Age-adjusted D-dimer to rule out deep vein thrombosis

PALLADIO Study Investigators

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ORIGINAL ARTICLE

Age-adjusted D-dimer to rule out deep vein thrombosis: findings from the PALLADIO algorithm

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Essentials

- The accuracy of the age-adjusted D-dimer in suspected venous thromboembolism is still debated.
- We assessed the performance of age-adjusted D-dimer combined with the PALLADIO algorithm.
- The age-adjusted threshold can reduce the need for imaging tests compared to the fixed cut-off.
- The safety of this approach should be confirmed in large management studies.

Summary. *Background:* Age-adjusted D-dimer has been proposed to increase specificity for the diagnosis of venous thromboembolism (VTE). However, the accuracy of this threshold has been recently questioned. *Objectives:* To assess the diagnostic performance of age-adjusted D-dimer combined with clinical pretest probability (PTP) in patients with suspected deep vein thrombosis (DVT). *Methods:* PALLADIO (NCT01412242) was a multicenter management study that validated a new diagnostic algorithm, incorporating PTP, D-dimer (using the manufacturer's cut-off) and limited or extended compression ultrasonography (CUS) in outpatients with clinically suspected DVT. Patients with unlikely PTP and negative D-dimer had DVT ruled out without further testing (group 1); patients with likely PTP or positive D-dimer underwent limited CUS (group 2); patients with likely PTP and positive D-dimer underwent extended CUS (group 3). Patients with DVT ruled out at baseline had a 3-month follow-up. In this *post-hoc* analysis we evaluated age-adjusted D-dimer cut-off (defined as age times 10 μg L^{-1}, or age times 5 μg L^{-1} for D-dimers with a lower manufacturer's cut-off, in patients > 50 years). *Results:* In total, 1162 patients were enrolled. At initial visit, DVT was detected in 4.0% of patients in group 2 and 53.0% in group 3. The age-adjusted D-dimer, compared with the fixed cut-off, resulted in 5.1% (95% CI, 4.0–6.5%) reduction of CUS. The incidence of symptomatic VTE during follow-up was: 0.24% (95% CI, 0.04–1.37) in group 1; 1.12% (95% CI, 0.44–2.85) in group 2; and 1.89% (95% CI, 0.64–5.40) in group 3. *Conclusions:* The PALLADIO algorithm using age-adjusted D-dimer slightly decreased the number of required imaging tests, but this approach should be confirmed in large management studies.

Keywords: algorithms; diagnosis; outpatients; ultrasonography; venous thrombosis.

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Introduction

D-dimer is a fibrin degradation product, and therefore a marker of coagulation activation and fibrinolysis [1]. The main clinical application of D-dimer is in the diagnostic algorithm for venous thromboembolism (VTE), both for deep vein thrombosis (DVT) and pulmonary embolism (PE). D-dimer has a high sensitivity and negative predictive value [2], but a low specificity, being raised by a number of different conditions, such as cancer, infections, trauma and heart failure, among others [3]. When included in the diagnostic algorithm for VTE, D-dimer

must be integrated with clinical pretest probability (PTP) scores (such as the Wells score or the revised Geneva score [4–6]) and VTE diagnosis should be confirmed by specific diagnostic imaging tests (such as compression ultrasound [CUS] for DVT or computed tomography pulmonary angiography [CTPA] for PE). The advantage of using D-dimer is to avoid unnecessary imaging tests in patients with a low PTP and negative D-dimer results [7,8]. However, D-dimer concentrations normally increase with age, and similarly the percentage of false-positive results: it has been reported that the specificity of D-dimer drops from 67% in patients ≤ 40 years to 10% in patients ≥ 80 years [9]. In order to increase the specificity without reducing the high sensitivity of D-dimer, an age-adjusted cut-off has been recently proposed [10–12]. Compared with the standard fixed cut-off, the age-adjusted D-dimer showed increased specificity in patients with suspected DVT or PE [10,12]. However, the use of this threshold has been recently questioned by studies showing that the negative predictive value was not better than the conventional threshold [13,14]. Furthermore, although the safety of the age-adjusted D-dimer cut-off in patients with suspected PE has already been validated in a management study [12], data in patients with suspected DVT are scarce and derived only from retrospective analysis [10,13]. Therefore, more evidence is needed on the accuracy of the age-adjusted threshold in the diagnosis of DVT.

The Prospective Algorithm incorporating Limited and whole-Leg Assessment of the Deep venous system In symptomatic Outpatients (PALLADIO) study [15] assessed the performance of a diagnostic algorithm (combining D-dimer, PTP and limited or extended CUS) that aimed to simplify the approach to patients with suspected DVT. The combination of PTP and D-dimer indeed allowed the identification of three groups of patients: (i) patients in whom DVT could be safely ruled out without the need for CUS; (ii) patients who needed a single limited CUS, without the need for a repeated CUS after a week; and (iii) patients who needed an extended CUS, in order to assess both proximal and distal veins. Therefore, the PALLADIO algorithm can eliminate the need for repeated serial CUS and reduce the risk of detecting isolated distal DVTs of uncertain clinical significance. The aim of this *post-hoc* analysis was to assess the accuracy of an age-adjusted D-dimer cut-off using the database of the PALLADIO study [15].

Materials and methods

Study design and population

The PALLADIO study (ClinicalTrials.gov number: NCT01412242) was an international multicenter management study of patients with suspected DVT [15]. Briefly, inclusion criteria were consecutive adult outpatients with clinically suspected DVT of the lower extremities, referred to eight thrombosis centers in five different countries from March 2011 to July 2014 (see Appendix for the full list of contributors). Exclusion criteria were: previous DVT in the same leg; concomitant suspicion of PE; ongoing or planned anticoagulant treatment for other indications; need for pharmacological thromboprophylaxis because of recent surgery, trauma or acute medical disease; inpatients; pregnancy; unavailability for follow-up; and age < 18 years. The study was approved by the local research and ethics committees and written informed consent was obtained from all patients before inclusion.

Study procedures

All patients underwent assessment of the pretest probability (PTP) of DVT using the Wells score [4] and measurement of the D-dimer. Different D-dimer tests were performed in each participating center and, in the original study, they were interpreted according to the manufacturer's cut-off (as reported in Table S1). Patients were divided into three groups based on PTP and D-dimer, according to the diagnostic algorithm summarized in Fig. 1. Patients with unlikely PTP and negative D-dimer had DVT ruled out without further testing (group 1). Patients with either likely PTP or positive D-dimer had a lower limb compression ultrasound (CUS) limited to the proximal veins (group 2). Patients with both likely PTP and positive D-dimer had a whole-leg CUS (group 3). Details regarding the ultrasonography technique have been reported in the original publication of the PALLADIO study [15].

All patients with DVT ruled out at baseline underwent a 3-month clinical or telephone follow-up. Patients with a suspicion of DVT or PE during follow-up underwent additional diagnostic tests at the discretion of the attending physicians (CUS, CTPA or ventilation-perfusion scan). Causes of death were adjudicated based on autopsy reports, if available, or clinical reports. All reported clinical outcomes were reviewed and adjudicated by a central adjudication committee composed of three authors (P.P., J.D.D. and M.R.), unaware of each patient management group.

Outcomes

The main outcome of the original PALLADIO study was the incidence of objectively documented DVT or PE during follow-up in patients in whom DVT was ruled out at baseline, using the manufacturer's cut-off for D-dimer. The primary aim of this *post-hoc* analysis was to assess the incidence of objectively documented thromboembolic events during follow-up by applying the new cut-offs. The secondary aim was the reduction of required imaging tests.

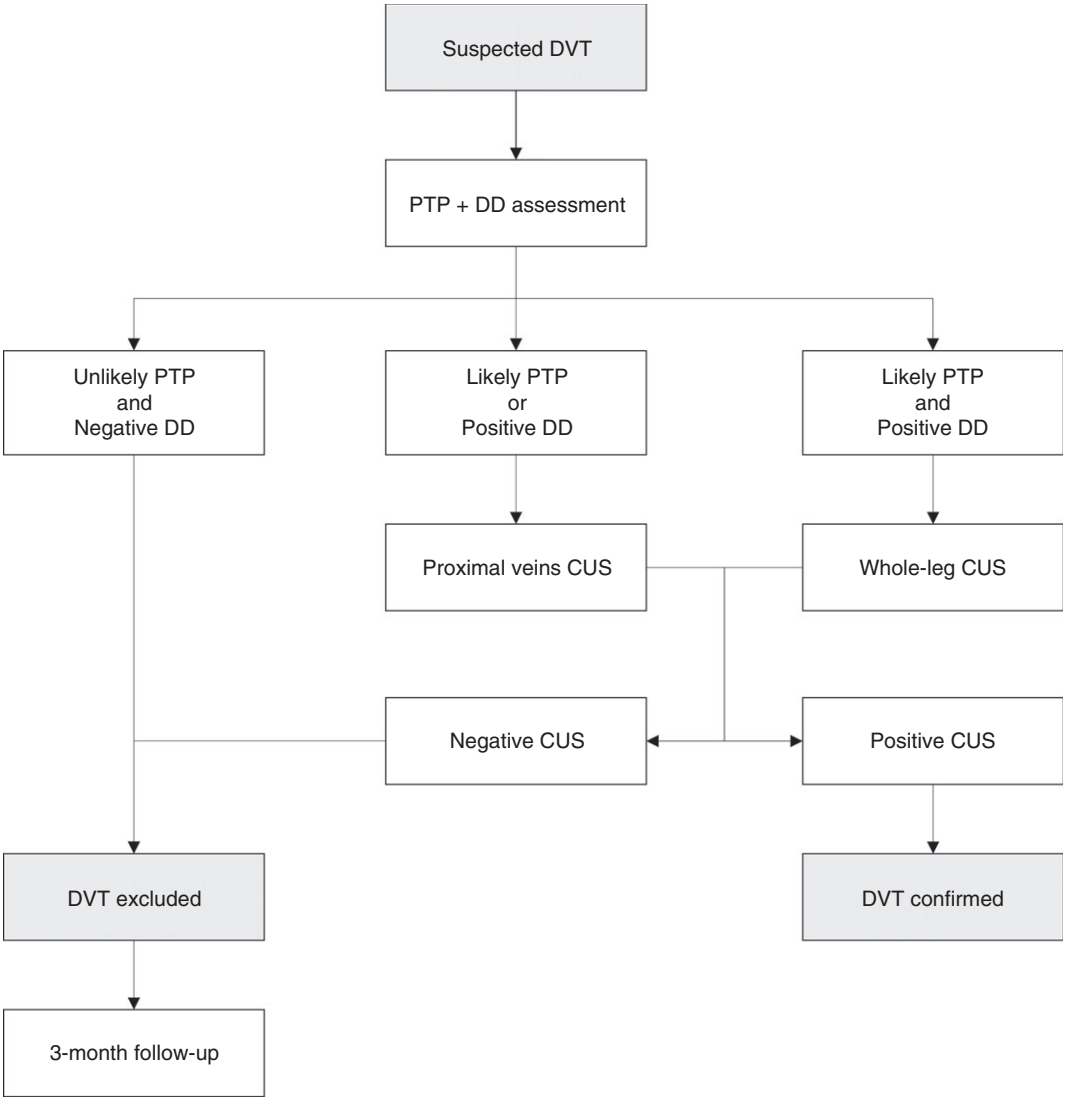

Fig. 1. Algorithm of the PALLADIO study. DVT, deep vein thrombosis; PTP, pretest probability; CUS, compression ultrasound; DD, D-dimer.

Statistical analysis

Baseline patient characteristics were expressed by means of descriptive statistics. Continuous variables were reported as mean with standard deviation (SD) or as median with interquartile range (IQR), according to the Wilk-Shapiro test; categorical variables were reported as counts and percentages. The incidence of venous thromboembolism was expressed as a percentage (with 95% Wilson confidence interval [CI]).

For the purpose of this *post-hoc* analysis, instead of using the manufacturer's cut-off for D-dimers, we applied an age-adjusted cut-off, calculated by multiplying the patient's age by 10 μg L^{-1} for patients older than 50 years, and keeping the standard fixed manufacturer's threshold of 500 μg L^{-1} for patients up to 50 years, as applied in several recent studies [10–12]. However, because three participating centers in the PALLADIO study used D-dimers with a lower manufacturer's cut-off (either 225 μg L^{-1} or 230 μg L^{-1}), we considered a halved age-adjusted threshold for these centers, defined as the patient's age times 5 μg L^{-1} for patients older than 50 years, and the conventional fixed manufacturer's threshold (either 225 μg L^{-1} or 230 μg L^{-1}) for patients up to 50 years, as suggested by a previous laboratory study [16]. The manufacturer's and age-adjusted D-dimer cut-offs are summarized in Table S1. In a sensitivity analysis, we evaluated whether the traditional age-adjusted cut-off (age times 10 μg L^{-1}) and the halved age-adjusted cut-off (age times 5 μg L^{-1}) resulted in a different incidence of VTE at 3-month follow-up.

We also calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence interval (CI) for the age-adjusted D-dimer in the entire cohort and within each PTP strata. True positive was defined as patients with D-dimer level

Table 1 Baseline characteristics of the population using the age-adjusted D-dimer threshold

	Group 1 (n = 410)	Group 2 (n = 399)	Group 3 (n = 353)
Demographic characteristics			
Age (years), median (IQR)	62 (44–75)	69 (54–79)	68 (51–80)
Female, n (%)	255 (62.2%)	244 (61.2%)	198 (56.1%)
Caucasian ethnicity, n (%)	397 (96.8%)	391 (98.0%)	340 (96.3%)
Clinical characteristics			
Time from onset of symptoms to assessment (days), median (IQR)	4 (2–7)	4 (2–7)	4 (2–7)
Involved leg:			
Left, n (%)	204 (49.8%)	204 (51.1%)	194 (55.0%)
Right, n (%)	206 (50.2%)	195 (48.9%)	159 (45.0%)
Symptoms:			
Whole leg, n (%)	69 (16.8%)	72 (18.1%)	107 (30.3%)
Thigh only, n (%)	19 (4.6%)	8 (2.0%)	6 (1.7%)
Calf only, n (%)	322 (78.5%)	319 (80.0%)	240 (68.0%)
Risk factors for DVT			
Age > 65 years, n (%)	183 (44.6%)	224 (56.1%)	194 (55.0%)
Cancer, n (%)	11 (2.7%)	19 (4.8%)	35 (9.9%)
Reduced mobility, n (%)	60 (14.6%)	82 (20.6%)	103 (29.2%)
Long distance travel, n (%)	1 (0.2%)	6 (1.5%)	10 (2.8%)
Surgical intervention, n (%)	11 (2.7%)	16 (4.0%)	31 (8.8%)
Trauma or fracture, n (%)	41 (10.0%)	47 (11.8%)	35 (9.9%)
Hormonal therapy*, n (%)	14 (5.5%)	7 (2.9%)	15 (7.6%)
Acute medical disease, n (%)	18 (4.4%)	19 (4.8%)	29 (8.2%)
Personal history of VTE, n (%)	16 (3.9%)	11 (2.8%)	28 (7.9%)
Family history of VTE, n (%)	6 (1.5%)	6 (1.5%)	9 (2.6%)
Thrombophilia, n (%)	9 (2.2%)	5 (1.3%)	9 (2.6%)

DVT, deep vein thrombosis; IQR, interquartile range; VTE, venous thromboembolism. *Proportion calculated in women only.

above the threshold and VTE at the initial visit or during follow-up. True negative was defined as patients with D-dimer level below the threshold and without VTE.

Data analysis was performed using the statistical software STATA SE 12 (StataCorp LP, College Station, TX, USA). Two-tailed P values less than 0.05 were considered statistically significant.

Results

Study population

The PALLADIO study enrolled 1162 outpatients with a clinical suspicion of DVT, with a median age of 66 years and a prevalence of female sex (60%) [15]. D-dimer results using the manufacturer's cut-off were negative in 516 (44%) patients and positive in 646 (56%) patients. Using the age-adjusted cut-off, D-dimer was negative in 632 (54%) patients and positive in 530 (46%) patients, resulting in a 10.0% (95% CI, 8.4–11.8%) decrease of positive results that might need further assessment.

Combining the age-adjusted D-dimer with the Wells PTP, which was likely in 575 patients (49%) and unlikely in 587 patients (51%), 35.3% patients (n = 410) were classified in group 1 (unlikely PTP and negative D-dimer), 34.3% (n = 399) in group 2 (either likely PTP or positive D-dimer) and 30.4% (n = 353) in group 3 (both likely PTP and positive D-dimer). Baseline characteristics of each group are reported in Table 1.

In the original analysis of the PALLADIO study, 30.2% patients (n = 351) were classified in group 1, 34.5% (n = 401) in group 2 and 35.3% (n = 410) in group 3. The age-adjusted D-dimer resulted in 59 more patients assigned to group 1, who would have had a DVT excluded without the need for CUS; 2 less patients assigned to group 2; and 57 less patients assigned to group 3, who would have had a proximal veins CUS instead of a whole-leg CUS. Therefore, the age-adjusted D-dimer would have resulted in a 5.1% (95% CI, 4.0–6.5%) decrease of patients requiring an imaging test (from 69.8% of patients needing a CUS with the original D-dimer cut-off to 64.7% using the age-adjusted cut-off) and a 4.9% (95% CI, 3.8–6.3%) decreased need for extended CUS (from 35.3% of patients needing an extended CUS with the original D-dimer cut-off to 30.4% using the age-adjusted cut-off).

Venous thromboembolic events

Using the original group assignment, the number of DVTs detected at the initial visit were 12 (3.0%) in group 2 and 200 (48.8%) in group 3, of which 82 were isolated distal DVTs. Using the age-adjusted cut-off, the number of DVTs detected at the initial visit became 16 (4.0%) in group 2 and 187 (53.0%) in group 3, of which 73 were isolated distal DVTs. Therefore, nine isolated distal DVTs, previously diagnosed in group 3 (extended CUS), would not have been detected at the initial visit if these

patients were included in group 2 (limited CUS). None of the new 59 patients in group 1 (who were D-dimer positive with the conventional cut-off and therefore underwent limited CUS in the original study) had DVT diagnosed at baseline.

The overall incidence of VTE at 3 months in the PALLADIO study was 0.87% (95% CI, 0.44–1.70%). Using the age-adjusted cut-off, the number of symptomatic VTE events during the 3-month follow-up and their distribution into the three groups would have remained the same as those obtained with the manufacturer's cut-off. The incidence rates of VTE events using the two different thresholds are summarized in Table 2. The results of the sensitivity analysis confirmed the results of the principal analysis (data not shown). Sensitivity and NPV of the age-adjusted D-dimer were 89.5% (95% CI, 84.7–93.3%) and 96.3% (95% CI, 94.5–97.6%), respectively (Table 3).

Discussion

To the best of our knowledge, this is the first time that the age-adjusted D-dimer cut-off has been applied, although in a *post-hoc* analysis, to an algorithm evaluating the need for limited or extended CUS in patients with suspected DVT. Our results show that the age-adjusted threshold included in the PALLADIO algorithm can reduce by approximately 5% the need for imaging tests, without increasing the incidence of VTE at the 3-month follow-up.

A D-dimer cut-off that gradually increases with age has been recently proposed to contrast the physiological rise of D-dimer levels with older age and to reduce the false-positive rates when used to rule out VTE in this population. A meta-analysis of 13 study cohorts involving more than 12 000 patients compared the conventional fixed threshold (500 μg L^{-1} for all patients) with an age-adjusted threshold (defined as age × 10 μg L^{-1} for patients aged > 50 years) [10]. The authors showed that specificity increased from 57.6% to 62.3% in patients 51–60 years old, from 39.4% to 49.5% in patients 61–70 years old, from 24.5% to 44.2% in patients 71–80 years old, and from 14.7% to 35.2% in patients > 80 years old, whereas sensitivity remained > 97% in all age categories [10]. Furthermore, a recently published individual patients' meta-analysis of more than 7000 patients with suspected PE showed that the combination of the Wells score and the age-adjusted D-dimer can increase by 5% the proportion of patients who can be managed without imaging [11].

Our study supports this finding because the age-adjusted cut-off was associated not only with a 5.1% reduction of CUS overall, but also a 4.9% reduction of extended CUS. Nonetheless, in our study the sensitivity

Table 2 Findings of the PALLADIO algorithm using the manufacturer's and the age-adjusted D-dimer thresholds

	Group 1 (no CUS)	Group 2 (limited CUS)	Group 3 (extended CUS)
Manufacturer's D-dimer threshold (original PALLADIO study)			
Patients enrolled, *n*	351	401	410
DVT detected at initial visit, *n* (%)	0	12 (3.0%)	200 (48.8%)
Patients eligible for follow-up*, *n*	351	371	202
VTE events during follow-up, *n*	1	4	3
VTE incidence (95% CI)	0.28% (0.05–1.60)	1.08% (0.42–2.74)	1.49% (0.51–4.27)
Age-adjusted D-dimer threshold			
Patients enrolled, *n*	410	399	353
DVT detected at initial visit, *n* (%)	0	16† (4.0%)	187 (53.0%)
Patients eligible for follow-up*, *n*	409	356	159
VTE events during follow-up, *n*	1	4	3
VTE incidence (95% CI)	0.24% (0.04–1.37)	1.12% (0.44–2.85)	1.89% (0.64–5.40)

CI, confidence interval; CUS, compression ultrasound; DVT, deep vein thrombosis; VTE, venous thromboembolism. *Excluding protocol violations, as detailed in the original publication of the PALLADIO study [15]. †However, nine distal DVTs, previously diagnosed in group 3, would not have been detected at the initial visit if included in group 2.

Table 3 Diagnostic accuracy of age-adjusted D-dimer

	Overall population (*n* = 1136*)	PTP unlikely (*n* = 580)	PTP likely (*n* = 556)
Sensitivity (95% CI)	89.5% (84.7–93.3%)	87.5% (47.3–99.7%)	89.6% (84.7–93.4%)
Specificity (95% CI)	65.1% (61.9–68.2%)	71.3% (67.4–75.0%)	54.7% (49.2–60.0%)
Negative predictive value (95% CI)	96.3% (94.5–97.6%)	99.8% (98.6–100.0%)	89.5% (84.6–93.3%)
Positive predictive value (95% CI)	38.1% (33.9–42.4%)	4.1% (1.7–8.3%)	54.9% (49.5–60.2%)

PTP, pretest probability; CI, confidence interval. *Excluding 26 protocol violations, as detailed in the original publication of the PALLADIO study [15].

of the age-adjusted D-dimer was approximately 90%, which is lower than the sensitivity reported in previously published meta-analyses [2,17]. However, these estimates are based on diagnostic studies evaluating only major VTEs as outcomes (proximal DVT and/or PE), whereas the sensitivity of D-dimer has been reported to be approximately 84% in patients with suspected isolated distal DVT [18]. Furthermore, in our study the sensitivity and NPV of the age-adjusted D-dimer threshold (89.5% and 96.3%, respectively) were lower than the sensitivity and NPV of the manufacturer's threshold in the original PALLADIO study (95.5% and 98.0%, respectively, PALLADIO study Investigators, unpublished data). [Corrections updated on December 23, 2017, after first online publication: the preceding sentence was incorrectly edited and has been corrected to include the percentages and the correct citation information.] The increase in false-negative results with the age-adjusted D-dimer was due to 13 DVTs, all detected at the initial visit in patients originally classified in group 3: nine isolated distal DVTs (that would not have been detected if these patients were shifted to group 2 [limited CUS]) and four proximal DVTs (that would have been detected even with the limited CUS). Even though the natural history of these nine unidentified distal DVTs cannot be ascertained, the incidence rate of VTE during follow-up in the three patient groups was similar to the original PALLADIO study.

The number of studies evaluating age-adjusted D-dimer cut-offs has increased exponentially over the past years. However, there was only one management study that evaluated the age-adjusted threshold in patients with suspected PE. In the ADJUST-PE study, patients with a low/intermediate or unlikely PTP (calculated using the revised Geneva score or the two-level Wells score) and a negative D-dimer result (according to the age-adjusted cut-off) had PE ruled out without CTPA [12]. During the 3-month follow-up there was one episode of VTE, corresponding to a D-dimer failure rate of 0.3% (95% CI, 0.1–1.7%) [12]. Furthermore, the majority of previous studies evaluated D-dimer tests with a standard fixed cut-off of 500 μg L^{-1} in fibrinogen-equivalent units (FEU), and defined the age-adjusted cut-off as age × 10 μg L^{-1} for patients aged > 50 years [10–12,19]. However, some laboratories use D-dimer tests that are expressed in D-dimer units (D-DU) and have lower cut-offs, because 1 FEU corresponds to approximately 2 D-DU [16].

Two recently published studies evaluated lower age-adjusted thresholds. Jaconelli *et al*. evaluated 1649 patients admitted to the emergency department with a suspected DVT or PE, and who had D-dimer testing [20]. Because the HemosIL D-dimer is measured in D-DU and the conventional cut-off is < 230 ng mL^{-1}, the authors compared the standard cut-off level (230 ng mL^{-1} in all patients) with a halved age-adjusted threshold (defined as patients age × 5 ng mL^{-1} for patients 50 years or older and 250 ng mL^{-1} for patients younger than 50 years). Among the 1324 patients with VTE unlikely (defined using the dichotomized Wells score), the age-adjusted cut-off would have resulted in almost 10% more patients with negative D-dimer, in whom VTE could have been ruled out without imaging and without any false-negative results [20]. Nobes *et al*. evaluated 1000 consecutive patients with suspected PE, who had both D-dimer testing and CTPA [21]. They evaluated the same age-adjusted cut-off (patients age × 5 ng mL^{-1} for patients 50 years or older and 250 ng mL^{-1} for patients younger than 50 years) and found that the combination of unlikely PTP (using the revised Geneva score) and age-adjusted D-dimer would have reduced unnecessary radiation exposure without missing any PE [21]. Because three participating centers in the PALLADIO study used D-dimer tests with reduced thresholds, we similarly decided to halve the age-adjusted cut-off in patients older than 50 years, but we kept the conventional fixed threshold for patients up to 50 years, as suggested by a previous laboratory study [16]. However, our results confirmed the safety of the approach proposed by Jaconelli and Nobes [20,21].

The use of an age-adjusted D-dimer threshold has been recently questioned by two studies. Takach Lapner *et al*. compared three different D-dimer interpretations in 1649 patients with a first suspected DVT or PE: the classical age-adjusted strategy (increasing D-dimer cut-off with increasing age), an inverse age-adjusted strategy (increasing D-dimer cut-off with decreasing age) and a mean D-dimer strategy (the same higher D-dimer cut-off for all patients) [13]. They found that the negative predictive value of D-dimer was above 99% with all three strategies, thus concluding that the classical age-adjusted threshold did not provide a better diagnostic strategy as compared with the mean D-dimer strategy [13]. Pernod *et al*. evaluated 1196 patients < 80 years old with suspected PE and found a similar performance of the conventional and age-adjusted D-dimer thresholds, the latter providing only a 2% increase of patients reclassified as PE ruled out without imaging [14,22]. However, patients with high clinical probability of PTP were excluded in the first study [13] and constituted less than 2% of the second study [14,22], probably because of the limited value of D-dimer in this subgroup of patients who are supposed to undergo imaging tests regardless of D-dimer value. The PALLADIO study, instead, included also patients with likely PTP of DVT, because the aim was not only to reduce the need for CUS but also to identify which patients should be examined for distal DVTs.

Our study has some limitations that need to be acknowledged. First, the age-adjusted D-dimer threshold was a *post-hoc* analysis of a management study with predefined endpoints and data collection. However, for the first time in patients with DVT, the age-adjusted D-dimer cut-off has been evaluated inside a diagnostic algorithm, including also clinical PTP and limited or extended CUS. Second, different D-dimer assays have been utilized by the participating centers; therefore, different age-adjusted

thresholds had to be applied. However, the fact that PALLADIO was an international multicenter study suggests that the age-adjusted D-dimer can be safely applied to different laboratory tests, provided that the cut-off is accurately set according to the D-dimer expressed as FEU or D-DU. Third, the reclassification of patients in a lower group would have resulted in more limited CUS and non-detection of nine isolated distal DVTs in patients changed from group 3 (extended CUS) to group 2 (limited CUS) with the age-adjusted D-dimer. Hence, being a *post hoc* analysis, it is not possible to evaluate the natural history of distal DVTs in these patients without the interference of anticoagulant treatment, because in the PALLADIO study an extended CUS was performed and they were treated accordingly.

In conclusion, using an age-adjusted D-dimer cut-off in combination with clinical PTP in patients with suspected DVT can possibly decrease the number of required imaging tests.

Addendum

P. Prandoni, W. Ageno, and N. Riva contributed to the study concept, design, and study management. P. Prandoni, J. D. Douketis, and M. Righini constituted the Central Adjudication Committee for clinical outcomes. N. Riva and W. Ageno contributed to acquisition and analysis of the data and drafted the article. G. Camporese, M. Iotti, E. Bucherini, M. Righini, P. W. Kamphuisen, P. Verhamme, J. D. Douketis, C. Tonello, and P. Prandoni contributed to the acquisition of data, interpretation of data, and critical revision of the manuscript. All authors provided final approval of the manuscript.

Disclosure of Conflict of Interests

J. Douketis reports grants from Boehringer Ingelheim and personal fees from Boehringer Ingelheim, Janssen, Pfizer, Bayer, Bristol Myers Squibb, Sanofi, and Daiichi Sankyo, outside the submitted work. P. Verhamme reports grants and personal fees from Boehringer-Ingelheim, Bayer-Healthcare, Daiichi-Sankyo, Sanofi, and Leo-Pharma, outside the submitted work. The other authors state that they have no conflict of interest.

Appendix

The PALLADIO Study Group

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. D-dimer tests and thresholds used in the original PALLADIO study and in this *post-hoc* analysis

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