



Letter to the Editors-in-Chief

Accuracy of age-adjusted D-dimer to rule out deep vein thrombosis in the elderly



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D-dimer is a very sensitive assay for the exclusion of venous thromboembolism (VTE), either deep vein thrombosis (DVT) or pulmonary embolism (PE). However, its low specificity mandates the use of specific imaging tests to confirm VTE diagnosis and the high rates of false positive D-dimers result in many negative imaging [1].

In order to increase D-dimer specificity, the use of an age-adjusted D-dimer has been proposed, with increasing cut-offs in parallel with increasing age in patients above 50 years old [2–4]. The use of age-adjusted D-dimer in patients with suspected PE has been included in the recently published guidelines of the American Society of Haematology [5], while its role in suspected DVT is still debated. We observed that age-adjusted D-dimer thresholds applied to the PALLADIO algorithm, which combines clinical pre-test probability (PTP) with D-dimer to drive the use of compression ultrasound (CUS) in patients with suspected DVT, can decrease the need for imaging tests, but the advantage was limited [6,7]. Nevertheless, it has been recently suggested that the benefit can be more pronounced in the elderly [8].

The aim of this study was to assess the accuracy of the age-adjusted D-dimer in elderly patients enrolled in the PALLADIO study.

1. Materials and methods

PALLADIO (NCT01412242) was an international prospective management study that included outpatients with clinically suspected DVT of the lower limbs, referred to 8 thrombosis centres between 2011 and 2014 (Appendix A). A new diagnostic algorithm, combining PTP (according to the two-category Wells score [9]), D-dimer (analysed locally according to fixed manufacturers' cut-off) and CUS (either limited- or extended-CUS) was validated [6].

Different diagnostic approaches were applied: 1) DVT was ruled out without further testing in patients with unlikely PTP and negative D-dimer (group 1); 2) a limited-CUS (proximal veins only) was executed in patients with likely PTP or positive D-dimer (group 2); 3) an

extended-CUS (proximal and distal veins) was executed in patients with likely PTP and positive D-dimer (group 3). In patients with DVT ruled out at baseline a 3-month follow-up was performed.

The main study outcome was the incidence of VTE during follow-up, objectively documented using CUS, computed tomography or ventilation-perfusion scan. The secondary outcome was the reduction of CUS when applying the age-adjusted thresholds to the PALLADIO algorithm.

Patient demographics were reported as median with interquartile range (IQR) or as counts and percentages. VTE incidence was reported as percentage (with 95% Wilson confidence intervals [CI]). Elderly patients were defined as those aged ≥ 75 years, as recently suggested [10]. Age-adjusted D-dimer was calculated as age times $10 \mu\text{g/L}$, or age times $5 \mu\text{g/L}$ for D-dimers with lower manufacturers' cut-off, as previously detailed [7]. The statistical software STATA SE 12 (StataCorp LP, College Station, TX, USA) was used for data analysis, considering statistically significant p values < 0.05 .

2. Results

Among the 1162 patients enrolled in the PALLADIO study, 403 (34.7%) were elderly. Median age was 81 years (IQR 77–85), ranging from 75 to 104 years; 272 (67.5%) were female. The left lower limb was involved in 233 (57.8%) and the right in 170 (42.2%); symptoms were located to the whole leg in 95 (23.6%), thigh only in 7 (1.7%) or calf only in 301 (74.7%), respectively. The most common risk factors for VTE were: reduced mobility (33%); trauma or fracture (8.7%); cancer (6.7%); acute medical disease (6.7%); personal history of VTE (5.7%); and surgery (4.0%).

Clinical PTP according to the Wells score was likely in 223 (55.3%) and unlikely in 180 (44.7%) patients. Overall, D-dimer was negative in 112 (27.8%) and positive in 291 (72.2%) using the manufacturers' cut-off; negative D-dimer increased to 191 (47.4%) using the age-adjusted cut-off. In the 180 elderly patients with unlikely PTP, the use of the age-

List of abbreviations: CI, confidence interval; CUS, compression ultrasonography; DD, D-dimer; DVT, deep vein thrombosis; PE, pulmonary embolism; PTP, pre-test probability; VTE, venous thromboembolism

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Table 1
Group assignment and findings of the PALLADIO algorithm according to the manufacturers' and age-adjusted D-dimer thresholds.

Group assignment and reduction of compression ultrasonography					
	Manufacturers' DD cut-off		Age-adjusted DD cut-off		CUS reduction (95% CI)
	Group 1, n (%)	Groups 2–3, n (%)	Group 1, n (%)	Groups 2–3, n (%)	
Elderly population (n = 403)	73 (18.1%)	330 (81.9%)	108 (26.8%)	295 (73.2%)	8.68% (6.31–11.84)
Divided by age decades:					
Age 75–84 years (n = 277)	60 (21.7%)	217 (78.3%)	81 (29.2%)	196 (70.8%)	7.58% (5.01–11.31)
Age 85–94 years (n = 117)	13 (11.1%)	104 (88.9%)	27 (23.1%)	90 (76.9%)	11.97% (7.26–19.09)
Age 95–104 years (n = 9)	0	9 (100%)	0	9 (100%)	–
Findings of the PALLADIO algorithm in the elderly					
	Manufacturers' DD cut-off		Age-adjusted DD cut-off		
	DVT prevalence as detected at initial visit, n/N (%)	VTE incidence during follow-up, n/N % (95% CI)	DVT prevalence as detected at initial visit, n/N (%)	VTE incidence during follow-up, n/N % (95% CI)	
Elderly population	79/403 (19.6%)	4/317 ^a 1.26% (0.49–3.20%)	70 ^b /403 (17.4%)	4/317 ^a 1.26% (0.49–3.20%)	
Divided by groups:					
Group 1	0/73 (0%)	0/73 0% (0–5.0%)	0/108 (0%)	0/108 0% (0–3.43%)	
Group 2	1/146 (0.7%)	2/142 1.41% (0.39–4.99%)	3/155 (1.9%)	2/139 1.44% (0.40–5.09%)	
Group 3	78/184 (42.4%)	2/102 1.96% (0.54–6.87%)	67/140 (47.9%)	2/70 2.86% (0.79–9.83%)	

Group 1 includes patients with unlikely PTP and negative DD in whom DVT was ruled out without further testing; group 2 includes patients with likely PTP or positive DD in whom a limited-CUS was performed; group 3 includes patients with likely PTP and positive DD in whom an extended-CUS was performed.

Legend: CI = confidence interval, CUS = compression ultrasonography, DD = D-dimer, DVT = deep vein thrombosis, PTP = pre-test probability, VTE = venous thromboembolism.

^a Excluding patients with DVT detected at initial visit and excluding protocol violations, as detailed in the original publication of the PALLADIO study [6].

^b 9 isolated distal DVT, diagnosed in group 3 with the original PALLADIO algorithm, would not have been detected at initial visit if these patients were shifted to group 2.

adjusted cut-off increased the number of patients with negative D-dimer from 73 (40.6%) to 108 (60.0%).

According to the original PALLADIO algorithm, 73 (18.1%) patients were classified in group 1, 146 (36.2%) in group 2 and 184 (45.7%) in group 3. The limited-CUS in group 2 was positive in 1 out of 146 patients (0.7%), while the extended-CUS in group 3 was positive in 78 out of 184 (42.4%).

Using the age-adjusted D-dimer thresholds, 108 (26.8%) patients were classified in group 1, 155 (38.5%) in group 2 and 140 (34.7%) in group 3. Therefore, the age-adjusted D-dimer would have resulted in 8.68% (95% CI, 6.31–11.84) reduction of CUS and in 10.92% (95% CI, 8.23–14.34) reduction of extended-CUS. The average number of CUS per patient would have decreased from 0.82 to 0.73. The limited-CUS in group 2 was positive in 3 out of 155 (1.9%), while the extended-CUS in group 3 was positive in 67 out of 140 (47.9%). None of the patients with DVT diagnosed at limited-CUS (group 2) was shifted to group 1 (no need for CUS), while 9 patients with isolated distal DVT detected at extended-CUS (group 3) were shifted to group 2, and with a limited-CUS these events would have been undetected.

Among the 142 elderly patients with positive age-adjusted D-dimer and DVT excluded by CUS at baseline, an alternative cause was identified in 80 (56%). The most commonly reported alternative diagnosis were: 27.5% cutaneous or subcutaneous infections (e.g. erysipelas, cellulitis); 27.5% osteoarticular diseases; 15.0% lymphatic disorders

(e.g. lymphangitis, lymphedema); 11.3% chronic venous insufficiency.

According to the original PALLADIO group assignment, no symptomatic VTE during follow-up occurred in group 1, two events (isolated distal DVT) occurred in group 2, and two events (proximal DVT) occurred in group 3. Using the age-adjusted D-dimer thresholds, the distribution of events in the three groups remained the same and the VTE incidence rate was similar to the previous analysis (Table 1).

3. Discussion

Our results suggest that the use of age-adjusted D-dimer cut-off in elderly outpatients with suspected DVT can increase the proportion of those in whom DVT can be excluded without the need for imaging, with no symptomatic VTE during the 3-month follow-up. These findings are consistent with a sub-analysis of the ADJUST-PE study [2], which prospectively evaluated the use of the age-adjusted D-dimer threshold in elderly patients with suspected PE and reported an increase in the proportion of those with unlikely clinical probability and negative D-dimer from 6.4% to 29.7%. Similarly, no VTE was reported during follow-up (incidence rate 0%; 95% CI, 0–1.9%) [2].

The optimal D-dimer threshold is a currently debated topic [3,7,8]. A recent study considering > 3800 patients showed that the age-adjusted cut-off increased specificity from 44.8% to 51.1% for DVT, and from 55.4% to 59.6% for PE [3]. We previously reported that the

specificity of the age-adjusted D-dimer for DVT using the PALLADIO algorithm was 65.1% [7]. In this sub-analysis we showed that the flexible cut-off can be especially beneficial in the elderly, with almost 9% reduction of the need for CUS, and that the CUS reduction effect is greater with increasing age, reaching approximately 12% in patients aged 85–94 years. These findings confirm the results of a recent meta-analysis that reported 12% absolute increase of D-dimer efficiency using the age-adjusted cut-off to rule out PE in patients aged ≥ 75 years [8].

Our study has some limitations that need to be acknowledged. First, complete follow-up was not available for 7 patients in groups 2–3 due to protocol violations, as detailed in the original publication of the PALLADIO study [6]. Furthermore, in the age-adjusted D-dimer analysis, we were unable to evaluate the follow-up of 9 patients diagnosed with an isolated distal DVT at baseline in the original PALLADIO study. Since the age-adjusted D-dimer was negative, these patients would have been shifted to a lower group with less invasive imaging strategy and the isolated distal DVT, although of uncertain clinical importance, would not have been detected. Second, the small sample size resulted in large confidence intervals, especially when CUS reduction was evaluated by age decades. Finally, our analysis carries also the limitations of being a subgroup and post-hoc analysis.

In conclusion, the use of age-adjusted D-dimer cut-offs can be especially beneficial in the elderly with unlikely PTP, allowing approximately a 9% reduction of the need for CUS. However, the safety of this approach should be confirmed in large prospective and independent studies.

Conflicts of interest

The authors have no relevant conflicts of interest to declare in relation to this study.

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Authors' contributions

PP, WA and NR contributed to study concept, design and study management. PP, JDD and MR constituted the Central Adjudication Committee for clinical outcomes. NR, WA and MR contributed to acquisition and analysis of the data, and drafted the article. GC, MI, EB, PWK, PV, JDD, CT, and PP contributed to acquisition of the data, interpretation, and critical revision of the manuscript. All authors provided final approval of the manuscript.

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