Can an age-adjusted D-dimer level be adopted in managing venous thromboembolism in the emergency department? A retrospective cohort study

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Introduction **Patients suspected of having venous thromboembolism (VTE), with a low pretest probability, undergo D-dimer testing. A negative D-dimer, in a low-risk patient rules out VTE with a high degree of certainty because of its high sensitivity. It is, however, a poorly specific test, and the absolute value increases with age. The aim of this study was to establish whether an age-adjusted D-dimer could be safely used instead of a standard cut-off level in low-risk patients over the age of 50 years.**

Patients and methods **This was a retrospective review of 1649 patients with suspected VTE whose D-dimer levels were analysed. In low-risk patients (defined as 'VTE unlikely' using the dichotomized Wells' scores), the outcomes in terms of confirmed VTE diagnosis, hospital admission and investigations using an age-adjusted D-dimer level (measured in D-dimer units) of 5 × the age for patients over 50 years of age and 250 ng/ml for patients younger than 50 years of age, was compared with the cut-off standard level (230 ng/ml in all patients).**

Results **Of the total group of patients in the VTE unlikely group, the proportion of patients with a negative D-dimer when using the standard cut-off was 64.9% (859/1324). A further 130 patients had a negative D-dimer when the age-adjusted cut-off was used, increasing the proportion of all patients in whom VTE could be excluded without imaging to 74.7% (989/1324). For those patients of 75 years or older, the proportion of patients in whom VTE could be excluded without imaging increased from only 91/242 (37.6%) when using the standard D-dimer cut-off to 154/242 (63.6%) when the age-adjusted cut-off was used. These changes occurred without any additional false-negative findings.**

Conclusion **For patients over the age of 50 years suspected of having VTE with a low pretest probability, increasing the D-dimer cut-off level to 5 × the age increases the proportion of patients in whom VTE can safely be excluded without radiological imaging.** ***European Journal of Emergency Medicine*** **00:000–000 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.**

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Keywords: age-adjusted D-dimer, computed tomographic pulmonary angiography, deep vein thrombosis, pulmonary embolism, ultrasound

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Introduction

The standard work-up for patients suspected of having pulmonary embolism (PE) or deep vein thrombosis (DVT) [i.e. venous thromboembolism (VTE)] involves risk stratification with gestalt or with validated tools such as the Wells score [1] or Revised Geneva Score [2]. In patients with a low pretest probability of VTE, a serum D-dimer level is the next step recommended by NICE (UK). A negative D-dimer in low-risk patients effectively excludes VTE and avoids the need for further investigation such as computed tomographic pulmonary angiography (CTPA), ventilation/perfusion (V/Q) scanning or lower limb venous ultrasound.

D-Dimer can be measured at the bedside with a point of care qualitative finger prick stick test or more commonly using quantitative tests done in the laboratory. Most laboratories use a test which reports the D-dimer in fibrinogen equivalent units (FEUs). The cut-off for positive test is around 500 ng/ml, 500 μg/dl or 0.5 mg/ml. Some laboratories, including the one at York Hospital, use the D-dimer unit with a cut-off usually around less than 230 ng/ml. There is roughly 1 D-dimer unit to 2 FEUs [3].

Because of the high sensitivity of D-dimer testing and the growth in its use over recent years, many more patients are now being subjected to radiological investigations as a result of a D-dimer above the current normal cut-off level. The growth in demand for CTPA has been significant and the adverse effects and cost of such an increase in radiological investigations has been documented [4]. In addition to the problems with radiation dose to a patient, there can be adverse effects from the contrast media used in this test as well as the time and costs involved in conducting the test. There is growing concern about the increasing number of subsegmental pulmonary emboli being found on CTPA and the clinical

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significance of these smaller clots and the wisdom of treating these patients with anticoagulant therapy [4]. The growth in demand for ultrasound scanning has been similar, and whilst radiation dose is not an issue, there are significant costs associated with conducting this test in terms of staff and patient time and hospital visits.

It is well known that the serum level of D-dimer increases with age [5]. It has been proposed that the cut-off level for D-dimer should increase as the patient gets older. Specifically, large derivation studies and a meta-analysis on D-dimer levels have suggested that increasing the cut-off level to 10× the age for patients over the age of 50 years (assuming the D-dimer is measured in FEUs) would result in very similar sensitivities for the test, whilst increasing the specificity and hence resulting in a reduction in the need for radiological investigations for older patients [6–8].

The aim of this study was to evaluate and confirm the impact of previous research around age-adjusted D-dimer in a UK population, by conducting a large retrospective review of all patients who had a D-dimer test requested in York Hospital Emergency Department and to document the outcome in terms of radiological investigations performed, diagnoses made and treatments instituted. The study specifically wanted to find out whether increasing the D-dimer cut-off level when D-dimer is measured in D-dimer units to 5× the age for patients of 50 years and over, and 250 ng/ml for younger patients, would result in an acceptable sensitivity for the diagnosis of VTE, whilst simultaneously increasing the proportion of patients in whom VTE could be excluded without the need for radiological imaging. We wanted to make the new rule simple to remember, but also wanted it to be clearly related to those described in previous literature on this issue, which used the age of 50 years as the cut-off to apply a multiplier. The 5× rule was thus applied to those of 50 years and above, and hence the figure of 250 ng/ml for patients younger than this. We then compared this to the manufacturer's recommendation of 230 ng/ml for all patients regardless of age.

Patients and methods

Patient sample, data collection and analysis

This was a retrospective review of all patients evaluated for possible VTE (PE or DVT), who presented to the Emergency Department (ED) at York Hospital between 1 November 2013 and 31 July 2014.

NHS Management Permission and Research Governance approval was obtained from the R&D Unit at York Hospital. Formal ethics approval was not required.

The patient group was identified by reviewing the ED records and subsequent electronic hospital records (which include the reports of pathology tests, radiology investigations and clinical letters) of all patients who had a D-dimer test performed during the study period. In our department, investigations (including blood tests such as D-dimer) can be arranged on patients with suitable symptoms by the triage nursing staff as well as during the medical evaluation. The Laboratory Medicine Department at York Hospital provided the list of patients who had had a D-dimer performed along with the actual result of the test. D-dimer was measured in D-dimer units (not FEUs) using an ACL TOP 500 coagulation analyser and HemosIL D-dimer HS reagent (Beckman Coulter Inc., High Wycombe, UK).

The clinical records were scrutinized by one of the investigators (T.J., M.E. or S.C.) to determine which patients were investigated for PE, DVT and for other possible diagnoses. It was assumed that in all patients presenting with dyspnoea, chest pain, collapse or other similar symptoms, the D-dimer test had been performed primarily to exclude PE. Patients investigated for lower limb pain or swelling were assumed to be investigated to exclude lower limb DVT. Patients in whom upper limb DVT or thoracic aortic dissection were the documented reasons for taking the D-dimer test were excluded from the analysis.

All patients in whom possible PE or lower limb DVT (VTE) was the focus of the evaluation were divided into VTE likely and VTE unlikely categories using the Wells score. If the Wells score was documented in the notes, this was used to estimate the pretest probability of VTE. Patients for whom the Wells score was not documented, it was calculated using data available from the contemporaneous notes. In such patients investigated for possible PE, the 'PE is the most likely' definition given to those patients in whom PE was documented as either the potential only diagnosis or the first in the list of differentials given at the end of the patient assessment – that is, there was evidence that the clinician felt that PE was 'the most likely' diagnosis. In terms of the other aspects of the Wells score, where no comment was made within the patient record with regard to these, it was assumed that it was absent (e.g. if no mention was made of a past history of VTE, it was assumed that the patient had no prior PE or DVT).

Only patients in the VTE unlikely group were included in the final analysis, as those patients who were VTE likely should have further investigation regardless of their D-dimer result. The notes of the first 50 cases identified were independently reviewed by all three investigators and the Wells category (VTE likely or unlikely) assigned to each case by each investigator was used to estimate the level of agreement (free marginal κ statistic) using an online tool [9].

We collected demographic data, disposal (hospital admission or discharge) and length of hospital stay if admitted. We documented the duration of symptoms before attendances as there is evidence that D-dimer levels decline during the period after VTE and that D-dimer levels taken later in the course of symptoms

may not be as reliable as those taken at symptom onset [10,11]. We also collected data on the number and type of radiological investigations performed to exclude VTE (ultrasound, CTPA or V/Q scanning) and the diagnosis given at the end of the index attendance/admission. We reviewed subsequent hospital records to determine whether patients had returned to the ED or hospital, been diagnosed with VTE or died within the 3 month period following the index presentation.

The primary outcome was the diagnosis of VTE (either DVT or PE). This was defined as positive if confirmed on a radiological test (ultrasound, CTPA or V/Q scanning), or deemed likely and treated by the attending physicians on clinical grounds either during the index attendance/admission or within 3 months of the index presentation.

We estimated the potential impact that increasing the D-dimer cut-off would have on the proportion of patients in whom VTE could be excluded without radiological imaging and upon hospital admission rates. In addition, we derived data for the sensitivity and specificity for the current D-dimer cut-off in the diagnosis of VTE in these low-risk patients, and compared this to the likely outcome if the D-dimer cut-off was increased to 5 × the age for those aged 50 years and over and 250 ng/ml for younger patients.

Sample size

The sample consisted of all patients who had a D-dimer test taken during an ED attendance throughout the study period. This was a convenient sample of 1649 patients.

Statistical analyses were performed using MedCalc for Windows, version 12.7.7 (MedCalc Software, Ostend, Belgium).

Results

From 1 November 2013 to 31 July 2014, a total of 1667 patients had a D-dimer test taken in York ED. Of these patients, 18 were specifically done to investigate for aortic dissection or upper limb thrombosis leaving 1649 patients who were investigated for VTE. Of these, 986 patients underwent investigation for suspected PE and 663 for suspected DVT.

The Wells score was documented contemporaneously in the notes in 543/663 (82%) of those evaluated for DVT, but in only 115/986 (12%) of those in which the D-dimer test had been done to help exclude PE. The total number of patients classified as VTE unlikely through the Wells score was 1324 (384 investigated for DVT and 940 for PE). Agreement among the three investigators for assignment of the Wells score was good (κ statistic = 0.81).

Patient demographics of the VTE unlikely patients are shown in Table 1.

A total of 145 CTPAs, 209 lower limb ultrasounds and nine V/Q scans were completed on these VTE unlikely patients during their index presentation. The flow chart describes the evaluation and diagnostic outcome for the patients (Fig. 1).

A total of 261 (20%) patients returned to the hospital and 34 (2.6%) had died within 3 months of their index presentation.

Of the 1324 patients in the VTE unlikely group, 60 had VTE confirmed and were diagnosed with PE ($n = 34$), DVT ($n = 24$) or both ($n = 2$) within 3 months of their attendance. The rest had alternate diagnoses.

The raw data of the two D-dimer cut-offs is given in Tables 2 and 3.

Of the total group of patients in the VTE unlikely group, the proportion of patients with a negative D-dimer when using the standard cut-off was 64.9% (859/1324). A further 130 patients had a negative D-dimer when the age-adjusted cut-off was used. This would increase the proportion of all patients in whom VTE could be excluded without imaging by nearly 10–74.7% (989/1324).

The absolute increase was greater in those older than 50 years of age, with 414/764 (54.2%) having a negative D-dimer when using the standard cut-off and 544/764 (71.2%) having a negative D-dimer when the age-adjusted cut-off was used (an increase of 17%). Predictably, the figures for those patients of 75 years or older were greater still, with 91/242 (37.6%) having a negative D-dimer when using the standard cut-off and 154/242 (63.6%) having a negative D-dimer when the age-adjusted cut-off was used (an absolute increase in the proportion of patients in whom VTE could be excluded without radiological imaging of 26%).

The diagnostic performance of the two D-dimer cut-offs has been compared in Table 4.

The three patients who were diagnosed with VTE within 3 months of their index D-dimer test were not identified using either the old D-dimer or proposed new D-dimer cut-off. Only one patient was diagnosed at the index presentation. This patient was an intravenous drug user whose ultrasound was reported as showing 'probable old thrombus', but was nevertheless treated for DVT by the clinician involved. The other two patients both re-presented within 3 months of discharge. One was another intravenous drug user who had a negative ultrasound scan at initial presentation, who continued to use intravenous drugs and returned later with a documented Wells' score of +4 and a DVT on ultrasound. The other was a female patient treated for confirmed lower respiratory tract infection as an inpatient, who returned after discharge with on going chest pain. On her second presentation she had another D-dimer test, which was positive (using both cut-off levels), and was diagnosed with a 'small PE amongst an area of on going

Table 1 Patient demographics of the venous thromboembolism unlikely patients

	All VTE unlikely patients ($n = 1324$) [n (%)]	Patients investigated for possible PE ($n = 940$) [n (%)]	Patients investigated for possible DVT ($n = 384$) [n (%)]
Male sex	566 (43)	413 (44)	153 (40)
Median age (range) (years)	54 (13–96)	51 (13–96)	61 (14–95)
Age ≥ 50 years	764 (57.7)	495 (52.7)	269 (70.1)
Age ≥ 75 years	242 (18.3)	135 (14.4)	107 (27.9)
Duration of symptoms < 1 week	1047 (79)	800 (85)	247 (64)
Admitted to a hospital bed	471 (36)	430 (46)	41 (11)

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

consolidation' on the CTPA. She was treated with 3 months of anticoagulation, but such a PE is of uncertain clinical significance [4,12].

Clinical impact

Of the 1324 patients who were deemed unlikely to have VTE, 130 (9.8%) would have had a negative D-dimer (instead of a positive one) using the new cut-off. These 130 patients had a total of 25 CTPAs, one V/Q scan and 52 ultrasounds during the study period. All were negative for VTE. Sixty-eight out of the 130 (52%) were admitted to a hospital bed with 26 of these being for a period of 24 h or less. Some of these investigations, in addition to the associated acute admissions, could have been avoided if the new cut-off of 5× the age in patients over 50 years (and 250 ng/ml in younger patients) were adopted.

Discussion

We have demonstrated that using an age-adjusted D-dimer level, rather than a single cut-off level for all patients, has the potential to increase the proportion of patients in whom VTE can be excluded without the need for radiological imaging. Within the limitations of this retrospective review, our results show that no additional patients with confirmed VTE would have been missed as a result of increasing the D-dimer cut-off value to 5× the age for patients older than 50 years or 250 ng/ml for younger patients.

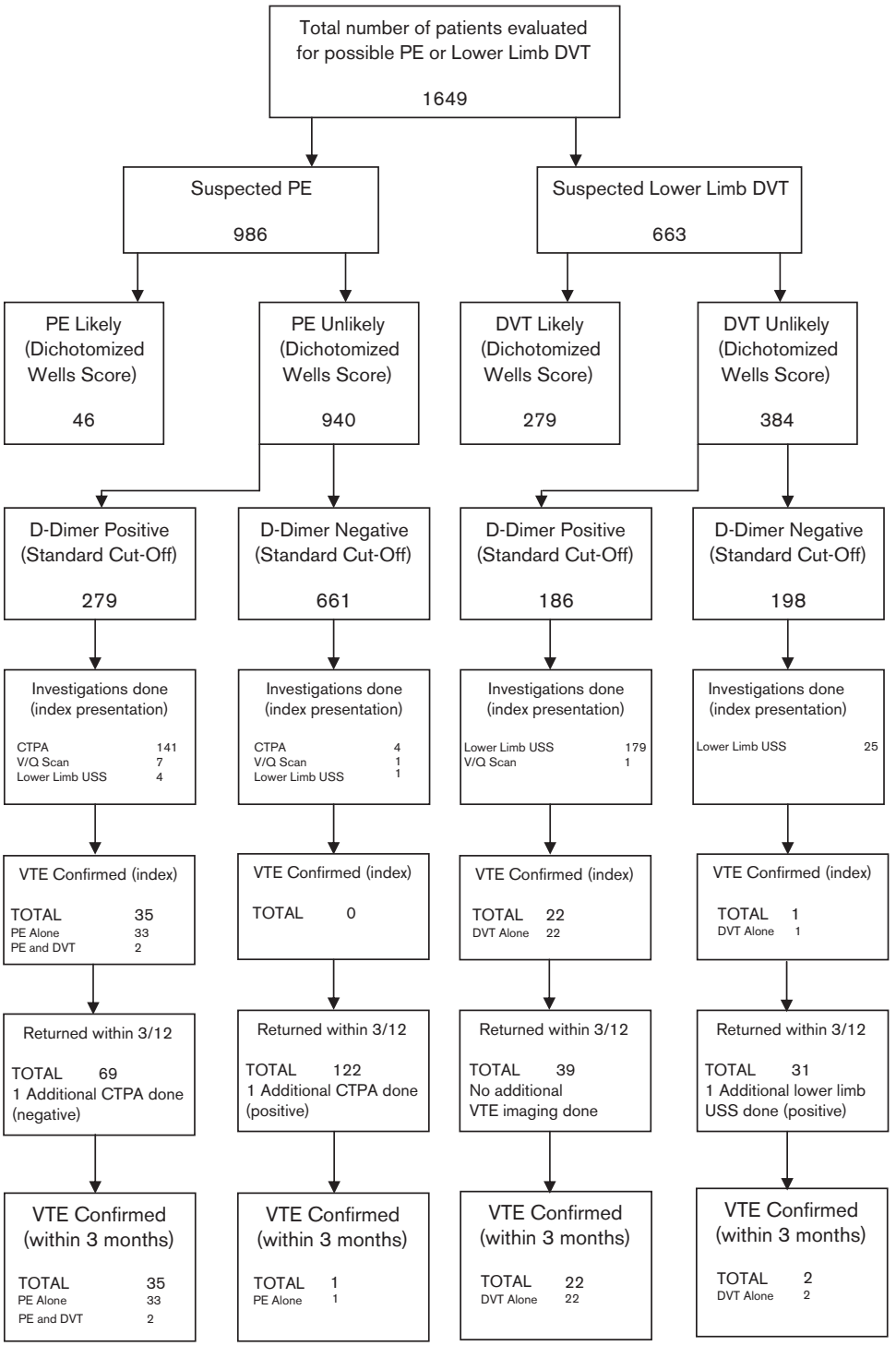
Our results add to a growing body of evidence which suggests that adjusting the upper limit of D-dimer for older patients will result in an acceptable sensitivity while simultaneously increasing the specificity of the test and reducing the number of hospital admissions and radiological investigations, which are required to exclude VTE [6–8,13–23].

To date there have been several systematic reviews conducted. Schouten *et al.* [6] looked at a large sample size of 12 497 patients with a nonhigh clinical probability of VTE. The results showed that in patients older than 80 using a standard D-dimer threshold the specificity was 14.7%, which increased to 35.2% using an age-adjusted (age × 10 μg/l) value. Sensitivities of the age-adjusted cut-off were not compromised, and remained above 97% in all age categories. More recently, van Es *et al.* [24] conducted a systematic review of studies evaluating the efficiency of age-adjusted D-dimer in 'PE unlikely' patients. This review did not include patients being worked up for possible DVT. A total of six studies evaluating 7268 patients with possible PE were included from various inpatient and outpatient settings (not just EDs). The review showed age-adjusted testing to be associated with a 5% absolute increase in the proportion of patients who could be discharged without imaging (from 28 to 33%). Overall in this review, the prevalence of confirmed PE was 22% and this is substantially higher than in most of the published literature to date and is higher than the confirmed PE rate in our study, which was 3.6%. The authors of the review comment that in such low-prevalence settings, the efficiency of an age-adjusted D-dimer is likely to be greater as confirmed in our study.

Other large studies include two works by Douma *et al.* [7], who did post-hoc analyses on prospectively collected cohort data looking at PE and DVT individually. The PE study [7] included 5132 consecutive patients with suspected PE, who were presented to four EDs. In patients aged over 50 years, using the standard cut-off value of 500 μg/l PE could be excluded in 36% of cases, compared with 42% of cases using the age-adjusted D-dimer value (age × 10 μg/l). A more recent post-hoc analysis of six prospective studies conducted by van Es and colleagues showed age-adjusted testing to be associated with a 5% absolute increase in the proportion of patients who could be discharged without imaging. Douma *et al.*'s [8] DVT study included 2818 consecutive outpatients with suspected DVT. In 1672 patients with nonhigh probability, DVT could be excluded in 850 (51%) patients with the age-adjusted cut-off value versus 707 (42%) patients with the conventional cut-off value.

Most of the studies in this area to date do not describe the actual use of the age-adjusted rule in the clinical setting. However, the ADJUST PE study [22] did use an age-adjusted D-dimer level of 10× the age in a multicentre prospective study of 3346 patients across 19 EDs, looking specifically at PE. It found that in patients 75 years or older using the conventional cut-off of 500 μg/l PE could be excluded in 43/673 (6.4%) patients and with the age-adjusted cut-off (age × 10 μg/) 200/673 (29.7%) patients could be excluded without any additional false-negative findings.

Fig. 1



Flow chart of patients in the study. CTPA, computed tomographic pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism; USS, ultrasound scan; VTE, venous thromboembolism; V/Q, ventilation/perfusion.

Similarly to some other work [23], our study assesses the impact of adjusting the D-dimer level for age when D-dimer is measured in D-dimer units (as opposed to FEUs). It seemed intuitive that if a level of 10× the age was suggested for results measured in FEUs, than a level of 5× the age would give similar results in our patients. We preferred this approach to one in which a fixed (higher) level was used for older patients. Although

Table 2 2 × 2 Table for the standard D-dimer cut-off

	VTE confirmed	VTE excluded	Total
D-Dimer positive	57	408	465
D-Dimer negative	3	856	859
Total	60	1264	1324

VTE, venous thromboembolism.

Table 3 2 × 2 Table for D-dimer cut-off 5 × age for those over 50 years or 250 ng/ml for younger patients

	VTE confirmed	VTE excluded	Total
D-Dimer positive	57	278	335
D-Dimer negative	3	986	989
Total	60	1264	1324

VTE, venous thromboembolism.

Table 4 Comparison of diagnostic performance of the two D-dimer cut-off thresholds

Diagnostic parameters	Standard D-dimer cut-off	Age-adjusted D-dimer cut-off
Sensitivity (95% CI) (%)	95 (86.1–99.0)	95 (86.1–99.0)
Specificity (95% CI) (%)	67.7 (65.1–70.3)	78.0 (75.6–80.3)
Negative Predictive Value (95% CI) (%)	99.7 (99.0–99.9)	99.7 (99.1–99.9)
Positive predictive Value (95% CI) (%)	12.3 (9.4–15.6)	17.0 (13.2–21.5)
LR− (95% CI)	0.07 (0.02–0.22)	0.06 (0.02–0.19)
LR+ (95% CI)	2.94 (2.67–3.25)	4.32 (3.84–4.87)

CI, confidence interval; LR, likelihood ratio.

potentially easier to recall, a fixed level does not fully adjust for the specific age of the patient and there have been variable reports of sensitivity with some work suggesting high sensitivity at a cut-off level of 750 ng/ml [25], but others demonstrating a much lower sensitivity [26]. In our patients, a fixed higher D-dimer cut-off level of 500 ng/ml (double the reference range) would have resulted in 15 false-negative tests (rather than three). An alternative approach to using decade age-adjusted D-dimer cut-off levels seems to yield promising results, but has only been suggested in a single, retrospective paper to date [19].

Many studies looking at the use of D-dimer in the exclusion of pulmonary embolus accept that the sensitivity of an age-adjusted D-dimer will be lower than a standard cut-off. It may be that some of the cases missed by a falsely negative D-dimer are small or subsegmental PEs. It is a matter of debate as to the clinical significance of such pulmonary emboli, and there is no consensus with regards to the need to treat these. Some have estimated that if the risk of PE in a population is very low, further testing will cause as much harm (e.g. through hospital admission, contrast reactions, cancer risk or bleeding from anticoagulation) as missing some smaller pulmonary emboli [27,28]. The level of PE risk below which it has been suggested further investigation would cause more harm than good is 1.4% [27]. Among the low-risk patients evaluated for possible PE in our study, the overall risk of confirmed PE was 34/940 (i.e. 3.6%). This suggests that it is still important to investigate such patients for the possibility of PE in our cohort. We have, however, shown that increasing the cut-off level for D-dimer does not compromise the efficient use of such investigation.

Before widespread real world use of age-adjusted cut-offs for D-dimer can be recommended, further prospective work in this area is required, such as a randomized trial of diagnostic strategies.

Limitations

This study is limited by its retrospective nature, relying on the accuracy of notes written at the time of consultation. In addition, there were a relatively small number of patients with confirmed VTE, with an overall VTE diagnosis rate of 4.5%.

In many cases, the Wells score was not calculated by the attending clinician and was therefore calculated by the investigator. In the majority of cases reviewed, only one author calculated the Wells score. Although a good inter-rater agreement was demonstrated for a sample of these ($\kappa = 0.81$), there remains some uncertainty in the Wells category assigned to each record. In addition, authors were not blinded to the patient outcome when calculating the Wells score, potentially introducing ascertainment bias.

Bias may also have been introduced in our definition of 'PE likely'. It is possible that some of these patients may have been allocated to the high-risk group inappropriately, thus excluding them from the analysis and potentially making our results for the performance of an age-adjusted D-dimer cut-off look more impressive than they actually are.

In addition, most of the patients with a negative D-dimer and many of those with a positive D-dimer (particularly those evaluated for possible PE) did not undergo diagnostic imaging. It is impossible to know whether any of these patients actually had VTE, but review of notes and records to 3 months after the presentation was designed to ensure that patients subsequently diagnosed with VTE were captured.

Our finding that only around half of the patients with a positive D-dimer in the PE unlikely group underwent diagnostic imaging is the biggest limitation of our work, but likely presents a picture of how D-dimer is used in actual emergency medicine practice. We suspect that many patients will have had a D-dimer requested as part of the initial evaluation of symptoms compatible with PE (either by nursing or junior medical staff), only for the PE diagnosis to be later questioned or excluded following more senior or specialist clinical evaluation. We recognize that this may have skewed our sample, but preferred to present data on all patients evaluated rather than a sample selected on the basis of a more senior assessment.

We relied on review of our hospital's electronic medical record in determining those patients who had died within 3 months of their index presentation. It is possible that some patients who had died were missed and the reported figure may be slightly higher than stated in our paper.

Conclusion

In patients suspected of having VTE with a low pretest probability, increasing the D-dimer cut-off level to 5× the age for patients over 50 years and 250 ng/ml for younger patients (when D-dimer is measured in D-dimer units) increases the proportion of patients in whom VTE can be excluded without the need for radiological imaging.

This study adds to the growing body of literature supporting an increase in the D-dimer cut-off level for older patients. A level of 5× the age for those over 50, if introduced would result in a modest reduction in admission rate and use of radiological investigations in these patients and help to reduce the pressure on in patient bed occupancy and radiological resources.

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T.J. and S.C. initiated the study, collected and analysed data and prepared the manuscript for the study. M.E. collected and reviewed data for the study.

Conflicts of interest

There are no conflicts of interest.

References

1 Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, *et al.* Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliREDD-dimer. *Thromb Haemost* 2000; **83**:416–420.
2 Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, *et al.* Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med* 2006; **144**:165–171.
3 Heim SW, Schectman JM, Siadaty SM, Philbrick JT. D-Dimer testing for deep venous thrombosis: a meta analysis. *Clin Chem* 2004; **50**() 1136–1147.
4 Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. *BMJ* 2013; **347**:f3368.
5 Harper PL, Theakston E, Ahmed J, Ockelford P. D-Dimer concentration increases with age reducing the clinical value of the D-dimer assay in the elderly. *Intern Med J* 2007; **37**:607–613.
6 Schouten HJ, Geersing GJ, Koek HL, Zuithoff NP, Janssen KJ, Douma RA, *et al.* Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. *BMJ* 2013; **346**:f2492.
7 Douma RA, le Gal G, Söhne M, Righini M, Kamphuisen PW, Perrier A, *et al.* Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. *BMJ* 2010; **340**:c1475.
8 Douma RA, Tan M, Schutgens REG, Bates SM, Perrier A, Legnani C, *et al.* 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; **97**:1507–1513.
9 Randolph JJ. Online kappa calculator (computer software). Available at: *http://justus.randolph.name/kappa*. [Accessed 24 May 2016.
10 Goldin Y, Pasvolsky O, Rogowski O, Shapira I, Steinvil A, Halpern P, *et al.* The diagnostic yield of D-dimer in relation to time from symptom onset in patients evaluated for venous thromboembolism in the emergency medicine department. *J Thromb Thrombolysis* 2011; **31**:1–5.
11 Heit JA, Minor TA, Andrews JC, Larson DR, Li H, Nichols WL. Determinants of plasma fibrin D-dimer sensitivity for acute pulmonary embolism as defined by pulmonary angiography. *Arch Pathol Lab Med* 1999; **123**:235–240.
12 Haldar S, Garg A, Barden S, Burkill G, Marchbank N. Most patients with isolated subsegmental pulmonary embolism do not need anticoagulants. *BMJ* 2013; **347**:f3368.
13 Penaloza A, Roy PM, Kline J, Verschuren F, LE Gal G, Quentin-Georget S, *et al.* Performance of age-adjusted D-dimer cut-off to rule out pulmonary embolism. *J Thromb Haemost* 2012; **10**:1291–1296.
14 Woller SC, Stevens SM, Adams DM, Evans RS, Lloyd JF, Snow GL, *et al.* Assessment of the safety and efficiency of using an age-adjusted d-dimer threshold to exclude suspected pulmonary embolism. *Chest* 2014; **146**:1444–1451.
15 Vossen JA, Albrektson J, Sensarma A, Williams SC. Clinical usefulness of adjusted D-dimer cut-off values to exclude pulmonary embolism in a community hospital emergency department patient population. *Acta Radiol* 2012; **53**:765–768.
16 Laruelle M, Descamps OS, Lesage V. D-dimer cut-off adjusted to age performs better for exclusion of pulmonary embolism in patients over 75 years. *Acta Clin Belg* 2013; **68**:298–302.
17 Polo Friz H, Pasciuti L, Meloni DF, Crippa M, Villa G, Molteni M, *et al.* A higher D-dimer threshold safely rules-out pulmonary embolism in very elderly emergency department patients. *Thromb Res* 2014; **133**:380–383.
18 Leng O, Sitaraaman HB. Application of age-adjusted D-dimer threshold for exclusion thromboembolism (PTE) in older patients: a retrospective study. *Acute Med* 2012; **11**:129–132.
19 Gupta A, Raja AS, Ip IK, Khorasani R. Assessing 2 D-dimer age-adjustment strategies to optimize computed tomographic use in ED evaluation of pulmonary embolism. *Am J Emerg Med* 2014; **32**:1499–1502.
20 Van Es J, Mos I, Douma R, Erkens P, Durian M, Nizet T, *et al.* The combination of four different clinical decision rules and an age-adjusted D-dimer cut-off increases the number of patients in whom acute pulmonary embolism can safely be excluded. *Thromb Haemost* 2012; **107**:167–171.
21 Verma N, Willeke P, Bicsán P, Lebiedz P, Pavenstädt H, Kümpers P. Age-adjusted D-dimer cut-offs to diagnose thromboembolic events: validation in an emergency department [in German]. *Med Klin Intensivmed Notfmed* 2014; **109**:121–128.
22 Righini M, van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, *et al.* Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism the ADJUST-PE study. *JAMA* 2014; **311**:1117–1124.
23 Cini M, Legnani C, Frascaro M, Sartori M, Cosmi B, Palareti G. D-Dimer use for deep venous thrombosis exclusion in elderly patients: a comparative analysis of three different approaches to establish cut-off values for an assay with results expressed in D-dimer units. *Int J Lab Hematol* 2014; **36**:541–547.
24 van Es N, van der Hulle T, van Es J, den Exter P, Douma R, Goekoop R, *et al.* Wells rule and D-dimer testing to rule out pulmonary embolism: a systematic review and individual-patient data meta-analysis. *Ann Intern Med* 2016; **165**:253–261.
25 Schouten HJ, Koek HL, Oudega R, Geersing GJ, Janssen KJ, van Delden JJ, *et al.* Validation of 2 age dependent D-dimer cut-off values for exclusion of deep vein thrombosis in suspected elderly patients in primary care: retrospective, cross sectional, diagnostic analysis. *BMJ* 2012; **344**:e2985.
26 Kline JA, Hogg MM, Courtney DM, Miller CD, Jones AE, Smithline HA. D-Dimer threshold increase with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography. *J Thromb Haemost* 2012; **10**:572–581.
27 Lessler AL, Isserman JA, Agarwal R, Palevsky HI, Pines JM. Testing low-risk patients for suspected pulmonary embolism: a decision analysis. *Ann Emerg Med* 2009; **55**:316–326.
28 Newman DH, Shriger DL. Rethinking testing for pulmonary embolism: less is more. *Ann Emerg Med* 2011; **57**:622–627.