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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

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ABSTRACT

BACKGROUND: D-dimer and ultrasound are part of the diagnostic work-up for lower extremity deep vein thrombosis (DVT). Recent studies have shown that adjusting D-dimer (DD) level cutoffs by age or by clinical pre-test probability (PTP) decreases the use of ultrasound.

OBJECTIVE: To compare diagnostic accuracy and safety of PTP-adjusted DD and age-adjusted DD for proximal and calf DVT diagnosis.

DESIGN, SETTING, AND PATIENTS: A prospective study in outpatients who were referred by the emergency department or by a primary care physician to our unit for clinically suspected DVT. All patients underwent a clinical evaluation, D-dimer (STA Liatest) and a B-mode and color Doppler ultrasonography examination. All the patients were followed up for 3 months to document the occurrence of symptomatic deep vein thrombosis or pulmonary embolism.

RESULTS: We enrolled 3883 patients (F: 61.1%; age: 65.3 ± 16.8 y). At whole-leg ultrasonography, proximal DVT was detected in 477 (12.4%) patients and isolated distal DVT in 342 (8.9%) patients; in the remaining 3064 patients there were 23 venous thrombo-embolic events (0.75%, 95%CI: 0.50–1.12) during the follow-up. Specificity of DD, age-adjusted DD, and PTP-adjusted DD in non-high PTP patients were 47% (95%CI: 45-49%), 61% (95%CI: 59-62%), and 67% (95%CI: 65-68%), respectively, the negative predictive value (NPV) was 96% in all the three diagnostic strategies. When only proximal DVTs were considered, the negative predictive value (NPV) increased to 99% in all the three diagnostic strategies. Imaging tests would be avoided in 37% of patients with the fixed cut-off DD, in 48% of patients with the age-adjusted DD and 52% of patients with the PTP-adjusted DD. The failure rate for all DVTs of the fixed cut-off DD, the age-adjusted DD, and the PTP-adjusted DD was 2.03%, 2.7% and 2.5% respectively

CONCLUSION: In comparison with the standard DD cut-off, both the age-adjusted and PTP-adjusted DD reduce the proportion of patients who require ultrasound at a cost of a small increase of the failure rate.

INTRODUCTION

Lower extremity deep vein thrombosis (DVT) accounts for approximately 90% of cases of deep vein thrombosis [1]. Since patients with DVT may develop pulmonary embolism (PE), it is necessary to promptly select patients who deserve anticoagulant treatment. The strategies for diagnosis of DVT combine the use of clinical pre-test probability (PTP) assessment, D-dimer, and imaging techniques [3-4]. The reference imaging test in the diagnostic management of patients presenting with clinically suspected DVT of the lower extremity is compression ultrasonography [1-5]. Two compression ultrasonography strategies are used in clinical practice: limited and whole-leg compression ultrasonography. Whole-leg ultrasonography explores the entire deep vein network of the leg from the common femoral vein to the distal veins of the calf, whereas limited compression ultrasonography is not able to exclude isolated calf DVT.

Diagnostic algorithms, that combine PTP and D-dimer measurements are able to rule out DVT without the need for ultrasound in several patients and current guidelines recommend that patients with low or intermediate PTP should be assigned to D-dimer test whereas patients with high PTP should be referred to imaging techniques []. The specificity of D-dimer, i.e the proportion of patients in whom DVT may be ruled out by a normal result, changes according to the age and the PTP. In order to categorize a higher proportion of D-dimer results as negative and to decrease the number of patients that need ultrasound, two approaches to interpreting D-dimer result have been proposed: the age-adjusted strategy and the PTP-adjusted strategy. D-dimer levels increase with age [7], and this may lead to a decreased specificity of the D-dimer in the **older** patients with suspected venous thrombo-embolism (VTE). Therefore, it has been suggested to increase the D-dimer thresholds according to age [8]. Data of the age-adjusted D-dimer cut-off in patients with suspected DVT seems in line with those regarding the suspected PE, suggesting an increased specificity of the age-adjusted cut-off values. However the use of the age-adjusted D-dimer cut-off has been recently questioned by a study showing a decreased sensitivity with a false-negative rate of 24% [11].

The PTP-adjusted D-dimer uses a cut-off that is twice as high in patients with a low PTP for VTE: Recently, a prospective study showed that this diagnostic approach can reduce the need for ultrasound of 47% []. However, it remains uncertain which approach among PTP-adjusted, age-adjusted, or standard fixed cut-off D-dimer value is better in ruling out DVT.

The diagnostic strategy of age-adjusted, PTP-adjusted D-dimer and standard fixed cut-off D-dimer for diagnosing proximal and calf DVT **has not been compared in the same population**. The aim of our study was to compare the accuracy, the failure rate and usefulness **of the different D-dimer cut-offs** in a large prospective management outcome study, in which all consecutive outpatients with suspected lower leg DVT underwent clinical probability assessment, D-dimer and whole leg ultrasound.

METHODS

Study design

This was a single centre, prospective, non-randomized, non-interventional clinical outcome management study on ambulatory patients with clinically suspected lower leg DVT. The study was performed from 30 June 2009 to 9 May 2018 in a tertiary care teaching hospital (University Hospital S. Orsola-Malpighi, Bologna, Italy). Symptomatic outpatients referred by general practitioners to the vascular emergency room for suspected acute DVT of the lower extremities were potentially eligible for the study. Patients were excluded if younger than 14 years, pregnant or in puerperium, with symptoms attributable to PE, with life expectancy of less than 3 months, already established diagnosis of DVT. Moreover, patients in whom treatment with anticoagulant drugs was ongoing or planned for indications other than VTE were excluded. We enrolled all consecutive eligible patients during business days. At enrolment, each patient underwent: a) medical history and physical examination; b) D-dimer, c) **ultrasonography**.

Patients with clinically suspected inferior vena cava thrombosis and/or clinically suspected pulmonary embolism were excluded from the study.

Patients with DVT were treated with anticoagulants, while all other patients were followed-up for 3 months. Study outcome was the cumulative 3-month incidence of objectively confirmed VTE (symptomatic DVT + fatal and non-fatal PE). In case of worsening symptoms and/or suspected VTE, the patients were invited to return to our outpatient service: patients underwent a whole leg ultrasound in case of suspected DVT, a spiral computed tomography in case of suspected pulmonary embolism. After at least three months *or later* ??, all patients received a phone call or a visit at our outpatient clinic. All outcome events were adjudicated by one investigator (B. C.) not involved in patient enrolment or follow-up. The study was approved by the local Ethics Committee. Written informed consent was obtained from all patients.

Clinical pre-test probability score

PTP score for DVT was assessed using a questionnaire developed by Wells and associates [5]. One point was added for each of the following positive finding: a) active cancer treatment ongoing or within previous 6 months or palliative; b) paralysis, paresis or recent plaster immobilization of the lower legs; c) recent immobilization for more than 3 days or major surgery within last 4 weeks; d) localized tenderness/pain along the distribution of the deep venous system; e) entire leg swollen; f) calf swelling by more than 2 cm when compared with the asymptomatic leg; g) pitting edema greater in the symptomatic leg; h) collateral superficial veins; i) previously documented DVT. Two points were subtracted from the total points if an alternative diagnosis as likely as or more likely than DVT was found. Based on such checklist, PTP for DVT could be estimated to be low (score = 0 or less), moderate (score = 1 and 2) or high (score = 3 or more) [1].

D-dimer

Blood samples for D-dimer testing were taken before ultrasonography investigation. Blood was drawn by clean venipuncture from an antecubital vein with a 19-gauge butterfly needle and collected into 4 ml plastic tubes containing 0.4 ml 0.106 M trisodium citrate. Whole blood was centrifuged at 2000×g for 20 min at 20°C. Technicians performing D-dimer testing were unaware of the symptoms of the patients. The STA-Liatest® D-Di (Diagnostica Stago, Asnières, France) is an

automated and rapid microlatex D-dimer assay. Special monoclonal antibody-coated latex particles agglutinate in the presence of D-dimer fibrin degradation products. The STA Liatest® D-dimer was performed on the STA Compact® coagulation analyzer as previously described [Aguilar DD, Cini ??]. The results were expressed in $\mu\text{g/ml}$ fibrinogen equivalent unit (FEU). As previously described, the fixed cut-off value for DVT exclusion was 0.50 $\mu\text{g/ml}$ FEUs [Aguilar DD] and it was employed for patient management. Age-adjusted cut-off was applied retrospectively and DVT would have been excluded in those with a D-dimer value lower than 0.50 $\mu\text{g/ml}$ if patient younger than 50 years, whereas in patient 50 years or older, the D-dimer test result was considered negative when the D-dimer value was lower than the age multiplied by 10. PTP-adjusted D-dimer cut-off was also applied retrospectively, and the cut-off used to categorize D-dimer results as negative was <1.00 $\mu\text{g/ml}$ FEUs in patients with low PTP and <0.50 $\mu\text{g/ml}$ FEUs in patients with moderate or high PTP

Whole leg ultrasound

Patients underwent a complete real-time B-mode and color Doppler compression ultrasonography examination of both legs as previously described []. Ultrasonography investigation was carried out with an EnVisor C HD instrument (Philips Medical System S.p.A, Monza, Italy) and was performed by board-certified vascular medicine physicians using a standardized examination protocol. The proximal deep veins were examined first, and then the calf veins were evaluated. The following veins were scanned in the transverse plane over their entire length: external iliac vein, common femoral vein, deep femoral vein, femoral vein, popliteal vein, posterior tibial veins, fibular veins, medial and lateral gastrocnemius veins, and soleal veins. DVT diagnosis was confirmed if there was lack of compression of the vein.

Statistical analysis

Analysis was carried out using the IBM SPSS™ software package (version 15.0; IBM Corp. Armonk, NY, USA). Relationships between variables were assessed using Pearson correlation (r) for continuous variables and using Spearman correlation (ρ) for categorical or ordinal variables. Categorical variables were expressed as frequency and percentage with 95% confidence interval;

continuous variables were expressed as mean \pm SD. Receiver operating characteristic (ROC) curves were prepared by plotting the sensitivity versus 1-specificity. The area under the ROC curves (AUCs) for the discriminatory accuracy of the D-dimer were calculated. For each D-dimer cut-off threshold, the sensitivity, specificity, positive predictive value, negative predictive value, number of **ultrasonographies** avoided, and **ultrasonographies** avoided per false negative (Echo/FN) were determined. The Echo/FN measure was calculated using a ratio of the ultrasound estimated as avoided through the number of all D-dimer tests newly classified as negative to the number of positive confirmatory tests found (i.e. False Negatives) within those based on each adjustment to the threshold. Safety (i.e. proportion of patients left untreated on the basis of normal testing with the proposed strategy who develop thromboembolic events during follow-up) and efficiency (i.e. proportion of patients in whom DVT can be excluded on the basis of the proposed strategy) were also calculated. The significance level was two sided and set at $\alpha=0.05$.

RESULTS

We enrolled 3883 enrolled patients (mean age 65.3, range 14-103 year), the majority of participants were female (61.1%). The most frequent symptoms were pain (19.7%) and oedema (18.5%), while the most frequent risk factor for thrombosis was hormonal therapy (5%). In 22 (0.6%) participants PTP **was** not calculated, **while** PTP was low in 2170 (55.9%), moderate in 1390 (35.8%) and high in 301 (7.8%) participants. The values of D-dimer according to PTP are reported in table 1 and increased in parallel with the PTP ($\rho=0.336$, $p<0.0001$); D-dimer was also correlated with age ($r=0.178$, $p<0.0001$). The area under the receiver operating characteristics curve (AUC) for the discriminatory accuracy of the D-dimer for risk of all DVTs identified on whole leg ultrasound was 0.85 ± 0.008 $p<0.0001$, whereas the AUC for the discriminatory accuracy of the D-dimer for risk of proximal DVT identified on whole leg ultrasound was 0.91 ± 0.007 $p<0.0001$. In the whole population, using the $0.50\text{ }\mu\text{g/ml}$ FEUs threshold for DVT exclusion, D-dimer was negative in 1479 (38.1%) participants; using a PTP-adjusted threshold for DVT exclusion, D-dimer was negative in 2050 (52.8%) participants; using the age-adjusted threshold for DVT exclusion, D-dimer was negative in 1924 (49.5%) participants.

All participants underwent whole leg ultrasound: proximal DVT was detected in 477 (12.4%) participants and isolated distal DVT in 342 (8.9%) participants (table 2 ??? non riporta dati su DVT). DVT frequency in low, moderate, and high PTP groups was 5.3%, 35.0%, and 72.4%, respectively ($P=0.0001$). The remaining 3064 participants (including the 22 participants which PTP **was not** calculated) without DVT were followed-up for at least 90 days: there were 16 (3-month incidence: 0.52%, 95%CI: 0.32–0.84) non-fatal VTE and 18 deaths (3-month mortality: 0.59%, 95%CI: 0.37–0.93) that included 7 deaths related to PE (3-month incidence: 0.23%, 95%CI: 0.11–0.47). There were **xx** participants that we were not able to contact (lost of follow-up). The safety (i.e cumulative 3-month incidence of non-fatal VTE and VTE related deaths) of a diagnostic algorithm

base only on the whole leg ultrasound was 0.75% (95%CI: 0.50–1.12), the efficiency was 78.9% (95% CI 77.6–80.2%).

Since current guidelines recommend that patients with high PTP should proceed directly to whole-leg ultrasonography, the diagnostic accuracy of the age-adjusted and PTP adjusted D-dimer threshold for DVT exclusion were calculated in participants with low and intermediate PTP (n=3560). The AUC for the discriminatory accuracy of the D-dimer values for risk of all DVTs identified on whole leg ultrasound is reported in figure 1 (panel A for ???, panel B panel ???) . As shown in table 2, the D-dimer fixed cut-off value had a sensitivity of 91% (95%CI: 88-93%), a specificity of 47% (95%CI: 45-49%), with a negative predictive value of 96% (95%CI: 95-97%), and a positive predictive value of 26% (95%CI: 24-27%) for the diagnosis of all DVTs. The age-adjusted D-dimer had a sensitivity of 87% (95%CI: 84-89%), specificity of 61% (95%CI: 59-62%), with a negative and positive predictive value of 96% (95%CI: 95-97%), and 31% (95%CI: 29-33%), respectively for the diagnosis of all DVTs (table 2). The PTP-adjusted D-dimer had a sensitivity of 88% (95%CI: 85-89%), a specificity of 67% (95%CI: 65-68%), with a negative predictive value of 96% (95%CI: 95-97%), and a positive predictive value of 34% (95%CI: 32-37%) for the diagnosis of all DVTs (table 2).

When only proximal DVTs were considered, in participants with low and intermediate PTP the age-adjusted D-dimer had a sensitivity of 94% (95%CI: 91-96%), specificity of 57% (95%CI: 55-59%), with a negative and positive predictive value of 99% (95%CI: 98-99%), and a positive predictive value of 16% (95%CI: 15-18%), respectively for the diagnosis of proximal DVT (table 3). The PTP-adjusted D-dimer had a sensitivity of 94% (95%CI: 91-96%), a specificity of 62% (95%CI: 60-63%), with a negative predictive value of 99% (95%CI: 98-99%), and a positive predictive value of 18% (95%CI: 16-20%) for the diagnosis of proximal DVT (table 3). The AUC for the discriminatory accuracy of the D-dimer for risk of only proximal DVTs identified on whole leg ultrasonography are reported in figure 1 (panel ??).

According to current guidelines, **ultrasonography** can be omitted in case of low/moderate PTP and "normal" D-dimer. The D-dimer fixed cut-off value (0.50 µg/ml FEUs) for participants with low and moderate PTP would have avoided 1452 (37.4%) **ultrasonographies** at a cost of 9 **missed** proximal DVTs, 47 **missed** isolated distal DVTs and 23 VTE during the follow-up with a safety of 2.03% (95%CI: 1.63–2.52) and an efficiency of 76.2% (95% CI 74.8–77.5%). The diagnostic algorithm based on age-adjusted D-dimer cut-off value for participants with low and moderate PTP would have avoided 1881 (48.4%) **ultrasonographies** at a price of 18 missed proximal DVTs, 63 missed isolated distal DVTs and 23 VTE during the follow-up with a safety of 2.68% (95%CI: 2.22–3.24) and an efficiency of 76.2% (95% CI 74.8–77.51%). A diagnostic algorithm based on PTP adjusted cut-off value for participants with low and moderate PTP would have avoided 2002 (51.6%) ultrasounds at a price of 17 missed proximal missed DVTs, 57 missed isolated distal DVTs and 23 VTE during the follow-up with a safety of 2.50% (95%CI: 2.05–3.04) and an efficiency of 76.15% (95% CI 74.78–77.46%). The safety, efficacy, **ultrasonographies** avoided, and **ultrasonographies** avoided per false negative is reported in table 2.

DISCUSSION

Our management study shows that the age-adjusted and PTP-adjusted D-dimer diagnostic strategies reduce the proportion of patients who require ultrasonography in comparison with the standard D-dimer cut-off threshold at the cost of a slight increase of the failure rate. The diagnostic strategy based solely on whole-leg ultrasonography was safe being the 3-month VTE incidence < 1.2%.

Two distinct ultrasound approaches are available for lower extremity DVT diagnosis: limited compression ultrasonography (CUS), and whole-leg ultrasonography. Whole-leg ultrasonography is able to exclude thrombosis of the entire deep vein network of the leg from the common femoral vein to the distal veins of the calf, whereas limited compression ultrasonography is able to exclude only femoral and popliteal DVT. In our study, whole-leg ultrasonography was used. Several studies have already demonstrated that anticoagulant therapy can be safely withheld after negative complete compression ultrasound without further testing in outpatients [Stevens SM, Elliott CG, Chan KJ, Egger MJ, Ahmed KM (2004) Withholding anticoagulation after a negative result on duplex ultrasonography for suspected symptomatic deep venous thrombosis. *Ann Intern Med* 140:985–991, Johnson SA, Stevens SM, Woller SC, Lake E, Donadini M, Cheng J, Labarère J, Douketis JD (2010) Risk of deep vein thrombosis following a single negative whole-leg compression ultrasound: a systematic review and meta-analysis. *JAMA* 303:438–445] and in inpatients [Sevestre MA, Labarère J, Casez P, Bressollette L, Haddouche M, Pernod G, Quéré I, Bosson JL (2010) Outcomes for inpatients with normal findings on whole-leg ultrasonography: a prospective study. *Am J Med* 123:158–165]. Two randomized studies that compared a diagnostic strategy based on PTP, D-dimer and repeated CUS and a strategy based only on whole-leg ultrasonography in symptomatic outpatients with suspected DVT showed that there were no significant differences between the serial CUS strategy and a single whole-leg ultrasonography

[Gibson NS, Schellong SM, Kheir DY, Beyer-Westendorf J, Gallus AS, McRae S, Schutgens RE, Piovella F, Gerdes VE, Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. *J Thromb Haemost.* 2009 Dec;7(12):2035-41; Bernardi E, Camporese G, Büller HR, Siragusa S, Imberti D, Berchio A, Ghirarduzzi A, Verlato F, Anastasio R, Prati C, Piccioli A, Pesavento R, Bova C, Maltempi P, Zanatta N, Cogo A, Cappelli R, Bucherini E, Cuppini S, Noventa F, Prandoni P; 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 Oct 8;300(14):1653-9.]. However, whole-leg ultrasonography is not widely available and it is more time and cost consuming in comparison with CUS. Thus, many diagnostic strategies incorporated the D-dimer assay to reduce the number of patients requiring ultrasonography. Current guidelines recommend to conduct either CUS or whole-leg ultrasonography only in patients with a high PTP of DVT, whereas in patients with low PTP, DVT can be ruled out on the basis of normal D-dimer without imaging scan [Blood Advance].

The role of D-dimer assays in the diagnosis of patients with suspected DVT has been extensively studied [1]: it has proven to be a highly sensitive but non-specific test for the presence of venous thromboembolism [2] and the negative predictive value for proximal DVT in different patient populations is near 99% [3]. The clinical usefulness of D-dimer **is** relies on the proportion of patients in whom DVT may be ruled out by a normal result and i.e. the D-dimer specificity. However, D-dimer levels increase with age, leading a decreased specificity of the D-dimer in the elderly. Data from five large prospective cohort studies including 2818 outpatients with suspected DVT of the lower extremities have shown that adjusting D-dimer level cut-offs by age could improve the clinical utility of the test to rule out DVT in elderly patients and **than prevent unnecessary ultrasonographies** further reducing the number of patients requiring ultrasonography [Douma RA, Tan M, Schutgens RE, Bates SM, Perrier A, Legnani C, Biesma DH, Ginsberg JS, Bounameaux H, Palareti G, Carrier M, Mol GC, Le Gal G, Kamphuisen PW, Righini M. 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 Oct;97(10):1507-13]. The PALLADIO study tested a diagnostic algorithm combining D-dimer, PTP and limited or extended CUS to simplify the approach to patients with suspected DVT, thus avoiding the need for repeated serial CUS and reducing the risk of detecting isolated distal DVTs of uncertain clinical significance, but the use of age-adjusted D-dimer only slightly decreased the number of patients that required imaging tests [Riva N, Camporese G, Iotti M, Bucherini E, Righini M, Kamphuisen PW, Verhamme P, Douketis JD, Tonello C, Prandoni P, Ageno W; PALLADIO Study Investigators. Age-adjusted D-dimer to rule out deep vein thrombosis: findings from the PALLADIO algorithm. *J Thromb Haemost*. 2018 Feb;16(2):271-278. doi: 10.1111/jth.13905. Epub 2017 Dec 8. PMID: 29125695.]. Jaconelli et al. evaluated 1649 patients admitted to the emergency department with a suspected DVT or PE, and who had D-dimer testing: the proportion of patients in whom VTE could be excluded without imaging increased from 38% to 64% in patients of 75 years or older, when the age-adjusted cut-off was used and such increase occurred without any additional false-negative findings. However, there were only 384 patients investigated for DVT and the study was retrospective [Can an age-adjusted D-dimer level be adopted in managing venous thromboembolism in the emergency department? A retrospective cohort study]. In 688 patients from China, Innovance D-Dimer with age-adjusted cutoff value and Wells PTP score has a specificity of 67% and NPV of 99% []. Recently De Pooter et al. confirmed that the diagnostic strategy of VTE based on the age-adjusted cut-off level for D-dimer in patients over 50 years was found to be safe, with NPV above 99%, and cost-effective [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], but, again, that there were only 173 patients with suspected DVT. Till now, studies on age-adjusted cut-off level for D-dimer enrolled only few patients with suspected DVT. Our series included 3883 participants and to our knowledge is the largest study on age-adjusted for D-dimer in patients with

suspected DVT. We clearly show that the age-adjusted cut-off level for D-dimer increases the specificity from 47% to 61% without affecting the NPV.

Another D-dimer cut-off value strategy has been proposed on the basis of the SELECT study. In this study, D-dimer <1000 ng/mL in patients with low PTP and <500 ng/mL in those with moderate PTP still had a negative predictive values of 100% and 99.6%, respectively [Linkins LA, Bates SM, Lang E, et al. Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. *Ann Intern Med* 2013;158:93-100.]. Thus the clinical pre-test probability based D-dimer thresholds has been proposed. Recently Kearon et al. demonstrated in a prospective management study that using such threshold to exclude DVT was safe and decreased the number of ultrasonography. However, only proximal CUS ultrasonography was assessed and the examination of the calf veins distal to the calf vein trifurcation was actively discouraged [Kearon BMJ]. Our findings are in line with those of Kearon et al.: the age-PTP adjusted D-dimer increased the specificity from 47% to 67% without affecting the NPV.

It is not clear what is the best strategy for suspected DVT: the advice of recent guideline is **are** mostly based on indirect comparisons between the various strategies. In fact, intra-individual comparisons and randomized trials in this particular field are scarce. An individual patient data meta-analysis compared the sensitivity, specificity, negative predictive value, and utility (the proportion of all patients who have a negative D-dimer test) of the age-adjusted and the PTP-adjusted D-dimer [Parpia JTH]. Such meta-analysis included 2544 patients included and showed that both PTP-adjusted and age-adjusted strategy had higher specificity compared with the standard strategy, but the utility of PTP-adjusted and age-adjusted strategy were similar [Parpia JTH]. Design of our study is an intra-individual comparison showing that PTP-adjusted D-dimer performed slightly better than age-adjusted D-dimer: it avoided more scans and had more favourable failure rate in comparison with the age-adjusted threshold.

We have already demonstrated that the Wells score and D-dimer poorly predicts isolated distal DVT in outpatients []. Both age-adjusted and PTP-adjusted D-dimer missed several IDVT

and the failure rate was mostly due to missed IDDVT. In our study, all the IDDVT were treated with anticoagulant therapy, but the clinical relevance of IDDVT with negative D-dimer is still a matter of debate and the need of its diagnosis and treatment is unknown. It has to be noted that if only proximal DVT were considered, NPV was 99% for both the diagnostic algorithm.

Some limitations of the present study should be acknowledged. It was a single centre study performed by dedicated experienced vascular medicine physicians. No inter-observer variability was assessed for iIDDVT diagnosis and the possibility of false positive diagnosis of IDDVT cannot be ruled out. There were xx patients lost of follow-up. Moreover, 9% of participants had IDDVT and whether it is worthwhile diagnosing IDDVT in patients with negative D-dimer is not known. Since IDDVT were treated with anticoagulant therapy, we were not able to calculate the safety and efficiency of all the diagnostic strategies for only proximal DVT.

In summary, the algorithm based on PTP adjusted cut-off value avoided 52% of image technique, the algorithm based on age-adjusted cut-off value avoided 48% of image technique, whereas the fixed threshold avoided only 37% of image technique; the algorithm based on age-adjusted cut-off had a failure rate for all DVTs of 2.03% (upper CI: 2.52) that increased to 2.68% (upper CI: 3.24%) for the age-adjusted D-Dimer, and to 2.5% (upper CI: 3.04) for the PTP-adjusted D-Dimer.

Addendum

M. Sartori designed the study, analysed the data and wrote the paper; B. Cosmi analysed the data and revised the paper; M. Sartori, E. Lasala and E. Favaretto were involved in the patient management and collected the data; L. Borgese collected the data. All the authors revised the manuscript and gave final approval of the version to be submitted.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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Figure legend

Figure 1

Receiver Operating Characteristic (ROC) curve analysis of accuracies of D-dimer test for the presence of lower leg deep venous thrombosis (panel a) and for the presence of lower leg proximal deep venous thrombosis. * Indicates cut-off value of 500 ng/mL