Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded

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ABSTRACT

Background
D-dimer testing to rule out deep vein thrombosis is less useful in older patients because of a lower specificity. An age-adjusted D-dimer cut-off value increased the proportion of older patients (>50 years) in whom pulmonary embolism could be excluded. We retrospectively validated the efficacy of this cut-off combined with clinical probability for the exclusion of deep vein thrombosis.

Design and Methods
Five management study cohorts of 2818 consecutive outpatients with suspected deep vein thrombosis were used. Patients with non-high or unlikely probability of deep vein thrombosis were included in the analysis; four different D-dimer tests were used. The proportion of patients with a normal D-dimer test and the failure rates were calculated using the conventional (500 μg/L) and the age-adjusted D-dimer cut-off (patient's age x 10 μg/L in patients >50 years).

Results
In 1672 patients with non-high probability, deep vein thrombosis could be excluded in 850 (51%) patients with the age-adjusted cut-off value *versus* 707 (42%) patients with the conventional cut-off value. The failure rates were 7 (0.8; 95% confidence interval 0.3-1.7%) for the age-adjusted cut-off value and 5 (0.7%, 0.2-1.6%) for the conventional cut-off value. The absolute increase in patients in whom deep vein thrombosis could be ruled out using the age-adjusted cut-off value was largest in patients >70 years: 19% among patients with non-high probability.

Conclusions
The age-adjusted cut-off of the D-dimer combined with clinical probability greatly increases the proportion of older patients in whom deep vein thrombosis can be safely excluded.

Key words: deep vein thrombosis, D-dimer, diagnosis, hemostasis, pulmonary embolism, venous thromboembolism.

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Introduction

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal disorder.[1] The diagnostic management of DVT based on signs and symptoms is non-specific and diagnostic testing based on a sequential strategy including clinical risk estimation, D-dimer testing and compression ultrasonography (CUS) is, therefore, mandatory. The diagnosis of DVT can be safely excluded based on the combination of a low or intermediate clinical probability combined with a negative D-dimer blood test, in which case imaging studies can be avoided.[2-5] With increasing age, however, the specificity of the D-dimer test decreases, resulting in more false positive test results in older patients than in younger ones.[6,7] In clinical practice, this means that VTE can less often be excluded based on the clinical probability/D-dimer combination in older patients than in younger patients, hence older patients more often need additional testing (i.e. computed tomography in the case of suspected PE or CUS of the leg in the case of suspected DVT). It has been stated that D-dimer testing has little clinical value and is not cost-effective in patients over 80 years, since less than 5% of these patients have a negative D-dimer result.[6,8]

Recently, a new age-adjusted D-dimer cut-off value was derived and retrospectively validated in patients with suspected PE older than 50 year of age.[9] It was shown to increase the proportion of older patients in whom the diagnosis could be excluded, without compromising safety.[9] The new age-adjusted D-dimer cut-off value is calculated by multiplying the patient's age by 10 in patients older than 50 years. For example, the D-dimer cut-off value of a patient 65 years of age will be 650 μg/L fibrinogen equivalent units (FEU) instead of the conventional 500 μg/L FEU cut-off.

The goal of the current study was to retrospectively analyze the safety and usefulness of this age-adjusted D-dimer cut-off value combined with clinical probability for the exclusion of DVT.

Design and Methods

We analyzed data from five large prospective cohort studies, totaling 2818 outpatients with suspected DVT of the lower extremities. The outcome studies were designed to evaluate diagnostic strategies for DVT, combining clinical probability assessment, D-dimer testing and lower limb venous CUS, impedance plethysmography and venography (Table 1). All studies were approved by the institutional review boards of the participating institutes and written informed consent was obtained from all patients. In all studies, the outcome of interest was the development of VTE (DVT or PE) during 3 months of follow-up in patients in whom DVT was considered excluded after initial diagnostic investigation and who did not receive anticoagulants during follow-up. Patients were followed up by a clinic visit or telephone contact at the end of 3 months and were instructed to contact their physician if their leg symptoms worsened or if they developed symptoms suggestive of PE. In cases of suspected VTE during follow-up, the usual criteria were used to confirm the event.[3]

Cohort 1

The first study was conducted in four hospitals in the Netherlands and comprised 812 patients.[3] The inclusion and exclusion criteria and the results of the study have been published previously.[3] All patients underwent a sequential diagnostic evaluation, including pre-test probability testing using the Wells rule[10] and a highly sensitive plasma D-dimer test (Tinaquant, Roche, Germany). DVT was ruled out based on: (i) a non-high clinical probability score in combination with a normal D-dimer test (D-dimer value <500 FEU μg/L), (ii) negative results from (first) lower limb venous CUS in combination with a normal D-dimer test, (iii) normal results from a first and repeated CUS (after 1 week) in the case of an abnormal D-dimer test. DVT was established by a positive result from CUS. DVT was established in the case of lack of compressibility of the common femoral vein at the inguinal ligament or the popliteal vein at the knee-joint line traced down to the point of the trifurcation of the calf veins.

Cohort 2

In the second cohort, 1012 patients were studied presenting with clinically suspected DVT or PE at the University Hospital of Geneva, Geneva, Switzerland, and the Hôpital Saint-Luc, Montreal, Canada, between November 1996 and October 1997.[2] In the current analysis, only patients with suspected DVT were included, 474 patients in total. The results and the inclusion and exclusion criteria were published previously.[2] All patients underwent a sequential diagnostic investigation, starting with clinical probability assessment on the basis of risk factors for VTE, symptoms and signs commonly encountered in PE or DVT and the likelihood of an alternative diagnosis. Clinical probability was rated as low (0-20%), intermediate (21-79%), or high (80-100%). All patients then underwent D-dimer testing (rapid ELISA, Vidas DD, bioMérieux, France). DVT was ruled out based on: (i) a normal D-dimer test (<500 μg/L FEU), (ii) a normal CUS in combination with a non-high clinical probability, or (iii) a normal phlebography in the case of a normal CUS and a high clinical probability. DVT was established based on non-compressibility of the common femoral or popliteal vein with CUS. Ascending phlebography was done according to a technique described previously.[2,11]

Cohort 3

The third study cohort comprised consecutive patients with suspected DVT or PE who were included in a study evaluating a new latex D-dimer test (HemosIL-D-dimer HS 500, Instrumentation Laboratory).[12] In the original study, management

Table 1. Specifications of diagnostic tests and cut-off values used in the five study cohorts.

Study cohort	N.	Clinical probability assessment	Type of D-dimer	Imaging technique to confirm DVT
1. Schutgens *et al.* 2003[3]	812	Non-high: Wells score ≤2	Tinaquant	(repeat) CUS
2. Perrier *et al.* 1999[2]	474	Non-high: clinical score (< 80%)	VIDAS	CUS, phlebography
3. Legnani *et al.* 2010 [13]	401	Non-high: Wells score ≤2	STA LIA	CUS, impedance plethysmography
4. Bates *et al.* 2003[4]	556	Non-high: Wells score ≤2	MDA	(repeat) CUS, venography
5. Tan *et al.* (submitted)	617	Unlikely: Wells score <2	STA LIA / Tinaquant	(repeat) CUS

CUS: compression ultrasonography; DVT: deep vein thrombosis.

was based on the STA-Lia D-dimer test, and the results of the new D-dimer test were compared with this reference test. In the current analysis, the 401 patients with suspected DVT were included, using the results obtained with the STA-Lia test. The study was performed at four hospitals in Bologna (Italy), Ottawa (Canada), Nice (France) and Durham (South Africa) between January 2006 and January 2008. The inclusion and exclusion criteria were published previously.[12] In all patients clinical probability was assessed using the Wells score.[13] DVT was ruled out based on: (i) a low clinical probability in combination with a normal D-dimer STA-Liatest (cut-off <500 μg/L FEU), (ii) a normal result on CUS or impedance plethysmography in patients with an abnormal D-dimer test and/or a high clinical probability of DVT. Patients with an intermediate clinical probability of DVT and a normal D-dimer test underwent imaging studies at the treating physician's discretion. DVT was established by finding a proximal DVT on CUS or impedance plethysmography.

Cohort 4

The fourth study was conducted between August 1999 and November 2001 at three hospitals in Ontario, Canada, affiliated with McMaster University in Hamilton.[4] The results and inclusion and exclusion criteria have been reported previously.[4] All patients underwent a sequential diagnostic investigation, consisting of clinical probability assessment using the Wells rule[13] and a quantitative latex D-dimer test (MDA D-Dimer assay, bioMérieux, Inc.). DVT was ruled out based on: (i) a non-high clinical probability in combination with a normal D-dimer test result or (ii) a normal (repeated) CUS result in patients with a high clinical probability of DVT or an abnormal D-dimer test result – CUS was repeated in patients with normal results on CUS at presentation on days 6 to 8 and days 13-15. DVT was diagnosed in the presence of non-compressibility of the common femoral or popliteal vein (with or without involvement of adjacent segments) on CUS. Non-compressibility isolated to the superficial femoral vein or trifurcation was further evaluated with venography.

Cohort 5

The fifth study was conducted in three hospitals in the Netherlands from January 2009 until December 2010 and included 698 outpatients with suspected DVT (Tan *et al.*, submitted for publication). Patients were eligible if they were 18 years or older. Patients were excluded if they were pregnant, received more than 24 hours of anticoagulant therapy at therapeutic doses before presentation or in whom pre-test risk stratification had already been performed by the general practitioner.

During the study period ten patients were pregnant, 19 patients received more than 24 hours of therapeutic anticoagulation and 52 patients had already been stratified as 'likely' having DVT by the general practitioner and had a direct indication for CUS.

All patients underwent a sequential diagnostic evaluation, including pre-test probability testing using the Wells rule[14] and a D-dimer test (either the STA-Lia test or Tinaquant, Roche, Germany). In this study, DVT was excluded based on an 'unlikely' probability score (Wells <2) in combination with a normal D-dimer test. Otherwise, the diagnostic strategy to exclude or diagnose DVT was similar to the strategy described for cohort 1.

Data analysis

In all but the second cohort, clinical probability was assessed based on the Wells clinical prediction rule for DVT.[10,13,14] Patients were classified as having a "low/intermediate" (non-high) clinical probability for DVT in the case of a Wells score ≤2, and a "high" clinical probability in the case of a Wells score of >2. For the second cohort, the classification used in the original study was used. In the fifth cohort, patients were classified as having an 'unlikely' or 'likely' clinical probability of DVT (Wells score <2 for 'unlikely' instead of ≤2 for 'non-high').[14] Patients with a non-high (cohorts 1-4) or unlikely (cohort 5) clinical probability were included in the analysis.

In all cohorts the conventional D-dimer cut-off was set at <500 μg/L FEU, irrespectively of the patient's age. The age-adjusted D-dimer cut-off value was calculated as follows: [patient's age x 10 μg/L FEU] for patients > 50 years, and 500 μg/L FEU for patients ≤ 50 years of age.

We then calculated the proportion of patients in whom DVT could be excluded based on a non-high (cohorts 1-4) or an unlikely clinical probability (cohort 5) together with a normal D-dimer test result – first using the conventional cut-off value, and then using the age-adjusted cut-off value. Furthermore, the false negative rates, defined as the number of patients with VTE at diagnostic evaluation or during follow-up, were calculated for the conventional and the age-adjusted D-dimer cut-off values in combination with a non-high clinical probability.

All cohorts were analyzed separately. Cohorts 1 to 4, in which patients were categorized as having a non-high or high probability, were combined for a pooled analysis. Cohort 5 was analyzed separately because of a different clinical probability categorization ('unlikely' *versus* 'likely').

Exact 95% confidence intervals (CI) were calculated using CIA software version 1.0 (Gardner *et al. Confidence Interval Analysis* (*CIA*), BMJ Books 1989). All other analyses were performed with SPSS version 15.0 (SPSS, Chicago, IL, USA).

Results

The five cohorts comprised 2818 patients in total, of whom 1884 (67%) had a non-high or unlikely clinical probability of DVT. Age was not recorded in three patients with a non-high clinical probability (cohort 1); these patients were not included in the analysis. The clinical characteristics of the patients included in each of the five cohorts are depicted in Table 2. A personal history of VTE was lowest in cohort 4 (0%) and highest in cohort 5 (20%). The prevalence of DVT also differed between the cohorts, ranging from 10% in cohort 4 to 39% in cohort 1.

Cohorts 1 to 4

Among the patients with a non-high clinical probability, the proportions of patients with a normal D-dimer test result according to the conventional cut-off value were 36% (n=168), 30% (n=127), 43% (n=129) and 59% (283) for cohorts 1 to 4, respectively (Figure 1). The false negative rates among patients with a normal D-dimer test result ranged from 0.4% (95% CI 0.1%-2.0%, n=1, cohort 4) to 1.6% (95% CI 0.2%-5.6%, n=2, cohort 2), (Table 3).

Using the age-adjusted D-dimer cut-off value, the proportions of patients with a normal D-dimer test result were 41% (n=195), 39% (n=164), 53% (n=156) and 69% (n=335) for cohorts 1 to 4, respectively (Figure 1). The false negative rates using this cut-off value ranged from 0.3% (95% CI 0.1%-1.7%, n=1, cohort 4) to 1.3% (95% CI 0.2%-4.6%, n=2, cohort 3), respectively (Table 3). Figure 1 and Table 3 present the results for each cohort separately, stratified according to various age groups.

The absolute increases in the proportions of patients with a normal D-dimer using the age-adjusted D-dimer cut-off value instead of the conventional cut-off value ranged from 5.7% to 11% in the four cohorts. The

Table 2. Clinical characteristics of the patients in the five cohorts.

Characteristics	Cohort 1 (n=812)	Cohort 2 (n=474)	Cohort 3 (n=359)	Cohort 4 (n=556)	Cohort 5 (n=617)
Age in years, mean (SD)	59 (17)	61 (19)	66 (17)	65 (16)	58 (18)
Age in years, median (IQR)	60 (33-87)	62 (47-75)	70 (57-79)	65 (41-89)	59 (47-74)
Female gender, n. (%)	518 (64)	294 (62)	237 (59)	343 (62)	355 (58)
Personal history of VTE, n. (%)	93 (11)	54 (17)	52 (14)	0 (0)	126 (20)
Outpatient, n. (%)	812 (100)	474 (100)	359 (100)	556 (100)	617 (100)
Active malignancy, n. (%)	44 (5.4)	36 (11)	34 (9.5)	50 (9.0)	49 (7.9)
Clinical probability					
Non-high, n. (%)	475 (58)	419 (88)	297 (83)	484 (87)	NA
Unlikely, n. (%)	NA	NA	NA	NA	212 (34)
Incidence of DVT, n. (%)	317 (39)	111 (23)	82 (23)	56 (10)	225 (37)

SD, standard deviation; IQR, interquartile range; VTE, venous thromboembolism; DVT, deep vein thrombosis; NA, not applicable.

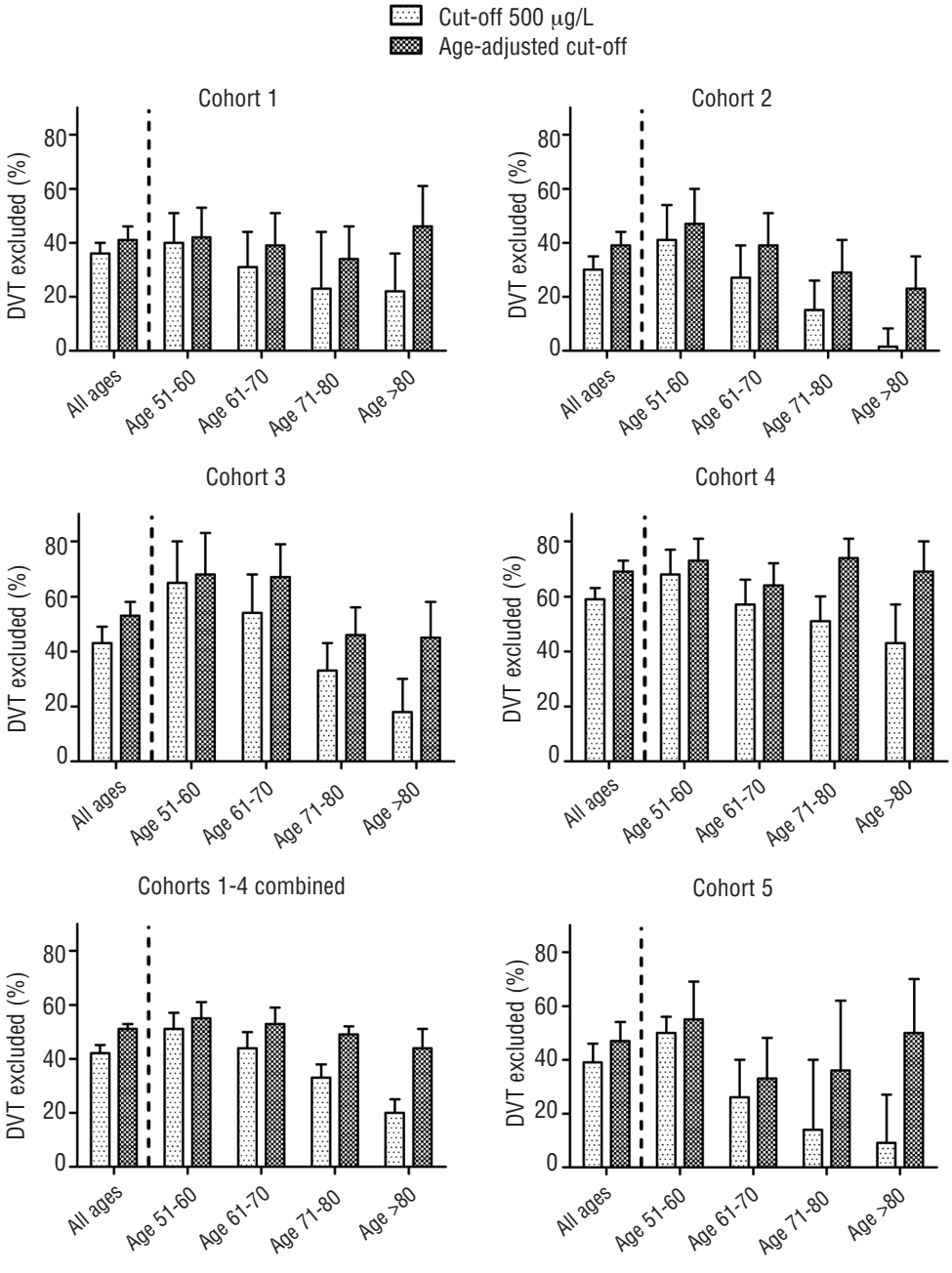

Figure 1. Proportion of patients with a normal D-dimer according to the conventional cut-off and age-adjusted cut-off. Data displayed for different age-groups among patients with a non-high clinical probability (cohorts 1-4, and cohorts 1-4 combined) or unlikely probability (cohort 5) for deep vein thrombosis.

increase was most prominent among patients in the age groups >70 years; with absolute increases ranging from 20% to 28% (Figure 1).

Combining the results of these four cohorts, 1672 of the total number of 2201 patients (75%) had a non-high clinical probability. With the conventional cut-off value, 707 patients (42%) had a normal D-dimer value, compared with 850 patients (51%) when the age-adjusted D-dimer cut-off value was used (Table 4). The absolute increase in patients in whom DVT could be ruled out (i.e. with a non-high clinical probability of DVT with a D-dimer level below the cut-off value) was 8.6% (95% CI 7.3% to 10%) for patients of all ages and highest among patients in older age groups: 19% absolute increase in patients >70 years old (28% with the conventional cut-off value compared with 47% with the age-adjusted cut-off value in patients >70 years). The false negative rates were comparable for the two D-dimer cut-off values: 5 (0.7%; 95% CI 0.2% to 1.6%) for the conventional cut-off compared with 7 (0.8; 95% CI 0.3% to 1.7%) for the age-adjusted cut-off (Tables 3 and 4).

Table 3. False negative rates with the conventional (500 μg/L FEU) and the age-adjusted D-dimer cut-off values in the different cohorts.

	All patients with non-high clinical probability	Age 51-60 years	Age 61-70 years	Age 71-80 years	Age > 80 years
Cohort 1					
N. (% of total)	**472**	**93 (20)**	**65 (14)**	**79 (17)**	**46 (9.7)**
Age, years (median, IQR)	56 (45-71)	55 (53-59)	66 (63-69)	75 (72-78)	85 (83-89)
False negative rate with conventional cut-off, n., % (95% CI)	1/168 (0.6, 0.0-3.3)	0/37 (0, 0-9.5)	0/20 (0, 0-17)	0/18 (0, 0-19)	0/10 (0, 0-31)
False negative rate with new cut-off, n., % (95% CI)	2/195 (1.0, 0.3-3.7)	0/39 (0, 0-9.0)	0/25 (0, 0-14)	0/27 (0, 0-13)	1/21 (4.8, 0.1-24)
Cohort 2					
N. (% of total)	**419**	**64 (15)**	**77 (18)**	**72 (17)**	**65 (16)**
Age, years (median, IQR)	61 (45-74)	56 (54-59)	65 (62-68)	75 (72-77)	86 (83-88)
False negative rate with conventional cut-off, n., % (95% CI)	2/127 (1.6, 0.2-5.6)	0/26 (0, 0-13)	0/21 (0, 0-16)	0/11 (0, 0-29)	0/1 (0, 0-..)
False negative rate with new cut-off, n., % (95% CI)	2/164 (1.2, 0.2-4.3)	0/30 (0, 0-12)	0/30 (0, 0-12)	0/21 (0, 0-16)	0/15 (0, 0-22)
Cohort 3					
N. (% of total)	**297**	**34 (11)**	**57 (19)**	**92 (31)**	**60 (20)**
Age, years (median, IQR)	71 (58-79)	57 (54-59)	66 (64-68)	76 (74-78)	84 (83-86)
False negative rate with conventional cut-off, n., % (95% CI)	1/129 (0.8, 0.01-4.2)	0/22 (0. 0-15)	0/31 (0, 0-12)	0/30 (0, 0-12)	1/11 (9.1, 0.2-41)
False negative rate with new cut-off, n., % (95% CI)	2/156 (1.3, 0.2-4.6)	0/23 (0, 0-15)	1/38 (2.6, 0.1-14)	0/42 (0, 0-8.4)	1/27 (3.7, 0.1-19)
Cohort 4					
N. (% of total)	**484**	**80 (17)**	**117 (24)**	**118 (24)**	**51 (11)**
Age, years (median, IQR)	65 (42-88)	55 (51-59)	66 (62-70)	75 (71-79)	84 (81-88)
False negative rate with conventional cut-off, n., % (95% CI)	1/283 (0.4; 0.1-2.0)	0/54 (0; 0-6.6)	0/67 (0; 0-5.4)	0/60 (0; 0-6.0)	0/22 (0; 0-15)
False negative rate with new cut-off, n., % (95% CI)	1/335 (0.3; 0.1-1.7)	0/58 (0; 0-6.2)	0/75 (0; 0-4.9)	0/87 (0; 0-4.2)	0/35 (0; 0-9.9)
Cohort 1-4 combined					
N. (% of total)	**1672**	**271 (16)**	**316 (19)**	**361 (22)**	**222 (13)**
False negative rate with conventional cut-off, n., % (95% CI)	5/707 (0.7; 0.2-1.6)	0/139 (0; 0-2.6)	0/139 (0; 0-2.6)	0/119 (0; 0-3.1)	1/44 (2.3; 0.1-12)
False negative rate with new cut-off, n., % (95% CI)	7/850 (0.8; 0.3-1.7)	0/150 (0; 0-2.4)	1/168 (0.6; 0.02-3.3)	0/177 (0; 0-2.1)	2/98 (2.0; 0.3-7.2)
Cohort 5					
N (% of total)	**212**	**44 (21)**	**43 (20)**	**14 (6.6)**	**22 (10)**
Age, years (median, IQR)	54 (44-77)	55 (53-56)	65 (63-67)	77 (77-77)	84 (83-91)
False negative rate with conventional cut-off, n, % (95% CI)	0/83 (0, 0-3.5)	0/22 (0, 0-13)	0/11 (0, 0-24)	0/2 (0, 0-78)	0/2 (0, 0-78)
False negative rate with new cut-off, n, % (95% CI)	0/100 (0, 0-3.0)	0/24 (0, 0-12)	0/14 (0, 0-19)	0/5 (0, 0-45)	0/11 (0, 0-24)
All cohorts combined					
N. (% of total)	**1884**	**315 (17)**	**359 (19)**	**375 (20)**	**244 (13)**
False negative rate with conventional cut-off, n., % (95% CI)	5/790 (0.6, 0.2-1.5)	0/161 (0, 0-2.3)	0/150 (0, 0-2.4)	0/121 (0, 0-3.0)	1/48 (2.1, 0.05-11)
False negative rate with new cut-off, n., % (95% CI)	7/950 (0.7, 0.4-1.50)	0/174 (0, 0-2.1)	1/182 (0.5, 0.02-3.0)	0/182 (0, 0-2.0)	2/109 (1.8, 0.2-6.5)

IQR: interquartile range; CI: confidence interval.

Cohort 5

In the fifth cohort, the clinical probability of DVT was 'unlikely' in 212 patients, of whom 83 patients (39%) had a normal D-dimer test result according to the conventional cut-off value (Table 3). The false negative rate was 0 (0.0%, 95% CI 0.0% to 3.5%). With the age-adjusted D-dimer cut-off value, 100 patients (47%) had a normal D-dimer test result, and the false negative rate was 0.0% (95% CI 0.0% to 3.0%) (Figure 1, Table 3). This resulted in an 8.0% absolute increase in the number of patients in whom DVT could be excluded. As in the other cohorts, the increase in patients with a normal D-dimer test result was most prominent in the older age groups (Figure 1), with a 33% absolute increase in patients aged >70 years.

Discussion

This analysis shows that an age-adjusted D-dimer cut-off value, which has recently been introduced for the diagnosis of PE,[9] might also be effective and safe in the exclusion of DVT. The number of older patients (>70 years) in whom DVT can be safely excluded based on a non-high clinical probability and a normal D-dimer test result is twice as high when the age-adjusted cut-off value is used, compared with the conventional cut-off value (500 μg/L FEU).

For this analysis, data from five large management studies on the diagnosis of DVT were used, totaling information from 2818 patients. An increase in the percentage of patients in whom DVT could be excluded was demonstrated in all five cohorts, with the absolute increase ranging from 20% to 33% in older patients. Increasing the D-dimer cut-off value did not compromise safety. In each cohort, the upper 95% confidence limits of the false negative rates using the age-adjusted cut-off value were comparable to those using the conventional cut-off. When data from the first four cohorts were combined, the upper 95% confidence limit for the total sample of patients of all ages was well below 3%, both with the conventional and with the age-adjusted D-dimer cut-off value.

The aim of the diagnostic management of DVT, like that of PE, is to identify patients in whom anticoagulant therapy can be withheld using a minimally invasive yet safe strategy, in order to avoid additional diagnostic testing and without missing a potentially fatal diagnosis. Even though CUS of the limb is non-invasive (no radiation exposure, no injection of iodine contrast agent), it is time-consuming and, in some hospitals, is not available around the clock, resulting in prolonged hospitalization. Serial CUS is used in many validated strategies, making the test more cumbersome. It would, therefore, be preferable to be able to exclude the diagnosis of DVT without the need for CUS, especially in the older population of patients.

An age-dependent increase in the D-dimer cut-off value has been proposed before: Harper and colleagues suggested a cut-off value of 500 μg/L FEU for patients <60 years and 1000 μg/L FEU for older patients.[6] Similarly, Haas *et al.* introduced a cut-off value of 750 μg/L FEU for patients ≥60 years. In both studies, the raised cut-off increased specificity and preserved a high sensitivity.[15] In the derivation study of the age-dependent cut-off value used in the current analysis, however, it was shown that the optimal D-dimer cut-off value gradually increases as age increases.[9] Using a coefficient to correct for the increasing age more elegantly adjusts the cut-off value to suit the increasing age, compared with a fixed change in cut-off at the age of 60 years. We showed the impact of this gradual increase of the D-dimer cut-off value on the clinical management of patients with suspected DVT.

In comparison with the results obtained previously in the diagnostic management of PE,[9] the increase in the proportion of patients with a normal D-dimer test using the age-adjusted D-dimer cut-off value was greater among patients with suspected DVT. In patients with suspected PE the increase in the proportion of patients with a D-dimer test result below the new *versus* the conventional cut-off was 5% to 6% overall and 13 to16% in patients >70 years old.[9] In this study among patients with suspected DVT, the absolute increase was 9% in patients of all ages and 20-30% in patients >70 years old. Point estimates showed similar safety for the age-adjusted cut-off in PE and DVT.

Table 4. Proportion of patients with a non-high clinical probability in whom deep vein thrombosis could be excluded based on a D-dimer level below the cut-off, stratified according to different age groups – combined outcome of cohorts 1 to 4.

	All patients with non-high clinical probability	Age 51-60 years	Age 61-70 years	Age 71-80 years	Age > 80 years
N. (% of total)	1672	271 (16)	316 (19)	361 (22)	222 (13)
Conventional D-dimer cut-off (500 μg/L FEU)					
Patients with normal D-dimer, n (%, 95%CI)	707 (42, 40-45)	139 (51, 45-57)	139 (44, 39-50)	119 (33, 28-38)	44 (20, 15-25)
False negative, n, % (95% CI)	5 (0.7, 0.2-1.6)	0 (0, 0-2.6)	0 (0, 0-2.6)	0 (0, 0-3.1)	1 (2.3, 0.1-12)
NNT	2.4	1.9	2.3	3.9	5.9
Age adjusted D-dimer cut-off (if age > 50 years: age x 10 μg/L FEU)					
Patients with normal D-dimer n. (%, 95%CI)	850 (51, 48-53)	150 (55, 49-61)	168 (53, 48-59)	177 (49, 44-52)	98 (44, 38-51)
False negative, n., % (95% CI)	7 (0.8, 0.3-1.7)	0 (0.0, 0-2.4)	1 (0.6, 0.02-3.3)	0 (0, 0-2.1)	2 (2.0, 0.3-7.2)
NNT	2.0	1.8	1.9	2.0	2.3
Increase in number of patients in whom DVT is excluded					
Absolute (%)	8.6	4.1	9.2	16	24
Relative (%)	20	7.9	21	49	123

CI: confidence interval; DVT: deep vein thrombosis; NNT: number needed to test.The number needed to test to rule out one DVT using the conventional or the age-adjusted D-dimer cut-off value was calculated as 1 divided by the proportion of patients in whom DVT could be excluded (based on the clinical probability and D-dimer test result).

Our study has some limitations. First, the diagnostic strategy and tests differed among the five cohorts. In our analysis, we used the classification for clinical probability as used in the original studies. In the first, third and fourth cohorts, a cut-off of ≤2 was used to determine "non-high" clinical probability compared to <2 in the fifth cohort to determine "unlikely" clinical probability. Because both cut-off points are used in clinical practice,[14-16] we wanted to investigate the effect of increasing the D-dimer cut-off value among all patients selected for having a "non-high" and "unlikely" probability of DVT. Second, the prevalence of DVT in the five cohorts differed, ranging from 10% to 39%. This was partially reflected in the proportion of patients with a non-high clinical probability (66% in cohort 1 with a DVT prevalence of 39% *versus* 87% in cohort 4 with a DVT prevalence of 10%) and an unlikely probability (34% in cohort 5 with a DVT prevalence of 37%). The absolute increase in patients with a normal D-dimer with the age-adjusted cut-off was largest in the cohort with the lowest DVT prevalence (11%) and smallest in the cohort with the highest DVT prevalence (5.7%). Third, different types of D-dimer tests were used. The effect of a raised D-dimer cut-off value on the number of normal D-dimer tests and false negative results was manifest and comparable in the five cohorts. However, it is unknown how the new cut-off value would perform when other D-dimer assays are used. In summary, the cohorts included in this analysis were heterogeneous. However, we believe that including different study cohorts reinforces the generalizability of our findings. Finally, although all tests were performed prospectively (clinical probability estimation, D-dimer testing, additional radiological examinations), this analysis was performed retrospectively. A suggestion for future research would, therefore, be to validate the age-adjusted D-dimer cut-off value prospectively in a diagnostic management study with follow-up of the patients.

In conclusion, in patients with a non-high or unlikely clinical probability of DVT, an age-adjusted D-dimer cut-off value greatly increases the proportion of older patients in whom DVT can be excluded, without reducing safety. After external validation in five cohorts of patients with suspected DVT, prospective validation should be performed before implementation in daily practice.

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