month VTE risk could not be compared with that of a control group whose treatment would have been managed using the conventional 500-µg/L cutoff. However, given the low rate of VTE events, a significant difference between the 2 strategies would have been unlikely. Moreover, the use of the 3-month VTE risk is widely used as the standard reference for the validation of VTE diagnostic strategies.

Third, compared with our previous pulmonary embolism study, a lower-than-expected number of patients had a D-dimer level 500 µg/L or greater but below their age-adjusted cutoff. The current study population was younger than the one enrolled in the ADJUST-PE study (median age, 57 years vs 63 years), resulting in a lower number of patients in whom the cutoff was adjusted based on age, which could account for this difference.

Fourth, study recruitment was longer than anticipated, due to challenges in securing peer-reviewed funding in each participating country and obtaining regulatory and ethical approvals at each site. Recruitment in Canada and Switzerland started in 2015, but sites in Belgium and France joined the study in 2019 and 2020, respectively. The COVID-19 pandemic later halted the study at most participating sites.

Fifth, several patients with negative D-dimer results underwent compression ultrasonography at initial assessment (185/531 in patients with a D-dimer level less than 500 µg/L and 94/161 in patients with D-dimer between 500 µg/L and their age-adjusted cutoff). The reason why a physician would decide to override the study diagnostic algorithm was not collected. One can speculate that physicians remained concerned about a possible DVT despite a negative D-dimer result or wanted to rule out an alternative diagnosis. These additional tests led to the diagnosis of 11 distal DVTs and 1 proximal DVT in patients with a D-dimer level less than 500 µg/L. No proximal or distal DVT was diagnosed in patients with a D-dimer level between 500 µg/L and their age-adjusted cutoff. The clinical relevance, management, and prognosis of distal DVT, a fortiori with a negative D-dimer result, are widely debated.[24] Many studies previously demonstrated a good outcome in patients with suspected DVT and D-dimer level below 500 µg/L,[25-27] despite others reporting a limited sensitivity of D-dimer tests for distal DVT.[28] Clinical practice guidelines strongly endorse the safety of not treating with anticoagulants patients with suspected DVT, a non-high pretest probability, and negative highly sensitive D-dimer result.[1,29]

Last, it is important to mention that these results cannot be extrapolated to other thrombosis locations/types, eg, upper extremity, cerebral, splanchnic, or gonadal vein thromboses.

Conclusions

A negative D-dimer result using the age-adjusted D-dimer cut-off may safely rule out leg DVT in outpatients with a non-high or unlikely pretest probability, with a very low risk of subsequent symptomatic venous thromboembolism. The age-adjusted cutoff significantly increases the proportion of patients in whom DVT can be excluded without the need for leg compression ultrasonography.

ARTICLE INFORMATION

Accepted for Publication: October 17, 2025.

Published Online: January 5, 2026. doi:10.1001/jama.2025.21561

Author Affiliations: Ottawa Health Research Institute, Ottawa, Ontario, Canada (Le Gal, Thiruganasambandamoorthy); EA3878 GETBO, Université de Brest, Brest, France (Le Gal); Division of Angiology and Hemostasis, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland (Robert-Ebadi, Righini); Department of Emergency Medicine, University of Ottawa, Ottawa, Ontario, Canada (Thiruganasambandamoorthy); Emergency Department, CHU Clermont-Ferrand, Université Clermont Auvergne, Clermont-Ferrand, France (Moustafa); Cliniques Universitaires St-Luc et Université Catholique de Louvain, Bruxelles, Belgium (Penaloza); Hôpital Edouard Herriot, Internal Medicine, Lyon University Hospital, Lyon, France (Catella); Centre Hospitalier d'Annecy, Vascular Medicine, Annecy, France (Grenot); Montfort Hospital, Ottawa, Ontario, Canada (Visser); Centre Hospitalier Universitaire Vaudois, Service d'angiologie, Lausanne, Suisse (Mazzolai); CHU Saint Pierre, Bruxelles, Belgium (Plumacker); Department of Vascular Medicine, University Hospital Zürich, Zürich, Switzerland (Barco); Calgary Hospital, Calgary, Canada (Lang); Jewish General Hospital, Montreal, Quebec, Canada (Tagalakis); Hôpital Edouard Herriot, Emergency, Lyon University Hospital, Lyon, France (Deroche); Thunder Bay Regional Health Sciences Centre, Thunder Bay, Ontario, Canada (Garnett); University Health Network, Toronto, Ontario, Canada (Hulme); Emergency Department, CHU d'Angers, l'UNAM Université, Angers, France (Roy); Liège University Hospital, Liège, Belgium (Ghuysen); Univ Brest, INSERM, UMR 1304-GETBO, Brest, France (Couturaud); Department of Internal and Respiratory Medicine, Centre Hospitalier Universitaire de Brest, Brest, France (Couturaud); Angiology Unit, HFR Fribourg, Fribourg, Switzerland (Engelberger); CHU de Nantes, Service des Urgences, Nantes, France (El Kouri); Department of General Internal Medicine, Bern University Hospital, University of Bern, Bern, Switzerland (Aujesky).

Author Contributions: Prof Righini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Le Gal, Thiruganasambandamoorthy, Lang, Ghuysen, Righini.
Acquisition, analysis, or interpretation of data: Le Gal, Robert-Ebadi, Thiruganasambandamoorthy, Moustafa, Penaloza, Catella, Chevallier Grenot, Visser, Mazzolai, Plumacker, Barco, Tagalakis, Deroche, Garnett, Hulme, Roy, Ghuysen, Couturaud, Engelberger, El Kouri, Aujesky, Righini.
Drafting of the manuscript: Le Gal, Robert-Ebadi, Thiruganasambandamoorthy, Deroche, El Kouri, Righini.

Critical review of the manuscript for important intellectual content: Robert-Ebadi, Thiruganasambandamoorthy, Moustafa, Penaloza, Catella, Chevallier Grenot, Visser, Mazzolai, Plumacker, Barco, Lang, Tagalakis, Garnett, Hulme, Roy, Ghuysen, Couturaud, Engelberger, Aujesky. *Statistical analysis:* Le Gal, Robert-Ebadi, Righini. *Obtained funding:* Le Gal, Lang, Righini. *Administrative, technical, or material support:* Le Gal, Thiruganasambandamoorthy, Moustafa, Penaloza, Visser, Plumacker, Barco, Deroche, Hulme, Ghuysen, Couturaud, El Kouri, Righini. *Supervision:* Moustafa, Barco, Hulme, Ghuysen, Engelberger, Righini.

Conflict of Interest Disclosures: Dr Le Gal reported receiving lecture honoraria not taken as income from Emcure and Takeda outside the submitted work. Dr Thiruganasambandamoorthy reported receiving support through a Physicians' Services Incorporated Foundation Mid-Career KT fellowship award and University of Ottawa Tier-1 Clinical Research Chair in Cardiovascular Emergencies award; receiving grant funding from Physicians' Services Incorporated Foundation, Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, Networks of Centres of Excellence through the Cardiac Arrhythmia Network of Canada (CANet), Ontario Centres of Innovation, and The Ottawa Hospital Academic Medical Organization; and serving as a consultant for the National Institutes of Health–funded project Practical Approaches to Care in Emergency Syncope (PACES). Dr Penaloza reported receiving support for symposia and research from Bayer, Daiichi, LEO Pharma, Viatris, BMS/Pfizer, Sanofi, Becton Dickinson, and Charities Aid Foundation and receiving support for a study sponsored by Stago outside the submitted work. Dr Garnett reported receiving grants from the Heart and Stroke Foundation of Canada during the conduct of the study and that she is an associate professor at NOSM University. Dr Roy reported receiving personal fees from Viatris Sante, Sanofi Winthrop Industry, Pfizer SAS, and Bristol Myers Squibb and receiving grants from the French Ministry of Health outside the submitted work. Dr Couturaud reported receiving research grants from BMS/Pfizer and Merck Sharp and Dohme, travel support from Sanofi, and personal fees from LEO Pharma and GlaxoSmithKline outside the submitted work. No other disclosures were reported.

Funding/Support: The study was supported by a grant from the Swiss National Research Foundation (32003B_159510). In Canada, the study was supported by the Heart and Stroke Foundation of Canada (Grant-in-Aid G-15-000903 and G-19-0026332). In Belgium, the study was supported by a grant from the Forum pour la Recherche Thrombo-Embolique aux Urgences. In France, the study was sponsored by a grant of the INVENT network and by a grant of the Clermont-Ferrand University Hospital. Dr Le Gal holds the Chair on Diagnosis of Venous Thromboembolism from the Department of Medicine, University of Ottawa. The study was also supported by the Center of Clinical Research, Geneva University Hospital, and by the Canadian Venous Thromboembolism Research Network (CanVECTOR).

Role of the Funder/Sponsor: The study funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The ADJUST-DVT investigators appear in Supplement 3.
Collaborators: *Belgium (382 patients):* Hôpital Erasme, Cliniques universitaires de Bruxelles (8); Centre Hospitalier Universitaire de Liège (33); Cliniques universitaires de Saint-Luc (264); Centre Hospitalier Universitaire Saint-Pierre (77). *Canada (1181 patients):* Humber River Hospital, Toronto (1); Foothills Hospital, Calgary (47); Jewish General Hospital, Montreal (44); Hôpital Montfort, Ottawa (89); The Ottawa Hospital, Ottawa (906); Queensway Carleton hospital, Ottawa (18); Royal University Hospital, Saskatoon (1); Thunder Bay Regional Health Sciences Centre, Thunder Bay (38); University Health Network, Toronto (37). *France (467 patients):* Centre Hospitalier, Annecy (94); Hôpital d'instruction des armées, Brest (13); Centre Hospitalier Universitaire, Clermont-Ferrand (32); Centre Hospitalier Universitaire, Angers (36); Centre Hospitalier Universitaire, Brest (25); Centre Hospitalier Universitaire, Nantes (24); Hôpital Edouard Herriot, Médecine interne et vasculaire, Lyon (179); Hôpital Edouard Herriot, Service des urgences, Lyon (43); Hôpital Lyon Sud, Lyon (21). *Switzerland (1175 patients):* Kantonsspital Baselland Bruderholz, Basel (5); Hôpital de Fribourg, Fribourg (15); Centre Hospitalier Universitaire Vaudois, Service d'angiologie, Lausanne (77); Hôpitaux Universitaires de Genève, Service d'angiologie, Geneva (1008); Universitätsspital Zürich, Klinik für Angiologie, Zürich (70).

Data Sharing Statement: See Supplement 4.

Additional Contributions: We express our gratitude to the members of the adjudication committee for their important contribution: Julien D'Astous, MD (Centre Hospitalier de l'Université de Montréal, Montréal, Quebec, Canada [chair]); Emmanuelle Le Moigne, MD, PhD (Centre Hospitalier Universitaire de Brest, Brest, France); Sébastien Miranda, MD, PhD (Centre Hospitalier Universitaire de Rouen, Rouen, France); Rick Ikesaka, MD, MSc (McMaster University, Hamilton, Ontario, Canada). We extend our gratitude to all the members of the data and safety monitoring board: Drahomir Aujesky, MD, PhD (Inselspital Bern, Bern, Switzerland [chair]); François Becker, MD (Chamonix, France); Emmanuel Nowak, PhD (Centre Hospitalier Universitaire de Brest, Brest, France [biostatistician]). No compensation was provided to any of the study committees members. We thank all the residents and physicians from the emergency departments and vascular medicine units of all participating centres. We thank study coordinators Louise Riberdy and Nadège Koffi Malan (Switzerland), Heather Langlois, Veronica Bates, Penny Philipps (Canada), Lara Absil (Belgium), and Camille Lucchini-Roche (France). We also thank all study nurses, clinical research nurses, secretaries, and clinical research technicians for their invaluable help. We extend our thanks to the staff of the Clinical Research Center, Geneva University Hospital, and in particular to Khaled Mostaguir (clinical research associate), who developed the electronic case report form for the study. Last but not least, we would like to express our gratitude to the patients who made the study possible by accepting to participate in the trial.

REFERENCES

1. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2(22):3226-3256. doi:10.1182/bloodadvances.2018024828

2. 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. doi:10.1016/S0002-9343(00)00493-9

3. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. *JAMA*. 2014;311(11):1117-1124. doi:10.1001/jama.2014.2135

4. Robert-Ebadi H, Robin P, Hugli O, et al. Impact of the age-adjusted d-dimer cutoff to exclude pulmonary embolism: a multinational prospective real-life study (the RELAX-PE study). *Circulation*. 2021;143(18):1828-1830. doi:10.1161/CIRCULATIONAHA.120.052780

5. Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD; Clinical Guidelines Committee of the American College of Physicians. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2015;163(9):701-711. doi:10.7326/M14-1772

6. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Respir J*. 2019;54(3):1901647. doi:10.1183/13993003.01647-2019

7. Riva N, Camporese G, Iotti M, et al; PALLADIO Study Investigators. Age-adjusted D-dimer to rule out deep vein thrombosis: findings from the PALLADIO algorithm. *J Thromb Haemost*. 2018;16(2):271-278. doi:10.1111/jth.13905

8. Sartori M, Borgese L, Favaretto E, Lasala E, Bortolotti R, Cosmi B. Age-adjusted D-dimer, clinical pre-test probability-adjusted D-dimer, and whole leg ultrasound in ruling out suspected proximal and calf deep venous thrombosis. *Am J Hematol*. 2023;98(11):1772-1779. doi:10.1002/ajh.27077

9. Sharma S, Soon L, de Wit K, et al. Validation of the ToDay, a simplified diagnostic algorithm for deep vein thrombosis. *J Thromb Haemost*. 2025;S1538-7836(25)00418-0. doi:10.1016/j.jtha.2025.06.029

10. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med*. 1998;129(12):997-1005. doi:10.7326/0003-4819-129-12-199812150-00002

11. Tritschler T, Kraaijpoel N, Girard P, et al; Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease. Definition of pulmonary embolism-related death and classification of the cause of death in venous thromboembolism studies: communication from the SSC of the ISTH. *J Thromb Haemost*. 2020;18(6):1495-1500. doi:10.1111/jth.14769

12. Righini M, Kamphuisen PW, Le Gal G. Age-adjusted D-dimer cutoff levels and pulmonary embolism—reply. *JAMA*. 2014;312(5):557-558. doi:10.1001/jama.2014.7607

13. Douma RA, Tan M, Schutgens RE, et al. Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. *Haematologica*. 2012;97(10):1507-1513. doi:10.3324/haematol.2011.060657

14. Hull R, Hirsh J, Sackett DL, et al. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. *Circulation*. 1981;64(3):622-625. doi:10.1161/01.CIR.64.3.622

15. Dronkers CEA, van der Hulle T, Le Gal G, et al; Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. *J Thromb Haemost*. 2017;15(5):1040-1043. doi:10.1111/jth.13654

16. Moores LK. Diagnosis and management of pulmonary embolism: are we moving toward an outcome standard? *Arch Intern Med*. 2006;166(2):147-148. doi:10.1001/archinte.166.2.147

17. Barrett L, Jones T, Horner D. The application of an age adjusted D-dimer threshold to rule out suspected venous thromboembolism (VTE) in an emergency department setting: a retrospective diagnostic cohort study. *BMC Emerg Med*. 2022;22(1):186. doi:10.1186/s12873-022-00736-z

18. De Pooter N, Brionne-François M, Smahi M, Abecassis L, Toulon P. Age-adjusted D-dimer cut-off levels to rule out venous thromboembolism in patients with non-high pre-test probability: clinical performance and cost-effectiveness analysis. *J Thromb Haemost*. 2021;19(5):1271-1282. doi:10.1111/jth.15278

19. van der Hulle T, Cheung WY, Kooij S, et al; YEARS study group. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet*. 2017;390(10091):289-297. doi:10.1016/S0140-6736(17)30885-1

20. Kearon C, de Wit K, Parpia S, et al; PEGeD Study Investigators. Diagnosis of deep vein thrombosis with D-dimer adjusted to clinical probability: prospective diagnostic management study. *BMJ*. 2022;376:e067378. doi:10.1136/bmj-2021-067378

21. Kearon C, de Wit K, Parpia S, et al. Diagnosis of deep vein thrombosis with D-dimer adjusted to clinical probability: prospective diagnostic management study. *BMJ*. 2022;376:e067378. doi:10.1136/bmj-2021-067378

22. Wauthier L, Favresse J, Hardy M, et al. D-dimer testing: a narrative review. *Adv Clin Chem*. 2023;114:151-223. doi:10.1016/bs.acc.2023.02.006

23. 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. doi:10.1111/j.1538-7836.2007.02328.x

24. Righini M, Robert-Ebadi H. Management of isolated distal deep vein thrombosis. *Vasa*. 2024;53(3):185-192. doi:10.1024/0301-1526/a001119

25. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med*. 2003;349(13):1227-1235. doi:10.1056/NEJMoa023153

26. Bernardi E, Camporese G, Büller HR, et al; Erasmus Study Group. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. *JAMA*. 2008;300(14):1653-1659. doi:10.1001/jama.300.14.1653

27. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet*. 1999;353(9148):190-195. doi:10.1016/S0140-6736(98)05248-9

28. Escoffre-Barbe M, Oger E, Leroyer C, et al. Evaluation of a new rapid D-dimer assay for clinically suspected deep venous thrombosis (Liatest D-dimer). *Am J Clin Pathol*. 1998;109(6):748-753. doi:10.1093/ajcp/109.6.748

29. Mazzolai L, Ageno W, Alatri A, et al. Second consensus document on diagnosis and management of acute deep vein thrombosis: updated document elaborated by the ESC Working Group on Aorta and Peripheral Vascular Diseases and the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. *Eur J Prev Cardiol*. 2022;29(8):1248-1263. doi:10.1093/eurjpc/zwab088