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The diagnostic and therapeutic management of pulmonary embolism

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CHAPTER 5

Variable D-dimer thresholds for
diagnosis of clinically suspected acute
pulmonary embolism

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ABSTRACT

Background

Computed tomography pulmonary angiography (CTPA) is frequently requested using diagnostic algorithms for suspected pulmonary embolism (PE). For suspected deep vein thrombosis, it was recently shown that doubling the D-dimer threshold in patients with low pretest probability safely decreased the number of ultrasonograms. We evaluated the safety and efficiency of a similar strategy in patients with suspected PE.

Methods

We performed a post-hoc analysis of 2213 consecutive patients of two cohort studies with suspected PE who were managed according to current standards: PE ruled out in case of unlikely probability (Wells rule ≤ 4 points) and a D-dimer level $< 0.5 \mu\text{g/mL}$. CTPA was performed in all other cases. All patients were followed for 3 months. We calculated 3-month venous thromboembolism (VTE) incidence and the number of required CTPAs for selective D-dimer thresholds in patients with low clinical probability (< 2 points, D-dimer threshold $< 1.0 \mu\text{g/mL}$) and intermediate probability (2–6 points, D-dimer threshold $< 0.5 \mu\text{g/mL}$).

Results

Using standard management, PE could be excluded without CTPA in 26% of patients, with a 3-month VTE incidence of 0.88% (95% confidence interval [CI] 0.29–2.1%). Using selective D-dimer thresholds, PE could be excluded without CTPA in 36% of patients, with a 3-month VTE incidence of 2.1% (95% CI 1.2–3.4%) in patients managed without CTPA, an increase of 1.2 percentage points (95% CI -0.3 to 2.2).

Conclusions

Applying selective D-dimer thresholds reduces the need for CTPA by 11 percentage points but is associated with an increased failure rate. Prospective studies should evaluate the safety and net clinical benefit of this approach.

INTRODUCTION

The preferred diagnostic algorithm for patients with suspected acute pulmonary embolism (PE) combines sequential testing with a clinical decision rule (CDR), categorizing patients into either unlikely or likely pretest clinical probability, followed by D-dimer testing and computed tomography pulmonary angiography (CTPA). This algorithm has been demonstrated to be safe and efficient with a 3-month venous thromboembolism (VTE) incidence < 2% [1]. Importantly, this diagnostic strategy obviates the need for CTPA in 20–30% of all referred patients and allows a fast and effective management decision in 98% of cases [1, 2]. Nonetheless, the low specificity of both D-dimer tests and CDR leads to a high frequency of false-positive results, in turn leading to a high number of 70–80% negative CTPAs [2, 3]. Since CTPA is associated with long-term radiation complications, allergic reactions to iodinated contrast material, contrast-induced nephropathy, and higher health care costs, one of the major challenges in the diagnostic workup of patients with suspected PE is to safely diminish the number of CT scans [4–6].

Several attempts have been made to accomplish a higher specificity of the D-dimer test for the diagnosis of acute PE. Previous studies that attempted to improve D-dimer specificity by increment of the D-dimer or CDR score cutoff levels led to increases in 3-month VTE incidence [7, 8]. For example, increasing the threshold of the CDR from 4 to 5 points resulted in a 3-month VTE incidence of 1.5% (95% confidence interval [CI] 0.6–3.0%) instead of 0.9% (95% CI 0.3–2.4%) and only increasing the D-dimer threshold from ≤ 0.5 $\mu\text{g/mL}$ to ≤ 0.6 $\mu\text{g/mL}$ resulted in a 3-month VTE incidence of 2.2% (95 CI 1.1–4.0%) [8]. The introduction of an age-dependent D-dimer threshold from < 0.5 $\mu\text{g/mL}$ to patient's age $\times 10$ ng/mL (for patients aged > 50) led to a decrease in the number of performed CT scans of 6 percentage points in a post-hoc analysis with 3-month VTE incidence of 0.2% (95% CI 0–1.0%) [9]. The safety of this strategy is currently being evaluated prospectively. However, no previous study investigated variable D-dimer thresholds dependent on pretest probability in PE-suspected patients.

A recent study reintroduced the three pretest probability categories, instead of two categories, of the Wells decision rule in patients with suspected deep venous thrombosis (DVT) to evaluate whether a higher D-dimer cutoff level (< 1.0 $\mu\text{g/mL}$ instead of < 0.5 $\mu\text{g/mL}$) is safe in the lowest pretest probability category [10]. This strategy reduced the proportion of required ultrasonography by 7.6 percentage points without a decrease in the negative predictive value (NPV). This would be of particular interest for patients with suspected PE, since it has been estimated that nearly one-third of all CTPAs are performed in patients with a D-dimer level < 1.0 $\mu\text{g/mL}$ [11].

Therefore, we evaluated the safety and efficiency of a comparable strategy, an algorithm with three different pretest probability categories and an increased D-dimer threshold of 1.0 $\mu\text{g/mL}$ in patients with a low pretest probability. We will compare the

3-month VTE incidence rate and the required number of CTPAs of this strategy to the current standard algorithm with a two-level Wells rule outcome and a fixed 0.5 µg/mL D-dimer threshold for patients with a 'PE unlikely' risk score.

METHODS

Patients

Data were obtained from two previously published multicenter prospective management studies performed in the Netherlands in patients with suspected PE [2, 3]. Both inpatients and outpatients with suspected PE were included. Exclusion criteria were treatment with therapeutic doses of unfractionated or low-molecular-weight heparin for > 24 hours, treatment with vitamin K antagonists, life expectancy < 3 months, pregnancy, geographic inaccessibility precluding follow-up, age < 18 years, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance < 30 mL/min), logistic reasons (e.g. unavailability of CT, patient too ill to undergo CT scanning), and hemodynamic instability. In the Prometheus study, previous PE also was an exclusion criterion. In all patients, the Wells rule was calculated [12]. The Christopher Study was a prospective cohort study conducted from November 2002 through December 2004 to evaluate a diagnostic algorithm consisting of sequential application of a clinical decision rule, D-dimer testing, and a CT scan within 24 hours of presentation [2]. According to the study protocol, D-dimer tests were performed only in case of an unlikely clinical probability assessed with use of the Wells rule. Even so, in 5 of 12 participating hospitals, D-dimer levels were also measured post-hoc in patients with a likely clinical probability for scientific purposes. Only patients from these hospitals (1614 of a total of 3306 patients) were included in the present analysis. The Prometheus study, conducted from July 2008 through November 2009, aimed to compare four clinical decision rules for suspected acute PE, including the Wells rule, using a computerized scoring system [3]. By protocol, D-dimer levels were assessed in all patients. In both studies, PE was ruled out in patients with an unlikely clinical probability in combination with a normal D-dimer test. In case of either a likely clinical probability or an elevated D-dimer level, patients were referred for CTPA and managed according to the CTPA result. All patients provided informed consent, and both studies were approved by the institutional review boards of all participating hospitals. Among the study centers, different high-sensitivity D-dimer assays were used: VIDAS D-Dimer Assay (bioMérieux, Marcy-l'Étoile, France), Tina-Quant Assay (Roche Diagnostica, Mannheim, Germany), STA Liatest D-Di (Diagnostica Stago, Asnières-sur-Seine, France), or Innovance D-Dimer (Siemens, Marburg, Germany).

Outcome and follow-up

All patients were followed for 3 months to evaluate the occurrence of symptomatic VTE (i.e. PE and/or DVT). An independent adjudication committee evaluated all episodes of suspected VTE and deaths. Deaths were classified as caused by PE in case of confirmation by autopsy, in case of an objective test positive for PE before death, or if PE could not be confidentially excluded as the cause of death. In case of clinically suspected VTE, an objective clinical test was performed (i.e. compression ultrasound for suspected DVT and a ventilation-perfusion scintigraphy or CTPA for suspected PE). Primary outcomes of the current analysis were the objective diagnosis of symptomatic DVT or PE in the 3-month period following study inclusion.

Standard diagnostic algorithm

Patients with a Wells score ≤ 4 points were categorized as 'PE unlikely', and patients with a Wells score > 4 points as 'PE likely'. In patients with a 'PE unlikely' score, a D-dimer test was indicated. In patients with a D-dimer level $< 0.5 \mu\text{g/mL}$, a PE was excluded without further testing. In patients with a D-dimer level $\geq 0.5 \mu\text{g/mL}$ or a 'PE likely' risk score, CTPA was indicated [1, 2].

Study algorithm

Patients with a Wells score < 2 points were categorized as low risk, patients with a Wells score of 2–6 points as moderate risk, and patients with a Wells score > 6 points as high risk. In patients with a lowrisk score, we evaluated an increased D-dimer threshold of $< 1.0 \mu\text{g/mL}$, while the D-dimer threshold in patients with a moderaterisk score remained at $< 0.5 \mu\text{g/mL}$. In patients with a D-dimer level equal to or above the specific threshold and in patients with a highrisk score, CTPA was indicated. In addition, we evaluated D-dimer thresholds between $0.5 \mu\text{g/mL}$ and $1.0 \mu\text{g/mL}$ with increments of $0.1 \mu\text{g/mL}$ in patients with a lowrisk category, while the threshold in patients with a moderaterisk score remained at $< 0.5 \mu\text{g/mL}$. Finally, we performed the analysis for hospitalized patients and outpatients separately.

Statistics

For each predefined pretest probability/D-dimer threshold scenario, the diagnostic failure rates, defined as the 3-month VTE incidence, were calculated in patients managed without CTPA and in all patients in whom a PE was excluded at baseline (including occurrences after a negative CTPA), with exact binomial 95% CIs. The difference of the 3-month VTE incidence between the standard algorithm and the study algorithm were assessed with use of 95% CIs. The number of CTPAs performed was calculated. The sensitivity, specificity, NPV, and positive predictive value (PPV) for both algorithms were calculated. For this calculation, we defined a positive test result as either a 'PE likely' or

high-risk Wells score or a D-dimer level equal to or above the specific D-dimer threshold. A diagnosis of PE was defined as either PE at baseline or DVT or PE during 3-month follow-up.

RESULTS

Of 2421 eligible patients, 159 were excluded because of missing D-dimer results, 3 because individual items of the Wells score were missing, and 46 because of treatment with anticoagulants for reasons other than VTE during follow-up, leaving a total of 2213 patients available for the current analysis (**Table 1**). Mean age was 53 years, and 57% of patients were female. The overall prevalence of PE was 23% (488 patients diagnosed with PE at baseline and 13 in the 3-month follow-up period). The mortality attributable to PE was 1.0% (5 of 488, 95% CI 0.3–2.4%) in patients diagnosed with PE at baseline and 15.4% (2 of 13, 95% CI 1.9–45.5%) in those who were diagnosed with PE during the follow-up period after a PE was excluded at baseline. Of these two patients, one had a CDR risk score of 4.5 points and a D-dimer level of 2400 µg/mL and the other patient had a CDR risk score of 5.5 points and a D-dimer level of 449 µg/mL. Based on these results, both patients were subjected to CTPA using the standard algorithm, with a false-

Table 1. Baseline characteristics of the study population (n = 2213).

Characteristics	Total population (n=2213)	Dichotomised CDR outcome		Original three pre-test probability categories		
		Unlikely (n=1517)	Likely (n=696)	Low (n=755)	Moderate (n=1347)	High (n=111)
Age in years	53 (SD 18)	52 (SD 18)	56 (SD 18)	51 (SD 18)	54 (SD 18)	58 (SD 16)
Female sex (n, %)	1259 (57%)	868 (57%)	391 (56%)	444 (59%)	750 (56%)	65 (59%)
Estrogen use (n, % of females)	260 (21%)	194 (22%)	66 (17%)	94 (21%)	155 (21%)	11 (17%)
Immobilization > 3 days or surgery (n, %)	480 (22%)	140 (9.2%)	340 (49%)	72 (9.5%)	331 (25%)	77 (69%)
History of VTE (n, %)	232 (10%)	90 (5.9%)	142 (20%)	62 (8.2%)	139 (10%)	31 (28%)
COPD (n, %)	220 (9.9%)	152 (10%)	68 (10%)	78 (10%)	133 (9.9%)	9 (8.1%)
Heart failure (n, %)	167 (7.5%)	115 (7.6%)	52 (7.5%)	61 (8.1%)	98 (7.3%)	8 (7.2%)
Malignancy (n, %)	375 (17%)	212 (14%)	163 (23%)	76 (10%)	247 (18%)	52 (47%)
Outpatients (n, %)	1729 (78%)	1267 (84%)	462 (66%)	646 (86%)	1013 (75%)	70 (63%)
PE at baseline (n, %)	488 (22%)	216 (14%)	272 (39%)	53 (7.0%)	371 (28%)	64 (58%)
Median D-dimer result (IQR) (µg/mL)	1.0 (0.40-2.3)	0.70 (0.30-1.7)	1.8 (0.81-4.0)	0.56 (0.28-1.2)	1.2 (0.51-2.7)	3.1 (1.3-5.7)

Note: CDR: clinical decision rule; SD: standard deviation; VTE: venous thromboembolism; COPD: chronic obstructive pulmonary disease; PE: pulmonary embolism; IQR: interquartile range.

negative result. However, when the study algorithm would have been applied, this CTPA would have been withheld in the latter patient. **Table 1** additionally depicts the baseline characteristics for all different risk categories by the Wells rule. VTE risk factors, including previous VTE, recent immobilization or surgery, and malignancy, were more prevalent in categories with a higher pretest probability. The median D-dimer levels were higher in patients with a higher pretest probability. Table S1 (available at [http://onlinelibrary.wiley.com/journal/10.1111/\(ISSN\)1538-7836/](http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1538-7836/)) provides baseline characteristics of the patients included in the original studies.

With use of the dichotomized algorithm, 69% (1517 of 2213) of patients had a 'PE unlikely' pretest probability and 31% (696 of 2213) had a 'PE likely' pretest probability, with a PE incidence at baseline of 14% and 39%, respectively. When applying the original three-level CDR risk score, 34% (755 of 2213) were categorized as low, 61% (1347 of 2213) as moderate, and 5% (111 of 2213) as high clinical probability. The PE incidences at baseline in these categories were 7.0%, 28%, and 58%, respectively.

In the standard algorithm, using the dichotomized Wells rule combined with a D-dimer threshold of < 0.5 $\mu\text{g/mL}$, additional testing with CTPA was needed in 74.4% (1646 of 2213) of the patients, of whom 30% showed PE. The 3-month VTE incidence in patients in whom PE was excluded with CDR and D-dimer was 0.88% (5 of 567, 95% CI 0.29–2.1%), and it was 0.93% (16 of 1717, 95% CI 0.53–1.5%) in all patients in whom a PE was excluded at baseline (**Table 2**). The sensitivity of the algorithm was 99.0% (95% CI 97.7–99.7%), with a specificity of 32.8% (95% CI 30.6–35.1%), NPV of 99.1% (95% CI 98.0–99.7%), and PPV of 30.1% (95% CI 27.9–32.4%), and the area under the receiver operating characteristic (ROC) curve was 0.66 (95% CI 0.64–0.68). Of the five patients with a false-negative algorithm result, four patients had a PE (three had peripherally

Table 2. Influence of varying D-dimer cut-offs in different CDR risk categories.

Number of CDR-risk groups	D-dimer cut-off level in unlikely risk category ($\mu\text{g/mL}$)	D-dimer cut-off level in low risk category ($\mu\text{g/mL}$)	D-dimer cut-off level in moderate risk category ($\mu\text{g/mL}$)	3-month VTE recurrence rate			Percentage CTPA performed in total population	Percentage CTPA positive for PE
				In patients managed without CTPA	In patients without a diagnosis of PE at baseline			
				n	% (95% CI)	% (95% CI)		
2	<0.5	-	-	5	0.88 (0.29-2.1)	0.93 (0.53-1.5)	74.4%	30%
3	-	<0.5	<0.5	10	1.5 (0.74-2.8)	1.2 (0.71-1.8)	70.8%	31%
3	-	<1.0	<0.5	17	2.1 (1.2-3.4)	1.5 (1.0-2.3)	63.7%	34%

Note: CDR: clinical decision rule; VTE: venous thromboembolism; CTPA: computed tomography pulmonary angiography.

located PE, in one patient the exact location was not specified) and one patient had a DVT. None of these patients died during follow-up.

Using the three Wells categories in combination with a D-dimer threshold in the low-risk and the moderate-risk category of $< 0.5 \mu\text{g/mL}$, CTPA was needed in 70.8% (1566 of 2213) of the patients, of whom 31% were positive for PE. The 3-month VTE incidence in patients in whom PE was excluded based on a low CDR risk score or a moderate-risk score and D-dimer $< 0.5 \mu\text{g/mL}$ was 1 of 346 and 9 of 301, respectively, resulting in a 3-month VTE recurrence rate in patients managed without CTPA of 1.5% (10 of 647, 95% CI 0.74–2.8%). The 3-month VTE recurrence rate in all patients in whom PE was excluded at baseline was 1.2% (20 of 1722, 95% CI 0.71–1.8%). The sensitivity of the algorithm was 98.0% (95% CI 96.4–99.0%), the specificity was 37.2% (95% CI 34.9–39.6%), the NPV was 98.5% (95% CI 97.2–99.3%), the PPV was 31.4% (95% CI 29.1–33.7%), and the area under the ROC curve was 0.68 (95% CI 0.65–0.70).

When raising the D-dimer cutoff level to $1.0 \mu\text{g/mL}$, the number of needed CT scans in the total cohort decreased from 74.4% (1646 of 2213) to 63.7% (1409 of 2213) (difference with the current standard algorithm of 10.7 percentage points [95% CI 8.0–13.4]). The 3-month VTE incidence was 8 of 503 in patients with a low-risk CDR score and a negative D-dimer threshold and 9 of 301 in patients with a moderate-risk CDR score and a negative D-dimer threshold, resulting in a 3-month VTE incidence of 2.1% (17 of 804, 95% CI 1.2–3.4%). The diagnostic failure rate in all patients in whom PE was excluded at baseline was 1.5% (27 of 1729, 95% CI 1.0–2.3%). The differences with the standard algorithm were 1.2 percentage points (95% CI -0.3 to 2.2) in patients managed without CTPA and 0.57 percentage point (95% CI -0.2 to 1.3) in all patients in whom a PE was excluded at baseline (thus including patients with a CTPA negative for PE at baseline). Also, this scenario resulted in an increase of the specificity to 46.0% (95% CI 43.6–48.4%) and a decrease of the NPV to 97.9% (95% CI 96.6–98.8%). The sensitivity was 96.6% (95% CI 94.9–98.0%), the PPV was 34.4% (95% CI 31.9–36.9%), and the area under the ROC curve was 0.71 (95% CI 0.69–0.74). Of the additional 11 patients in whom PE was falsely excluded by applying the study algorithm, 6 patients had a subsegmental PE, 2 had a segmental PE, 2 patients had a central PE, and in 1 patient the exact localization was not specified.

Applying fixed D-dimer thresholds levels between 0.5 and $1.0 \mu\text{g/mL}$ (with increments of $0.1 \mu\text{g/mL}$) in the low-risk category while the D-dimer threshold remained at $< 0.5 \mu\text{g/mL}$ in the moderate-risk group did not result in more favorable diagnostic failure rates (data not shown). When analyzing outpatients only with the study algorithm, the 3-month VTE incidence rate was 1.9% (95% CI 1.0–3.1%) in patients managed without CTPA and 1.3% (95% CI 0.8–2.0%) in all patients in whom PE was excluded at baseline. The number of patients who were managed without CTPA increased from 31.4% to 43.2%, an increase of 11.8 percentage points (95% CI 8.5–15.0). When we performed the

same analysis in hospitalized patients only, the 3-month VTE incidence rates were 5.3% (95% CI 1.1–14.6%) and 2.6% (95% CI 1.2–4.8%), respectively. The number of patients managed without CTPA increased from 5.0% to 11.8%, an increase of 6.8 percentage points (95% CI 3.2–9.9).

DISCUSSION

We investigated the safety of applying variable D-dimer thresholds in patients with a low clinical probability, using the three-level original pretest probability Wells score in a large cohort of patients with a clinically suspected PE, in an attempt to reduce the number of CTPA. Our study has the following interesting findings.

In patients with suspected PE, the combination of a low-risk CDR score and a D-dimer threshold of 1.0 µg/mL or an intermediate-risk CDR score with a D-dimer threshold of 0.5 µg/mL decreases the necessity of CTPA by 11 percentage points. This comes at the cost of an increase in the 3-month VTE failure rate in patients managed without CTPA of 1.2 percentage points (95% CI –0.3 to 2.2) and 0.57 percentage point (95% CI –0.2 to 1.3) in all patients in whom a PE was excluded at baseline. Also, all other D-dimer threshold modifications between 0.5 µg/mL and 1.0 µg/mL that we studied resulted in a higher 3-month VTE incidence. We were unable to define a modification of the algorithm that did not result in this increase of the 3-month VTE incidence. This contrasts with the results of the recently published study in DVT-suspected patients by applying a comparable algorithm [10]. One explanation for this difference may be the three times higher disease prevalence (23%) in our study cohort compared with the DVT cohort (7.1%); this overall DVT prevalence was lower than the PE prevalence of 7.4% in our low-risk category alone. Based on the high 3-month incidence rates of the study algorithm in hospitalized patients, we concluded that this strategy is not safe for hospitalized patients. Therefore, it seems reasonable to include outpatients only in a prospective validation study.

Traditionally, a 3-month VTE incidence of 1.7% with an upper limit of the 95% CI of 2.7% serves as the gold standard for safety in prospective diagnostic PE studies, which is the 3-month VTE incidence after a negative pulmonary angiography [13]. Although the 3-month VTE incidence in this post-hoc analysis exceeds this safety margin in patients managed without CTPA, the safety margin was not exceeded in the total cohort (all patients without PE at baseline). However, due to the design of the study, we were unable to determine the clinical outcome of the additional missed diagnoses of PE by the selective D-dimer algorithm. Therefore, these 3-month VTE incidence rates have to be interpreted cautiously. Furthermore, some observations in previous studies might suggest that subsegmental PEs may be clinically less relevant and may not require treatment [14]. First, in a diagnostic study that compared a strategy involving ventilation-

perfusion lung scanning to a CTPA-based algorithm, an additional 5.0% of patients were diagnosed with PE at baseline after CTPA compared with ventilation-perfusion lung scanning. However, the 3-month VTE incidence in patients with normal tests was not different between the strategies [15]. Second, it is known that the introduction of CTPA is associated with a rising PE incidence with only a minimal decrease in PE-related mortality, suggesting overdiagnosis [16]. The fact that the majority of the PEs that would have been missed were subsegmentally located might support this hypothesis. Therefore, only a prospective study will be able to determine the true clinical implications of the selective D-dimer strategy.

When considering the potential of applying the selective D-dimer threshold strategy in clinical practice, both its safety and feasibility should be taken into account. For that matter, the somewhat higher complexity of patients management in busy emergency departments using altered D-dimer thresholds in three probability categories compared with one general D-dimer threshold in two probability categories should be balanced against its benefit (i.e. a large saving of CTPAs, which may increase its clinical acceptance). The advantages of a diagnostic algorithm with an 11-percentage-point lower number of necessary CTPAs would be a reduction in valuable time, costs, and complications associated with performing CTPA. These complications include radiation exposure, allergic reactions to iodinated contrast material, and contrast-induced nephropathy [4-6]. The radiation dose of a single CTPA ranges from 3 to 5 mSv, with an estimated risk of 150 excess cancer deaths per 1 million exposures to a single CTPA [17]. The incidence of contrast-induced nephropathy ranges between 6.5% and 19% depending on the studied population and the definition of contrast-induced nephropathy that is used [4, 18].

Strengths of this analysis are the inclusion of two large and accurately documented cohorts from previous prospective management studies and the assessment of the primary outcome by an independent adjudication committee. The fact that our study was a post-hoc analysis is the most important study limitation. By design, we were therefore unable to establish the clinical course of the patients with a false-negative outcome of the algorithm since they received anticoagulant treatment. Another limitation is a result of the design of the original management studies, in which not all patients underwent the reference standard at baseline, CTPA. The fact that not all patients in whom PE was excluded in the study algorithm based on a low or intermediate probability combined with a negative D-dimer test result underwent the same verification test (i.e. clinical follow-up or CTPA) may have introduced verification bias. Furthermore, the exclusion of patients in whom no D-dimer test was performed is a limitation.

In conclusion, raising D-dimer thresholds in different pretest probability categories results in a decrease in the number of required CTPAs and an increase in the failure rate of the chosen algorithm. Applying the original three-level Wells rule for PE with a D-dimer cutoff level of $< 1.0 \mu\text{g/mL}$ for patients with a low pretest probability for PE

and a cutoff level of $< 0.5 \mu\text{g/mL}$ for patients with an intermediate pretest probability for PE resulted in a 3-month VTE incidence of 2.1% in patients managed without CTPA and 1.5% in whom a PE was excluded at baseline. However, since the outcome of the undiagnosed PE patients is unknown in this post-hoc analysis, a prospective study is needed to evaluate the safety and net clinical benefit of this approach. Also, a formal cost-effectiveness analysis will aid in conclusively establishing whether changing the current standard diagnostic strategy will result in a more optimal diagnostic management of suspected PE.

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