EM Advances

Combination pretest probability assessment and D-dimer did not reduce outpatient imaging for venous thromboembolism in a tertiary care hospital emergency department

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ABSTRACT

Introduction: Venous thromboembolism (VTE) is difficult to diagnose yet potentially life threatening. A low-risk pretest probability (PTP) assessment combined with a negative D-dimer can rule out VTE in two-thirds of outpatients, reducing the need for imaging. Real-life implementation of this strategy is associated with several challenges.

Methods: We evaluated the impact of introducing a standardized diagnostic algorithm including a mandatory PTP assessment and D-dimer on radiologic test use for VTE in our emergency department (ED). A retrospective review of all ED visits for suspected VTE in the year prior to and following the introduction of this algorithm was conducted. VTE diagnosis was based on imaging. Guideline compliance was also assessed.

Results: ED visits were investigated for suspected VTE in the pre- and postintervention periods (n = 1,785). Most D-dimers (95%) ordered were associated with a PTP assessment, and 50% of visits assigned a low PTP had a negative D-dimer. The proportion of imaging tests ordered for VTE in all ED visits was unchanged postintervention (1.9% v. 2.0%). The proportion of patients with suspected VTE in whom VTE was confirmed on imaging decreased postintervention (10.2% v. 14.1%).

Conclusion: In spite of excellent compliance with our algorithm, we were unable to reduce imaging for VTE. This may be due to a lower threshold for suspecting VTE and an increase in investigation for VTE combined with a high false positive rate of our D-dimer assay in low–pretest probability patients. This study highlights two common real-life challenges with adopting this strategy for VTE investigation.

RÉSUMÉ

Introduction: Les thromboembolies veineuses (TEV) sont difficiles à diagnostiquer, pourtant elles peuvent être mortelles. Une évaluation du risque avant intervention (ERAI) considérée comme faible, associée à l'absence de D-dimères permet d'écarter la présence d'une TEV chez les deux tiers des malades externes, d'où diminution de la nécessité de recourir aux examens par imagerie. Toutefois, l'application de cette nouvelle façon de faire soulève, en pratique, plusieurs problèmes.

Méthodes: Il y a eu détermination de l'incidence de l'application d'un nouvel algorithme de diagnostic uniformisé, comportant une ERAI obligatoire et un dosage des D-dimères, sur le recours aux examens radiologiques, dans les cas de TEV, au service des urgences (SU) de notre établissement. L'étude consistait en un examen rétrospectif de toutes les consultations faites au SU, dans les cas présumés de TEV, au cours de l'année précédant et suivant l'application de ce nouvel algorithme. Le diagnostic de TEV reposait sur l'imagerie. A aussi été évalué le respect des lignes directrices.

Résultats: Les consultations au SU pour des TEV présumées au cours des périodes précédant et suivant l'intervention (n = 1,785) ont fait l'objet d'examen. La plupart des demandes de dosage des D-dimères (95%) faisaient suite à l'ERAI, et 50% des patients considérés comme à faible risque ont obtenu des résultats négatifs à la recherche des D-dimères. La proportion des demandes d'examen par imagerie pour une TEV par rapport à toutes les consultations au SU n'a pas changé au cours de la période après intervention (1.9% contre [c.] 2.0%), mais la proportion de patients souffrant d'une TEV présumée chez qui l'accident thrombotique a été confirmé à l'imagerie a diminué au cours de la période après intervention (10.2% c. 14.1%).

Conclusion: Malgré le respect rigoureux de l'algorithme, il a été impossible de diminuer le nombre de demandes d'examen par imagerie dans les cas de TEV. Cela peut

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s'expliquer par une diminution du nombre de cas présumés de TEV et par une augmentation du nombre de cas soumis à des examens exploratoires en vue de confirmer ou d'infirmer une TEV, associées à un taux élevé de faux positifs du dosage des D-dimères chez les patients ayant un faible risque de TEV avant intervention. L'étude fait ressortir, en pratique, deux difficultés courantes de l'application de cette nouvelle démarche dans l'exploration des TEV.

Keywords: D-dimer, quality improvement, venous thromboembolism

Making the diagnosis of deep vein thrombosis (DVT) and pulmonary embolism (PE) can be challenging in the emergency department (ED). Imaging tests used to rule out these diagnoses include duplex ultrasonography (DUS), computed tomographic pulmonary angiography (CTPA), and ventilation perfusion ($\dot{V}/\dot{Q}$) scans. These tests are inconvenient and expensive, and CTPA increases patient exposure to radiation. Moreover, their diagnostic yield is only 5 to 25%, indicating that many patients spend prolonged time in the ED and are exposed to risks unnecessarily.[1]

To reduce the use of low-yield imaging studies to rule out venous thromboembolism (VTE), diagnostic strategies that combine the use of standardized clinical pretest probability (PTP) assessments with D-dimer testing have been developed.[2–4] Studies have shown that low clinical pretest probability for VTE combined with a negative, highly sensitive D-dimer assay can safely rule out VTE in low-risk patients.[5,6] The rate of thromboembolic events in this population when anticoagulation is withheld on this basis is low (0.45%), and this strategy has been found to be cost effective.[7,8] Real-life studies have identified challenges in implementing this diagnostic strategy, including inappropriate use of D-dimer testing in high-risk patients, noncompliance with the algorithms, difficulties with validating a cutoff value for D-dimer tests, false positive D-dimer tests, use of inappropriate low-sensitivity D-dimer assays, and a reduction in the threshold for investigating VTE leading to an increase in the use of diagnostic imaging.[9–12]

The objective of our study was to assess whether the introduction of a standardized clinical PTP assessment prior to ordering of D-dimer tests could reduce the use of subsequent radiologic imaging to investigate patients with suspected VTE in our ED.

METHODS

Our study was a retrospective review of electronic medical records of patients presenting to the ED of an academic hospital for suspected VTE over a 2-year period. This study was part of a quality improvement initiative and exempted from obtaining informed consent by our hospital's Research Ethics Board. All patients presenting with suspected VTE in the year prior to and in the year following the introduction of a formal, standardized algorithm for investigation of VTE were included. Patient visits for suspected VTE were defined as any ED visit in which a DUS to rule out DVT, a CTPA or $\dot{V}/\dot{Q}$ scan to rule out PE, or a D-dimer test to rule out VTE was ordered.

The preintervention cohort included all ED visits from April 2, 2006, to April 1, 2007, and the postintervention cohort included all ED visits from April 2, 2007, to April 1, 2008. Exclusion criteria were any patients who had the above tests done for reasons other than suspected VTE. Although D-dimer testing was available at our university teaching hospital prior to April 1, 2007, it was used only at the discretion of the treating ED physician. On April 1, 2007, formal algorithms for the investigation of patients with suspected DVT and PE were introduced in our ED. These algorithms included a formal PTP assessment based on the Wells score (Figure 1 and Figure 2) combined with a highly sensitive latex immunoassay D-dimer (HemosIL D-dimer, Instrumentation Laboratory Company, Bedford, MA). According to the algorithm, all patients first had a clinical PTP assessment, and only those deemed low risk according to the PTP assessment were recommended to have D-dimer testing. If the D-dimer test was negative, then the diagnosis of VTE was considered ruled out and no further testing was recommended. Patients with a moderate or high PTP assessment were to proceed directly to appropriate imaging without D-dimer testing (see Figure 1 and Figure 2). Completion of the PTP assessment prior to the D-dimer test was mandated by a requirement that all D-dimer samples be accompanied by the PTP score sheet without which the laboratory would not run the D-dimer assay.

To identify all patients presenting to our ED with suspected VTE within the specified time frame of our study, we searched three different databases:

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Clinical probability of DVT score[1]	Tick if yes	Value	Score
Immobilized – paralysis, paresis, recent cast		1	
Cancer, active (treatment ≤ 6 months or palliative)		1	
Pitting edema, symptomatic leg		1	
Alternative diagnosis *more likely* than DVT		-2	
Swelling (entire leg)		1	
Tenderness (localized along deep vein or chord)		1	
Immobilized #2 – bedridden > 3 days or surgery < 1 month		1	
Veins, superficial collateral		1	
Calf swelling (> 3 cm v. asymptomatic side)		1	
TOTAL SCORE			

Score	Pretest probability	D-dimer
≥3	High	Do **not** order
1 or 2	Moderate	Do **not** order
≤0	Low	**Order D-dimer**

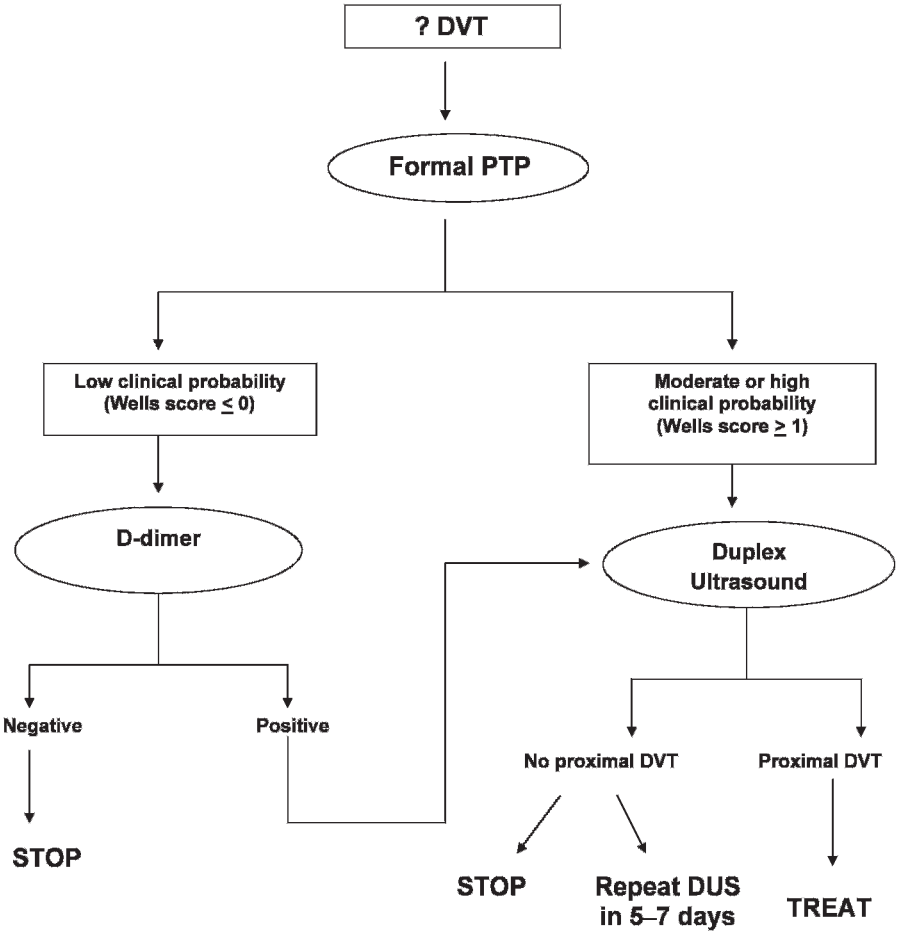

Figure 1. Deep vein thrombosis (DVT) pretest probability (PTP) assessment and algorithm. DUS = duplex ultrasonography.

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Clinical probability of PE score[1]	Tick if yes	Value	Score
Immobilization ≥ 3 d or surgery in previous 1 month		1.5	
Hemoptysis, bloody sputum		1	
Alternative diagnosis *less likely* than PE		3	
DVT signs (leg swelling, tenderness)		3	
Cancer, active (treatment ≤ 6 months or palliative)		1	
Previous proven DVT or PE		1.5	
Heart rate > 100 beats per minute		1.5	
TOTAL SCORE			

Score	Pretest probability	D-dimer
≥ 6	High	Do <u>not</u> order
2 to 5	Moderate	Do <u>not</u> order
0 to 1.5	Low	**Order D-dimer**

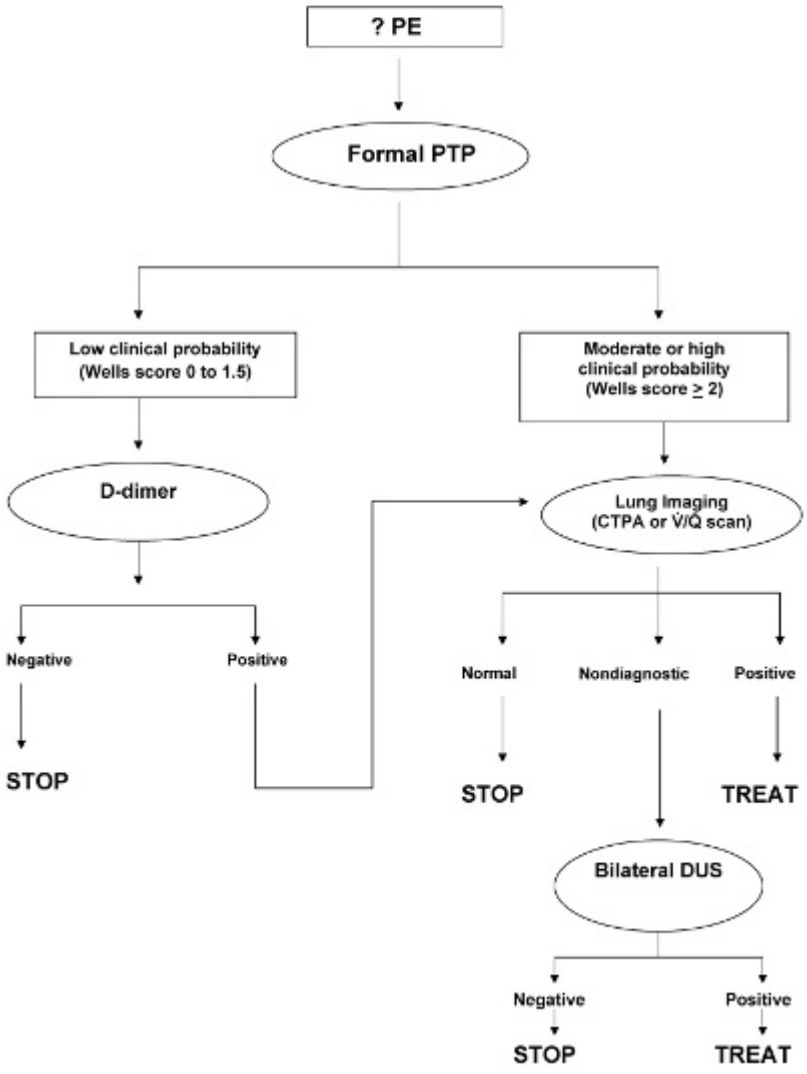

Figure 2. Pulmonary embolism (PE) pretest probability (PTP) assessment and algorithm. CTPA = computed tomographic pulmonary angiography; DUS = duplex ultrasonography; V/Q = ventilation/perfusion.

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1) administrative health records for procedure codes for DUS, CTPA, and V̇/Q̇ scans conducted in the ED; 2) electronic laboratory information for all D-dimers ordered in the ED; and 3) paper PTP forms from the ED that accompanied the D-dimer samples to the laboratory. We merged the lists of patients and removed any duplicate entries. The electronic patient record (EPR) was reviewed for each included patient, and the reason for ordering the CT, V̇/Q̇, and DUS was abstracted by one author (S.I.) from the electronic requisitions, as well as other information available through the EPR. Imaging studies or D-dimers that were ordered for reasons other than to rule out VTE were excluded. For example, a chest CT scan ordered to investigate chest trauma and not to rule out PE and a D-dimer ordered for suspected disseminated intravascular coagulation and not to rule out VTE were excluded. Of the included patients, each imaging report was reviewed and adjudicated into three categories: positive for VTE, negative for VTE, or nondiagnostic for VTE based on the predefined criteria listed in Table 1 that were established by three of the authors (S.I., R.S., W.G.) and adjudicated by one author (S.I.). Each PTP form was reviewed by one nonblinded author (S.I.) and separated into low-probability and non–low-probability forms. Three percent of the forms were illegible and could not be assigned into any category.

The age, sex, and proportion of patients who were admitted in each time frame studied were compared using *t*-tests and chi-square tests, respectively, depending on the variable, to ensure that there were no systematic differences from 1 year to the next in the demographics or severity of illness of the populations that were seen in our ED. The primary outcome was the total number of imaging tests for VTE performed over each of the two consecutive periods. Based on previous studies, we hypothesized that routine use of the algorithm would reduce the use of imaging tests by at least 20%.[5,6] Secondary outcomes were the proportion of patients with confirmed VTE (DVT or PE) after adjudication of the imaging based on the criteria listed in Table 1. Proportions of imaging tests and confirmed DVT, PE, and total VTE in each period were compared using the chi-square test for two independent proportions, and 95% confidence intervals (CIs) were calculated for all proportions.

RESULTS

During the prealgorithm period, there were 41,193 visits to our ED (the preintervention cohort). During

Table 1. Predefined adjudication criteria for confirmed venous thromboembolic disease

Imaging modality	Adjudicated result	Imaging result
Duplex ultrasonography	VTE not present	Negative
	VTE present	Positive proximal
		Positive calf
	Nondiagnostic	Nondiagnostic
Computed tomographic pulmonary angiography	VTE not present	Technically adequate and no PE
	VTE present	Positive for segmental or more proximal PE
	Nondiagnostic	''Positive'' for subsegmental PE
		Technically inadequate
Ventilation/perfusion scans	VTE not present	Normal
		Very low probability
	VTE present	High probability
		Segmental or greater mismatch
	Nondiagnostic	Matched defect
		Low probability
		Intermediate probability
		Intermediate–high probability
		Indeterminate

PE = pulmonary embolism; VTE = venous thromboembolism.

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the postalgorithm period, there were 40,680 visits (the postintervention cohort). There was no significant difference in the age (60 years v. 58 years), proportion of females (61% v. 58%), or patients who were subsequently admitted (25% v. 26%) between the pre- and postintervention cohorts.

The electronic health record search for procedure codes for DUS, CTPA, and V̇/Q̇ scans for the pre- and postintervention periods identified 3,033 codes over the 2-year period. The number of D-dimers ordered through laboratory information services during the same time was 628, and the number of PTP forms completed in the ED was 428. After merging the lists, duplicate entries were removed, resulting in 3,499 unique ED visits (Figure 3), and for each an electronic chart review was undertaken. Of 3,499 visits, 1,676 were excluded because imaging tests were ordered for a purpose other than for ruling out VTE, and 38 were excluded because they represented multiple visits for the same VTE episode. Thus, 1,785 ED visits for suspected VTE in the pre- and postintervention cohorts were included in the analysis, of which 789 (44%) were in the preintervention phase and 996 (56%) were in the postintervention phase.

The proportion of ED visits associated with investigation for VTE in the postintervention cohort was higher (2.4%, 95% CI 2.3–2.6) than in the preintervention cohort (1.9%; 95% CI 1.8–2.1; $p < 0.001$). There was no significant change in the proportion of VTE imaging tests (DUS, CTPA, and V̇/Q̇ scans) ordered

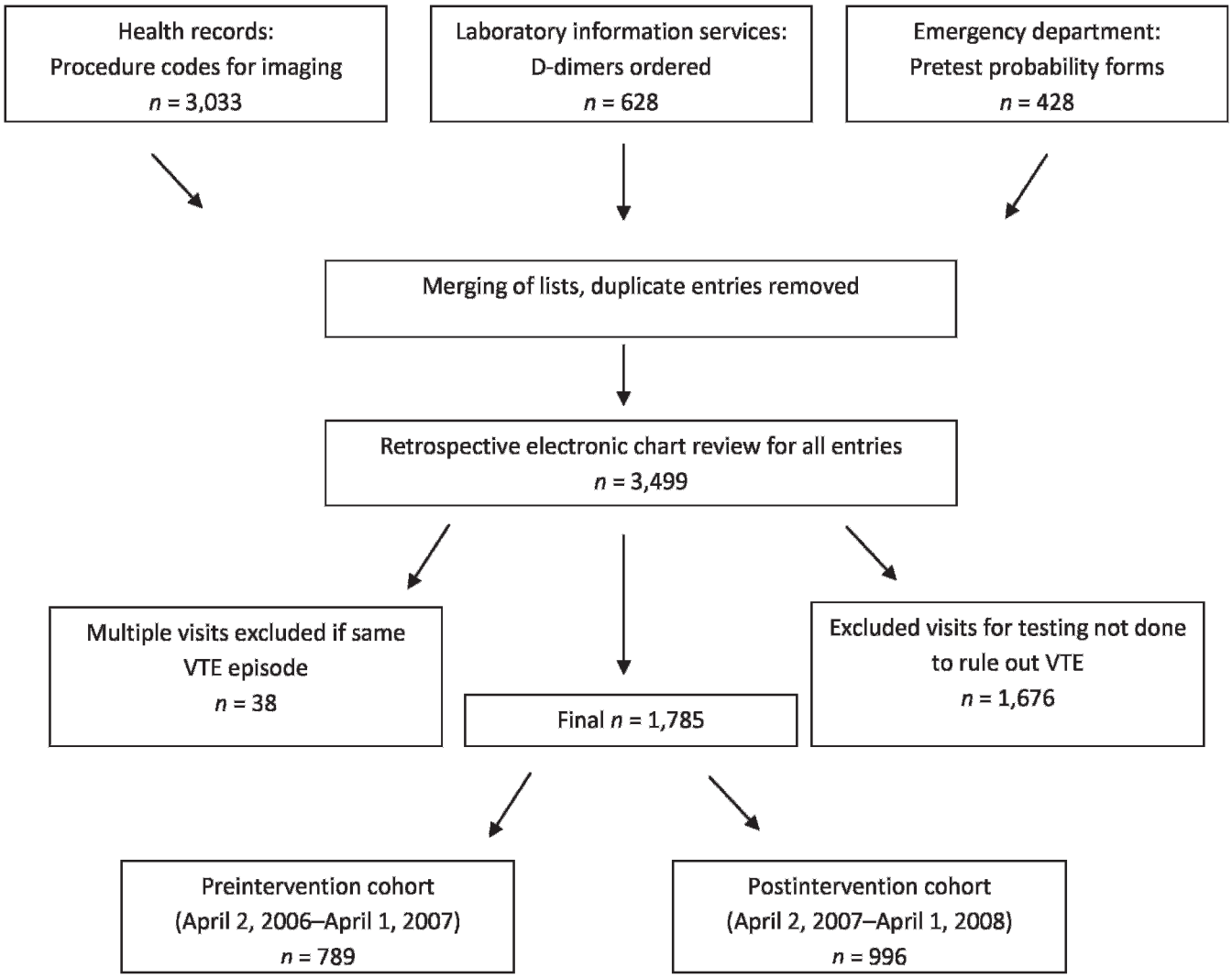

Figure 3. Methods and results. VTE = venous thromboembolism.

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Table 2. DUS in the pre- and postintervention cohorts

DUS, *n* (%; 95% CI)	Preintervention cohort	Postintervention cohort
Total	491	447
Negative	424/491 (86.4; 83.0–89.1)	376/447 (84.1; 80.4–87.2)
Positive (proximal)	53/491 (10.8; 8.3–13.8)	62/447 (13.9; 11.0–17.4)
Positive (calf)	10/491 (2.0; 1.1–3.7)	8/447 (1.8; 0.9–3.5)
Nondiagnostic	4/491 (0.81; 0.03–0.21)	1/447 (0.22; 0.04–1.25)

DUS = duplex ultrasonography.

during all ED visits between the preintervention and postintervention cohorts, respectively (2 % v. 1.9%; $p = 0.53$) (Table 2, Table 3, and Table 4).

The proportion of patients with suspected VTE in whom the diagnosis was confirmed on imaging decreased overall in the postintervention cohort compared to the preintervention cohort (difference [−]: 3.8%; 95% CI 0.8–6.9; Table 5). This was primarily due to a reduction in confirmed PE postintervention (3.8%; 95% CI 2.8–5.2) versus preintervention (6.8%; 95% CI 5.1–8.5) rather than DVT, which was not significantly different (Table 5).

Of the 449 D-dimers ordered in the postintervention cohort, 428 (95%) were accompanied by a PTP form. Ninety-five percent (406 of 428) of the D-dimer requests were accompanied by forms categorized as low probability, with 2% (9 of 428) being non–low probability and 3% (13 of 428) being illegible. Only 2% (5 of 214) of patients categorized as low PTP and negative D-dimer had imaging for VTE, and only 6% (12 of 214) of patients with positive D-dimers for VTE did not have further imaging, suggesting that physicians were compliant with the diagnostic algorithm in more than 90% of patients. Fifty percent (214 of 428) of visits assessed as low PTP had a negative D-dimer.

DISCUSSION

The results of our study show that working with the ED and the laboratory to mandate the use of a clinical, standardized PTP assessment prior to the use of D-dimer testing is feasible, as demonstrated by the high degree of compliance with the standardized algorithm. This is in contrast to a recent report in which published guidelines were not followed stringently, with 14% of ED patients with suspected VTE and a negative D-dimer undergoing imaging and 48% with a positive D-dimer not undergoing further imaging.[13] Examination of ED practice patterns at other sites has shown that fewer than 25% of physicians use a published prediction rule when investigating patients with suspected VTE.[14] In a retrospective review of ED patients with suspected PE, 64% of cases had no documentation of any PTP assessment.[15] Therefore, the ability to use the D-dimer assay appropriately by "mandating" a PTP assessment prior to analyzing the sample was an accomplishment.

Despite this, we were unable to demonstrate a reduction in diagnostic imaging for VTE. This finding may have been due to the following factors. First, easy access to the D-dimer assay in the context of this algorithm may have led to a lower threshold for

Table 3. CTPA in the pre- and postintervention cohorts

CTPA, *n* (%; 95% CI)	Preintervention cohort	Postintervention cohort
Total	255	273
Normal	185/255 (72.5; 66.8–77.7)	205/273 (75.1; 69.6–79.9)
Positive	47/255 (18.4; 14.1–23.7)	35/273 (12.8; 9.4–17.3)
Nondiagnostic	23/255 (9.0; 6.1–13.2)	33/273 (12.1; 8.7–16.5)

CTPA = computed tomographic pulmonary angiography.

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Table 4. $\dot{V}/\dot{Q}$ scans in the pre- and postintervention cohorts

V/Q scan, *n* (%; 95% CI)	Preintervention cohort	Postintervention cohort
Total	72	63
Normal	46/72 (63.9; 52.4–74.0)	37/63 (58.7; 46.4–70.0)
High probability	4/72 (5.6; 2.2–13.4)	2/63 (3.2; 0.09–10.9)
Nondiagnostic	22/72 (30.6; 21.1–42.0)	24/63 (38.1; 27.1–50.5)

$\dot{V}/\dot{Q}$ = ventilation/perfusion.

considering VTE as a diagnosis and an increase in the number of patients screened for this condition. In our study, a greater proportion of ED visits in the postintervention period had an investigation for VTE than in the preintervention cohort. Yet the increased proportion of patients investigated for VTE did not result in an increase proportion of confirmed VTE cases. Similar results have been seen in the literature with the introduction of D-dimer in the absence of guidelines,[9–12,16] in which two studies demonstrated a decreased prevalence of confirmed VTE.[9,12] One study that found an increase in the number of confirmed VTE with the introduction of D-dimer found no change in recurrent VTE or in mortality, raising the question whether the additional episodes of VTE found in this manner were clinically significant.[11]

A second factor is that subsequent to the completion of our study, an external quality assessment survey by Quality Management Program-Laboratory Services, the Province of Ontario's external quality assessment agency for laboratories, found that the D-dimer assay we were using had a higher false positive rate in a normal, volunteer population compared to other assays in the same population. This may have impacted our study, in which 47% of the ED visits in the postintervention cohort that were assigned a low PTP had a positive D-dimer. This could have contributed to an increase in imaging without a concomitant increase in confirmed VTE. This underscores an important real-life challenge when using the D-dimer for investigation of VTE, which is establishing a valid, local cutoff value for VTE exclusion. Establishing our local cutoff value for D-dimer rather than using the manufacturer cutoff would have been important in optimizing the use of the D-dimer assay for VTE exclusion. Yet conducting such a validation study was not feasible for our laboratory and is generally not feasible outside of the research setting. It requires follow-up of patients for 3 months after being managed with a PTP plus D-dimer strategy to document the incidence of recurrent VTE.

Aside from the challenges related to establishing and validating a universal threshold, recent derivation and validation cohorts have shown that using an age-dependent D-dimer cutoff increased the proportion of patients over 50 years old in whom PE could safely be excluded.[17] In our cohort with a mean age of 58 years, an age-dependent cutoff may have increased the number of low-probability patients in whom VTE could have been ruled out.

In our study, the proportion of confirmed PE decreased, whereas DVT was unchanged. This finding is seen throughout the literature.[18,19] One possible explanation is that there is a relative overinvestigation of PE in patients compared to DVT because although symptoms for both are nonspecific, the case fatality associated with PE is higher.

Table 5. Proportion of confirmed VTE

	Preintervention cohort	Postintervention cohort
Confirmed VTE, *n* (%; 95% CI)	111/789 (14.1; 11.4–16.1)	102/996 (10.2; 8.5–12.3)
Confirmed DVT, *n* (%; 95% CI)	57/789 (7.2; 5.4–8.9)	64/996 (6.4; 5.1-8.1)
Confirmed PE, *n* (%; 95% CI)	54/789 (6.8; 5.1–8.5)	38/996 (3.8; 2.8–5.2)

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

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There are other limitations to our study. Its retrospective nature does not allow us to assess the true clinical threshold at which VTE was suspected that triggered the completion of the PTP assessment. It is also possible that the PTP form may have been inaccurately filled out simply to gain access to the D-dimer test. It is unlikely that we missed many cases of suspected VTE because we collected data from three sources and our search strategy was overinclusive (all procedures codes and D-dimer results during that time were reviewed). Patients who were too hemodynamically unstable to have VTE investigation done would have been missed; however, the proportion of patients presenting in this manner is low, and PTP plus D-dimer testing has not been validated for use in critically ill patients.

CONCLUSION

We showed that a quality improvement initiative that mandated the use of a standardized diagnostic PTP algorithm prior to ordering D-dimer testing to rule out VTE was feasible. Despite this, use of the algorithm did not reduce imaging for VTE.

Competing interests: Rita Selby has received research support from Boehringer Ingelheim and Pfizer and honoraria from Boehringer Ingelheim, Bayer, and Sanofi Aventis. William Geerts received research support from Sanofi-Aventis, Pfizer, and Bayer Healthcare and honoraria from AstraZeneca, Calea, Eisai, Oryx Pharma, Pfizer, and Sanofi-Aventis and has worked as a consultant for AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Covidien, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Leo Pharma, Merck KGaA, Pfizer, Roche, and Sanofi Aventis.

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