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Comparison of five D-dimer reagents and application of an age-adjusted cut-off for the diagnosis of venous thromboembolism in emergency department

François Mullier^{a,b,c}, Dominique Vanpee^d, Jacques Jamart^e, Eric Dubuc^a, Nicolas Bailly^a, Jonathan Douxfils^b, Christian Chatelain^{c,f}, Jean-Michel Dogné^{b,c} and Bernard Chatelain^{a,c}

There is still a considerable uncertainty concerning D-dimer cut-off values used in exclusion of venous thromboembolic (venous thromboembolism, VTE) disease, especially among the elderly patients. The objectives were to compare five different D-dimer reagents in the daily practice of an emergency department and to test retrospectively the performances of an age-adjusted cut-off. A total of 473 consecutive ambulatory outpatients suspected of VTE (confirmed VTE = 21) were included in this study. Five commercially available tests were assessed: STA-Liatest D-Di (LI), AxSYM D-Dimer (AX), VIDAS D-Dimer (VI), INNOVANCE D-Dimer (IN), and HemosIL D-Dimer HS (HS). When using a cut-off value of 500 ng/ml fibrinogen equivalent units (FEUs), D-dimer reagents differ in their abilities to avoid further testing. Indeed, LI allowed exclusion of VTE diagnosis in statistically more patients than VI, AX, and IN but not HS. The use of an age-adjusted cut-off is cost-effective without increasing significantly the number of false negative results. The interest of such strategy is more or less pronounced, depending on the type of D-dimer reagent. The application of

an age-adjusted cut-off may be useful to reduce differences among D-dimer reagents to lower costly imaging studies. Prospective validation studies on large cohorts of patients are required to determine the safety of such strategy. *Blood Coagul Fibrinolysis* 24:000–000 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Clinical prediction models such as Wells pretest probability (PTP) have improved diagnostic accuracy of venous thromboembolism (VTE) [1]. The combination of a low PTP and a negative D-dimer has an extremely high negative predictive value (NPV) for VTE [1]. However, the knowledge of an abnormal D-dimer test before clinical examination leads to a higher clinical decision rule score [2]. This demonstrates that decision rules remain very subjective in spite of all efforts to improve clinical objectivity, and that they need to be complemented by the use of objective measures like D-dimer performed after clinical scoring. The high prevalence of VTE makes D-dimer assay an important diagnostic tool in daily clinical practice. Nevertheless, D-dimer standardization is still difficult as it concerns the detection in a complex mixture of fibrin degradation products of different sizes [1,3,4]. In addition, differences in D-dimer assays exist, which may complicate the interpretation of the results. Indeed, antibodies used in D-dimer assays react with cross-linked fibrin in general, including fibrin oligomers of variable size without prior proteolysis by plasmin [1,5]. Consequently, despite proposed models for the harmonization of test results

and improvement of between-center variation, there is still a lack of agreement of cut-off values between different assays [1,6–8]. The age of the patient is one of the main factors leading to this uncertainty. The clinical strategy for ruling out VTE is unclear in elderly patients as both D-dimer concentration and VTE prevalence increase with age [1,9]. Douma *et al.* [9] proposed cut-off values adjusted to age combined with clinical probability to improve the utility of the D-dimer test for the exclusion of VTE among older patients without reducing the safety.

These variations between D-dimer assays and the importance of age in cut-off uncertainty led us to conduct a comparison study of classical D-dimer reagents in the daily practice of an emergency department and to assess the age-adjusted cut-off point proposed by Douma *et al.* [9] on a large panel of reagents.

Materials and methods

Study design

Study population

This study initially included 473 consecutive unselected ambulatory outpatients with clinically suspected deep

vein thrombosis (DVT) or pulmonary embolism. In order to be in conformity with the daily practice of an emergency department, patients and emergency physicians were blinded to the ongoing study and to D-dimer results except for the VIDAS D-dimer result (BioMérieux, Craponne, France), which is the reagent currently used in routine in our laboratory.

The study was divided in two parts. The first part consisted of a prospective assessment of the strategy using standard cut-off of 500 ng/ml for five D-dimer reagents, whereas the second part aimed at retrospectively evaluating the incremental benefit of using an age-adjusted cut-off.

Patients were eligible if they had one or more of the following symptoms: swelling, redness, tenderness, pain of the lower extremity, edema, labored breathing, coughing, lung-related chest pain, and dyspnea. Patients were excluded if they were younger than 18 years, pregnant women, or had received low molecular-weight heparin (LMWH) or vitamin K antagonists (VKAs) [1].

Data collection

Patients were enrolled 24 h/day, 7 days/week. The assessment of clinical probability of pulmonary embolism or DVT was performed by one emergency physician and was based on the Wells scores [10,11]. In case of low or medium PTP, D-dimer was performed following international recommendations [1]. In case of positive VIDAS D-dimer, complete compression ultrasonography and multidetector spiral computed tomography were performed for suspected DVT and pulmonary embolism, respectively. In addition, complete compression ultrasonography and ventilation perfusion scintigraphy were performed for suspected subsegmental pulmonary embolism based on multidetector spiral computed tomography.

During 90 days of follow-up, venous thromboembolic complications and death caused by a possible thromboembolic event were recorded for all patients during a consultation or by a phone questionnaire (criteria: presence/absence of VTE, LMWH, or VKA during the

past 3 months). All clinical data were revised independently by two emergency physicians. The study was approved by the local ethical committee on human research.

Samples

The D-dimer analysis was performed on platelet-poor plasma (PPP). PPP was obtained after centrifugation during 15 min at 2080g at room temperature on a 109 mmol/l citrate Venosafe (Terumo Europe, Leuven, Belgium) whole blood sample.

Five different commercially available tests were assessed on the same PPP. STA-Liatest DDi (LI) (Diagnostica Stago, Asnières sur Seine, France), AxSYM D-Dimer (AX) (Abbott, Wiesbaden, Germany), and the VIDAS D-Dimer (VI) (BioMérieux) were performed on fresh samples within 3 h after sampling. STA-R Evolution, Abbott AxSYM, and BioMérieux mini VIDAS were used as instruments, respectively. INNOVANCE D-Dimer (IN) (Siemens, Marburg, Germany) and HemosIL D-Dimer HS (HS) (Instrumentation Laboratory, Bedford, Massachusetts, USA) were performed after freezing at -80°C and thawing during 5 min at 37°C . BCS coagulation analyzer and ACL-TOP were used as instruments, respectively. D-dimer was previously shown stable after freezing for 36 months at -60°C [12]. The results of LI, AX, VI, and IN are expressed in ng/ml of fibrinogen equivalent units (FEUs), as these assays use crude plasmin digested lysates of cross-linked fibrin clots as calibrators. The calibrator used in the HS consists of purified D-dimer fragments obtained from a plasmin-digested clot. The results of this assay are, therefore, expressed in ng/ml of D-dimer units. Results of HS were mathematically transformed by the ACL-TOP software (Instrumentation Laboratory) in ng/ml of FEU. The standard cut-off was, therefore, 500 ng/ml of FEU for all the D-dimer assays.

Data analysis

Patients were classified according to the Wells score in low, medium, or high PTP (Table 1). The correlation between VI and the four other D-dimer tests was assessed

Table 1 Baseline characteristics of patients with clinically suspected venous thromboembolism

Characteristics	Patients (N = 430)	Low PTP (N = 341, 79.3%)	Medium PTP (N = 59, 13.7%)	High PTP (N = 3, 0.7%)	Not determined PTP (N = 27, 6.3%)
Age (years): mean \pm SD	61+/-18	60+/-18	66+/-16	49+/-11	61+/-14
Female (%)	212 (49.3)	164 (48.2)	30 (50.8)	2 (66.7)	15 (55.6)
Venous thrombosis (% of suspected VTE, % of suspected DVT)	5 (1.2, 3.9)	1 (0.3, 1.1)	2 (3.4, 14.3)	0 (0, 0)	2 (7.4, 8.0)
Pulmonary embolism (% of suspected VTE, % of suspected PE)	13 (3.0, 4.3)	5 (1.5, 2.0)	7 (11.9, 15.6)	1 (33.3, 100)	0 (0, 0)
Venous thrombosis and pulmonary embolism (% of suspected VTE)	3 (0.7)	0 (0)	1 (1.7)	1 (33.3)	1 (3.7)
Lost to follow-up (% of suspected VTE)	10 (2.3)	7 (2.1)	1 (1.7)	0 (0)	2 (7.4)

Values are numbers (percentages) of patients unless specified otherwise. Data are presented for all patients and after subdivision in low, medium, or high pretest probability (PTP). DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

by Pearson coefficient. Paired *t*-test and Bland–Altman test were performed to compare mean D-dimer values for VI and LI above their quantification limit (45 and 220 ng/ml, respectively). Comparison of the five D-dimer tests was then performed for patients with low or medium clinical probability of VTE ($n=400$ for VI, LI, and AX, but only 382 for IN and 385 for HS due to insufficient sample).

Results of each test were dichotomized with either 500 ng/ml or an age-adjusted cut-off calculated as follows: [(age \times 10) (ng/ml) (if age is higher than 50 years)], as cut-off for all D-dimer reagents [9].

The sensitivity, specificity, NPV, and the number needed to test (NNT) [1] by D-dimer to rule out one VTE were then calculated with their exact 95% confidence intervals (CIs) based on F distribution. The NNT was defined as the number of patients in whom D-dimer must be measured to rule out one DVT or one pulmonary embolism. Binomial and χ^2 tests were used to compare proportions. Lost to follow-up was considered negative or excluded for the statistical

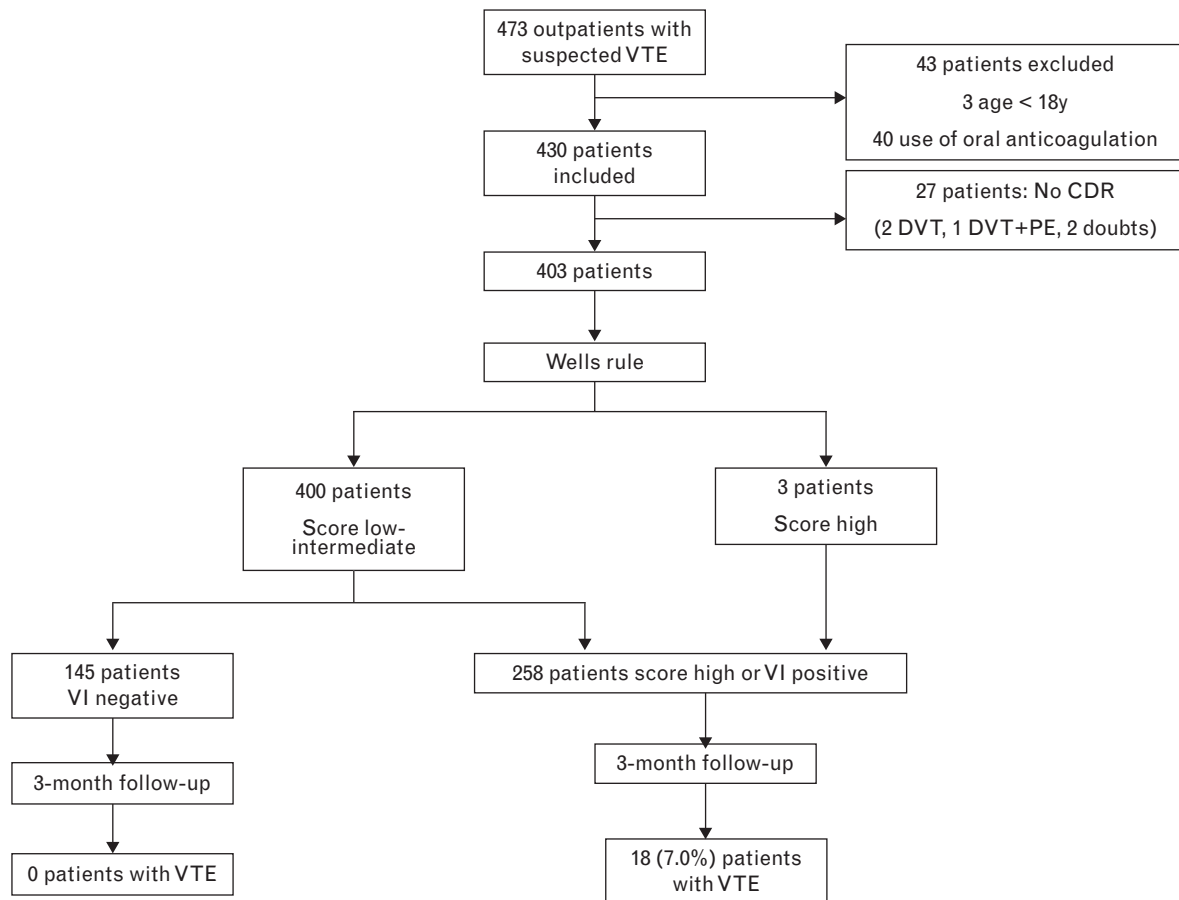
analysis. The analysis with lost to follow-up considered as positive was not shown as the 3-month thromboembolic risk in patients left untreated after normal proximal compression ultrasonography was 0.6% (95% CI: 0.4–0.9%), as reported in a review by Righini *et al.* [13]. Statistical analysis was performed by SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA), SC (Lambda-Plus, Gembloux, Belgium), and Medcalc (version 10.4.8; Gent, Belgium) statistical softwares.

Results

Patient characteristics

Of the 473 patients, three were less than 18 years and 40 received acenocoumarol at the time of inclusion. The data from the remaining 430 patients (91%) were used for our analysis (Fig. 1). Baseline characteristics of these patients are described in Table 1. Ten patients (2.3%) had negative imaging studies at the initial visit, but the follow-up at 3 months was not possible. Such patients were considered negative or excluded for the statistical analysis.

Fig. 1



Study flow chart. CDR, clinical decision rule; DVT, deep vein thrombosis; PE, pulmonary embolism; VI, VIDAS D-dimer; VTE, venous thromboembolism; y, years.

A total of 218 men and 212 women aged from 18 to 97 years (mean: 61 years, median: 63 years) were included in this study. The number of patients suspected of pulmonary embolism and DVT were 302 and 128, respectively. Three hundred thirteen patients (72.8%) were aged 50 years and older [165 men (52.7%), 148 women (47.3%)].

As shown in Table 1, 21 out of the 430 patients (4.9%) included in the study had DVT and/or pulmonary embolism. All DVT ($n = 8$) were proximal [14]. All pulmonary embolisms were nonsegmental. The patients were classified as having low ($N = 341/79.3\%$), medium ($N = 59/13.7\%$), and high PTP for VTE ($N = 3/0.7\%$). The PTP was not determined for 27 patients (6.3%).

Correlation between D-dimer assays

In comparison with the currently used D-dimer in the daily practice (VI), Pearson correlation coefficients for LI, AX, IN, and HS were 0.938, 0.965, 0.894, and 0.907, respectively ($P < 0.001$).

Comparison with clinical data

Lost to follow-up considered negative

With the cut-off value of 500 ng/ml, the VI was normal in 145 of 400 patients with a low or medium probability of VTE (36.2%), and no patient developed VTE during the initial investigation or the 3-month follow-up (0%, 95% CI: 0 to 2.5%; Tables 2 and 3). The sensitivity, specificity, and NPV were 100.0% (95% CI: 100.0–100.0%), 37.8% (95% CI: 32.9–42.8%), and 100.0% (95% CI: 100.0–100.0%), respectively. The NNT to rule out one VTE was 2.8.

Using the age-adjusted cut-off value, D-dimer test results were negative in 50% of the patients (200/400, NNT = 2.0) (Tables 2 and 3). This resulted in 13.8%

absolute increase in the number of patients in whom D-dimer levels were considered normal. The sensitivity, specificity, and NPV were 93.8% (95% CI: 69.7–99.0), 51.8% (95% CI: 46.7–56.9%), and 99.5% (95% CI: 97.2–100.0), respectively. Of these 200 patients, one developed pulmonary embolism during investigation (0.5%, 95% CI: 0–2.8%). VI, LI, AX, IN, and HS for this 86-year-old patient with a medium PTP were 659, 590, 789, 1170, and 719 ng/ml, respectively.

Using either 500 ng/ml or the age-adjusted cut-off as the cut-off value, the NPV and sensitivity (Table 3) were not statistically significant between the five D-dimer tests. However, the number of patients with results below the cut-off and specificity were statistically different. Indeed, with the standard cut-off of 500 ng/ml, the proportion of positive results was significantly lower for LI, AX, and HS than for VI ($P < 0.001$, $P = 0.016$, and $P < 0.001$, respectively). The proportion did not differ significantly between IN and VI ($P = 0.184$). The number of patients with results below the cut-off for VI, LI, AX, IN, and HS were 145 (36.2%, 95% CI: 31.5–41.2%), 204 (51.0%, 95% CI: 46.0–56.0%), 152 (38.0%, 95% CI: 33.2–43.0%), 147 (38.5%, 95% CI: 33.6–43.6%), and 174 (45.2%, 95% CI: 40.1–50.3%), respectively.

Thus, LI allowed exclusion of VTE diagnosis in statistically more patients than VI, AX, and IN ($\chi^2 P: < 0.0005$, $P < 0.0005$ and $P = 0.0006$, respectively).

Below 1000 ng/ml for VI ($n = 185$), mean LI is significantly lower than mean VI (paired Student's t -test $P: 0.0074$) with a mean difference [(LI–VI)/(LI/2 + VI/2)] $\times 100$ of 18.5% (Bland–Altman plot) (Fig. 2).

With the age-adjusted cut-off value, the differences are less pronounced between the D-dimer reagents. Indeed, only the proportion of positive results for LI and HS

Table 2 Comparison of VIDAS D-dimer with clinical outcome (presence or absence of venous thromboembolism) for patients with a nonhigh clinical probability (based on Wells clinical decision rule)

(A)		Cut-off: 500 ng/ml		Clinical outcome		Total
				VTE	No VTE	
VI	Above		16	239	255	
	Below		0	145	145	
Total			16	384	400	
(B)		Age-adjusted cut-off		Clinical outcome		Total
				VTE	No VTE	
VI	Above		15	185	200	
	Below		1	199	200	
Total			16	384	400	

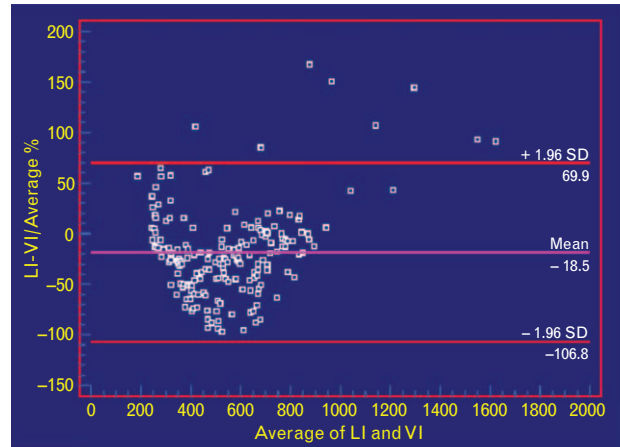
True positive, false positive, true negative, and false negative were shown according to a cut-off value of 500 ng/ml (A) or an age-adjusted cut-off value (B). Lost to follow-up was considered negative for the statistical analysis. $N = 400$ [All patients ($n = 430$) minus patients with a high clinical probability ($n = 3$) minus patients with no pretest probability ($n = 27$)]. VI, VIDAS D-dimer; VTE, venous thromboembolism.

Table 3 Comparison of the five D-dimer tests for patients with a nonhigh clinical probability (based on Wells clinical decision rule)

	VI (N = 400)	LI (N = 400)	AX (N = 400)	IN (N = 382)	HS (N = 385)
Cut-off value for D-dimer test = 500 ng/ml	145 (36.2/31.5–41.2)	204 (51.0/46.0–56.0)	152 (38.0/33.2–43.0)	147 (38.5/33.6–43.6)	174 (45.2/40.1–50.3)
No. (%/ 95% CI) of patients below cut-off value					
Number needed to test	2.8	2.0	2.6	2.6	2.2
Negative predictive value (95% CI)	100 (97.5–100)	100 (98.2–100)	100 (97.6–100)	100 (97.5–100)	100 (97.9–100)
Sensitivity (95% CI)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)
Specificity (95% CI)	37.8 (32.9–42.8)	53.1 (48.0–58.2)	39.6 (34.7–44.7)	40.1 (35.0–45.3)	47.0 (41.8–52.3)
Age-adjusted cut-off value for D-dimer test	200 (50.0/45.0–55.0)	235 (58.8/53.8–63.6)	205 (51.2/46.2–56.3)	184 (48.2/43.1–53.3)	213 (55.3/50.2–60.4)
No. (%/ 95% CI) of patients below cut-off value					
Number needed to test	2.0	1.7	2.0	2.1	1.8
Negative predictive value (95% CI)	99.5 (97.2–100)	99.1 (97.0–100)	99.5 (97.3–100)	100 (98.0–100)	99.5 (97.4–100)
Sensitivity (95% CI)	93.8 (89.7–99.0)	87.5 (81.6–98.1)	93.8 (89.7–99.0)	100.0 (100.0–100.0)	93.3 (88.0–98.9)
Specificity (95% CI)	51.8 (46.7–56.9)	60.7 (55.6–65.6)	53.1 (48.0–58.2)	50.1 (44.9–55.4)	57.3 (52.1–62.4)
Absolute increase in percentage of patients below cut-off value	13.8	7.8	13.2	9.7	10.1

The age-adjusted cut-off was age × 10 (ng/ml) (if age > 50). Number of patients below cut-off value, number needed to test, sensitivity, and specificity were determined with a cut-off value of 500 ng/ml or an age-adjusted cut-off value. Lost to follow-up was considered negative for the statistical analysis. AX, AxSYM D-dimer; CI, confidence interval; HS, HemosIL DDi HS; IN, Innovance DDi HS; LI, STA Liatest Ddi; NNT, number needed to test to find one normal D-dimer test result; NPV, negative predictive value; VI, VIDAS D-dimer.

Fig. 2



Bland-Altman plot showing D-dimer results below 1000 ng/ml for VIDAS D-dimer (VI; n = 185) and above the quantification limit [VI: 45 ng/ml, STA-Liatest DDi (LI): 220 ng/ml]. Mean LI is significantly lower than mean VI (paired Student's test *P*: 0.0074) with a mean difference [(LI–VI)/ (LI/2 + VI/2)] × 100 of 18.5%.

remains lower than for VI (*P* < 0.001 and *P* = 0.001, respectively).

Finally, as shown in Table 3, for VI, LI, AX, IN, and HS, there was a 13.8, 7.8, 13.2, 9.7, and 10.1% absolute increase in the number of patients with a nonhigh probability of VTE and with a negative D-dimer test result when the age-adjusted cut-off value was used, respectively.

Lost to follow-up excluded

The results were similar without any modification to the conclusions (data not shown).

Discussion

The high prevalence of VTE makes D-dimer assay a very important diagnostic tool in daily clinical practice. However, 20 years after its first use in the diagnostic workup of suspected VTE, there is still a lack of standardization of D-dimer assay values between different assays due to the complexity of the D-dimer entity [1]. Differences between D-dimer assays may be caused by the following parameters: antibody specificity, time dependence of neo-epitope expression in the course of fibrin formation and dissolution, assay format, purity or heterogeneity of the calibrator, possible matrix effects of plasma on epitope presentation, and interference by irrelevant (noncross-linked) analytes [5]. These discrepancies between different D-dimer assays as well as the two different reporting units in use and the influences of other variables such as age of the patient have led to a considerable uncertainty concerning the cut-off values used in exclusion of VTE [1,15–20].

In the present study, we demonstrate that while the five D-dimer reagents are highly correlated, their abilities to avoid further testing for diagnosing VTE are statistically significant. This is due to differences in mean D-dimer values in the low D-dimer range (<1000 ng/ml). Although all D-dimer tests studied in the present work use a cut-off value of 500 ng/ml (or 500 ng/ml FEU), this apparent agreement at 500 ng/ml represents harmonization of values at a single point and it cannot be assumed that the different assays are in agreement across a wider range as illustrated in Fig. 2. Furthermore, the use of an age-adjusted cut-off as suggested by Douma *et al.* [9] in a retrospective multicenter study is cost-effective without increasing significantly the number of false negative, whatever the D-dimer reagent. Indeed, in our institution, D-dimer, complete compression ultrasonography, multi-detector spiral computed tomography, or ventilation perfusion scintigraphy costs 3.37 €, 39.95 €, 127.77 €, and 259.76 € during the day, respectively. During the nights and the week-ends, the cost of a complete compression ultrasonography reaches 104.56 €. Using the cut-off of 500 ng/ml, the proportion of positive results and the specificity were statistically higher for LI, AX, and HS than for VI. However, the NPV and sensitivity were not statistically different between assays. LI allowed exclusion of VTE diagnosis in statistically more patients than VI, AX, and IN, but not HS. The use of the age-adjusted cut-off allowed lowering the differences between the reagents as only the proportion of positive results for LI and HS remains lower than for VI. This confirms that discordant D-dimer results of different quantitative assays are often related to age [15–17]. Our results are in agreement with previously published studies. The PROLONG study showed the interest of using different cut-off levels according to age to evaluate the individual risk of recurrent VTE after cessation of vitamin K antagonism [21]. Moreover, Haas *et al.* [16] previously showed that a cut-off level of 750 ng/ml for patients at least 60 years improves the clinical performance of STA-Liatest, Tina-quant (Roche, Mannheim, Germany), and INNOVANCE in combination with the PTP score without the loss of NPV. A recent large retrospective study using HemosIL DDi HS has shown that in older patients, elevated values (>1000 ng/ml) are more frequently associated with VTE, so the authors have also suggested the use of age-adjusted cut-offs [20]. The strengths of our study are the use of five different D-dimer assays on the same samples and the study design mimicking the real life of an emergency department.

Limitations

The limitations of our study are the limited sample size; the low prevalence of VTE in our study (21 cases, 4.9%) compared with other data reported in the literature [1]; the very low number of high PTP; and the retrospective application of the age-adjusted formula. The low number of high PTP may be explained by the quality of screening

of suspected VTE in this population. However, such low prevalence has already been reported by others [22] in the daily practice of an emergency department and is more representative of the real life than the current literature.

The limited sample size prevents drawing firm conclusions from these results as variation of false negative rate of one or two patients could strongly modify the results. However, our results have been supported by recent retrospective studies confirming that the age-adjusted cut-off increased the clinical usefulness of D-dimer to exclude VTE in older patients [23–25]. A large prospective study is still needed to assess the safety and usefulness of the age-adjusted cut-off before implementation in daily emergency practice.

Conclusion

When using a cut-off value of 500 ng/ml, D-dimer reagents differ in their abilities to avoid further testing to exclude VTE. The application of an age-adjusted cut-off may be useful to reduce differences among D-dimer reagents and to lower costly imaging studies. Interestingly, the information of age-adjusted cut-offs may be automatically included in the laboratory reports, as enabled by the modern laboratory information systems.

Prospective validation multicenter studies using reagent-specific values, are now required to determine the safety of such strategy and to confirm that clinicians can appropriately apply this formula in the chaotic emergency department setting.

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Conflicts of interest

The authors declare no competing financial interests.

The authors have no conflicts of interest to report.

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