ORIGINAL ARTICLE

Diagnosis of Pulmonary Embolism with D-Dimer Adjusted to Clinical Probability

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ABSTRACT

BACKGROUND

Retrospective analyses suggest that pulmonary embolism is ruled out by a D-dimer level of less than 1000 ng per milliliter in patients with a low clinical pretest probability (C-PTP) and by a D-dimer level of less than 500 ng per milliliter in patients with a moderate C-PTP.

METHODS

We performed a prospective study in which pulmonary embolism was considered to be ruled out without further testing in outpatients with a low C-PTP and a D-dimer level of less than 1000 ng per milliliter or with a moderate C-PTP and a D-dimer level of less than 500 ng per milliliter. All other patients underwent chest imaging (usually computed tomographic pulmonary angiography). If pulmonary embolism was not diagnosed, patients did not receive anticoagulant therapy. All patients were followed for 3 months to detect venous thromboembolism.

RESULTS

A total of 2017 patients were enrolled and evaluated, of whom 7.4% had pulmonary embolism on initial diagnostic testing. Of the 1325 patients who had a low C-PTP (1285 patients) or moderate C-PTP (40 patients) and a negative D-dimer test (i.e., <1000 or <500 ng per milliliter, respectively), none had venous thromboembolism during follow-up (95% confidence interval [CI], 0.00 to 0.29%). These included 315 patients who had a low C-PTP and a D-dimer level of 500 to 999 ng per milliliter (95% CI, 0.00 to 1.20%). Of all 1863 patients who did not receive a diagnosis of pulmonary embolism initially and did not receive anticoagulant therapy, 1 patient (0.05%; 95% CI, 0.01 to 0.30) had venous thromboembolism. Our diagnostic strategy resulted in the use of chest imaging in 34.3% of patients, whereas a strategy in which pulmonary embolism is considered to be ruled out with a low C-PTP and a D-dimer level of less than 500 ng per milliliter would result in the use of chest imaging in 51.9% (difference, –17.6 percentage points; 95% CI, –19.2 to –15.9).

CONCLUSIONS

A combination of a low C-PTP and a D-dimer level of less than 1000 ng per milliliter identified a group of patients at low risk for pulmonary embolism during follow-up. (Funded by the Canadian Institutes of Health Research and others; PEGeD ClinicalTrials.gov number, NCT02483442.)

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The primary goal of diagnostic testing for pulmonary embolism is to identify which patients should be treated with anticoagulant agents and which should not. The patients who should be treated are those who have pulmonary embolism that has a substantial risk of recurrence or progression.[1-4] The remaining patients, who are not expected to benefit from treatment, include those who do not have pulmonary embolism and those who have pulmonary embolism that is very unlikely to progress. Chest imaging with computed tomographic (CT) pulmonary angiography is the usual method of diagnostic imaging for pulmonary embolism. Chest imaging has high negative and high positive predictive values for pulmonary embolism, and it often identifies alternative diagnoses. It has the disadvantages of radiation exposure, contrast reactions, high cost, and the fact that it can be time-consuming to complete. Our premise is that the use of chest imaging should be avoided when possible. This is most often achieved by ruling out pulmonary embolism through a combination of clinical assessment and D-dimer testing.

Assessment of clinical pretest probability (C-PTP), usually through the use of clinical prediction rules such as the Wells score, can stratify a patient's probability of having pulmonary embolism into low, moderate, and high categories.[1,2,5] D-Dimer is formed when cross-linked fibrin is broken down; among patients who are suspected of having pulmonary embolism, blood D-dimer levels correlate with the probability of having pulmonary embolism.[6,7] D-Dimer tests are dichotomized as negative or positive, usually with the use of a threshold level of less than 500 ng per milliliter, which yields a test with high negative predictive value. It is now well established that pulmonary embolism can be considered to be ruled out if patients have a low C-PTP for pulmonary embolism and a D-dimer level of less than 500 ng per milliliter.[1-3,5,8] This combination of findings, however, occurs in only approximately 30% of outpatients.

There are two ways that it may be possible to increase the percentage of patients with suspected pulmonary embolism who can have pulmonary embolism ruled out with the use of C-PTP assessment and D-dimer testing: by increasing the D-dimer threshold level used to define a negative test or by using D-dimer testing to rule out pulmonary embolism in more than just patients with a low C-PTP. Preliminary findings suggest that pulmonary embolism is ruled out by a D-dimer level of less than 1000 ng per milliliter in patients with a low C-PTP and by a D-dimer level of less than 500 ng per milliliter in patients with a moderate C-PTP.[1,9-11] In the Pulmonary Embolism Graduated D-Dimer (PEGeD) study, we tested the strategy of ruling out pulmonary embolism in outpatients with a low C-PTP and a D-dimer level of less than 1000 ng per milliliter (i.e., twice the usual threshold used to rule out pulmonary embolism) and in those with a moderate C-PTP and a D-dimer level of less than 500 ng per milliliter.

METHODS

STUDY PATIENTS

Outpatients (e.g., in emergency departments or outpatient clinics) or inpatients (because only one inpatient was enrolled, we shall refer to the study population as outpatients) with symptoms or signs suggestive of pulmonary embolism were potentially eligible to be included in this prospective management study. Patients were excluded if they were younger than 18 years of age, had received full-dose anticoagulant therapy for 24 hours, had undergone major surgery in the past 21 days, had a D-dimer level that was known before the C-PTP was assessed, had undergone chest imaging contrary to the protocol (i.e., before the C-PTP was documented, or despite having a D-dimer level of <1000 ng per milliliter for a low C-PTP or <500 ng per milliliter for a moderate C-PTP), had undergone contrast-enhanced CT of the chest for another reason, had an ongoing need for anticoagulant therapy, had a life expectancy of less than 3 months, or were pregnant or geographically inaccessible for follow-up.

Patients were enrolled prospectively at university-based clinical centers in Canada. The study was approved by the research ethics boards at the participating institutions, and all patients provided informed consent. Depending on the preference of the research ethics board at the clinical center, patients either provided written consent before diagnostic testing or provided written or verbal consent within days after having undergone diagnostic testing that was con-

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sistent with the study protocol. The study was funded by the Canadian Institutes of Health Research. The funding body had no role in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit it for publication. The authors vouch for the accuracy and completeness of the data and for the adherence of the study to the protocol (available with the full text of this article at NEJM.org).

PATIENT ENROLLMENT AND CARE MANAGEMENT

At the time of enrollment, clinical centers registered patients with the use of a central Web-based system, which ensured that data from all enrolled patients were analyzed. Physicians used the seven-item Wells clinical prediction rule (scores range from 0 to 12.5, with higher scores indicating a higher probability of pulmonary embolism) to categorize the patient's C-PTP as low (Wells score, 0 to 4.0), moderate (4.5 to 6.0), or high (≥6.5) (Table 1).[1,2,5,12,13] They had access to a hard copy of the Wells prediction rule but did not receive individual training in its completion. Patients with a low or moderate C-PTP had D-dimer measured with the locally available assay (Table 1). We managed patients' care according to the PEGeD algorithm, which was as follows: patients with a low C-PTP and a D-dimer level of less than 1000 ng per milliliter or with a moderate C-PTP and a D-dimer level of less than 500 ng per milliliter underwent no further diagnostic testing for pulmonary embolism and did not receive anticoagulant therapy (Fig. 1). All other patients, including all patients with a high C-PTP, underwent chest imaging (CT pulmonary angiography or, at the physician's discretion, ventilation–perfusion lung scanning). If chest imaging showed pulmonary embolism, patients received anticoagulant therapy; otherwise, patients did not receive anticoagulant therapy.

FOLLOW-UP AND OUTCOMES

Study outcomes were assessed at 90 days after initial diagnostic testing, either over the telephone or in the clinic. In addition, at enrollment, study participants were instructed to urgently contact study personnel or to go to the emergency department if their initial symptoms did not improve or if new symptoms developed that were compatible with deep-vein thrombosis or pulmonary embolism. During follow-up, patients with symptoms that aroused suspicion for pulmonary embolism or deep-vein thrombosis underwent appropriate diagnostic imaging; D-dimer testing was discouraged (see the protocol).

The primary outcome was symptomatic, objectively verified venous thromboembolism, which included pulmonary embolism or deep-vein thrombosis. All outcome events were evaluated with the use of predefined criteria by a central adjudication committee whose members were unaware of the results of diagnostic testing at initial presentation and of whether patients had received anticoagulant therapy.

STATISTICAL ANALYSIS

The sample size was driven by the requirement that the percentage of patients with venous thromboembolism be estimated with high precision in the combined patients with a low or moderate C-PTP who have pulmonary embolism ruled out by D-dimer testing (expected to be 0.8%). With a one-sided alpha level of 5%, a sample of 1036 patients would give the study 90% power to rule out a percentage with venous thromboembolism of 2.0% and would yield an upper boundary of the 95% confidence interval of 1.5%. Assuming that this group is 52% of the total study population and adding 1.5% for possible losses to follow-up, we estimated that a sample of 2000 was required.

Outcome measures were summarized as point estimates, expressed as percentages, with 95% confidence intervals calculated with the use of the exact binomial distribution; confidence intervals for secondary outcomes were not adjusted for multiple comparisons. The primary analysis examined the incidence of venous thromboembolism during the 90-day follow-up period among the combined patients with a low or moderate C-PTP with negative D-dimer testing who did not receive anticoagulant therapy. The secondary analyses included the percentage of patients with venous thromboembolism in predefined subgroups (see the protocol), the number of bleeding events and deaths overall, and the percentage of patients who avoided undergoing chest imaging because they had a low C-PTP and a D-dimer level of 500 to 999 ng per milliliter or had a moderate C-PTP and a D-dimer level of less than 500 ng per milliliter. The Agresti–Min

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Table 1. Baseline Characteristics of the Patients and Initial Diagnostic Testing.*

Characteristic	All Patients (N=2017)	Low C-PTP (N=1752)	Moderate C-PTP (N=218)	High C-PTP (N=47)
Age — yr	52±18	52±17	54±19	57±14
Female sex — no. (%)	1335 (66)	1155 (66)	146 (67)	34 (72)
Weight — kg	81±23	80±23	87±28	85±26
Days of symptoms — median (range)	5 (0–365)	4 (0–365)	5 (0–108)	5 (0–101)
Components of the Wells score — no. (%)				
Clinically suspected DVT: 3 points	138 (7)	59 (3)	45 (21)	34 (72)
Alternative diagnosis is less likely than pulmonary embolism: 3 points	423 (21)	195 (11)	182 (83)	46 (98)
Heart rate >100 beats/min: 1.5 points	685 (34)	508 (29)	145 (67)	32 (68)
Immobilization or surgery in previous 4 wk: 1.5 points	149 (7)	84 (5)	42 (19)	23 (49)
History of VTE: 1.5 points	164 (8)	94 (5)	51 (23)	19 (40)
Hemoptysis: 1 point	93 (5)	81 (5)	7 (3)	5 (11)
Cancer or treatment for cancer within 6 mo: 1 point	187 (9)	142 (8)	27 (12)	18 (38)
Wells score	1.7±1.9	1.1±1.1	4.9±0.6	8.0±1.0
D-Dimer assay performed — no. (%)				
STA-Liatest		1250 (71)	147 (67)	NA
HemosIL HS 500		329 (19)	34 (16)	NA
Innovance		124 (7)	20 (9)	NA
Triage		31 (2)	10 (5)	NA
Other†		18 (1)	7 (3)	NA
Imaging performed for pulmonary embolism — no. (%)‡	691 (34)	465 (27)	179 (82)	47 (100)
CT pulmonary angiography	616 (31)	415 (24)	159 (73)	42 (89)
Ventilation–perfusion scanning	88 (4)	58 (3)	24 (11)	6 (13)
Pulmonary embolism diagnosed by initial testing — no. (%)	149 (7)	87 (5)	43 (20)	19 (40)

* Plus–minus values are means ±SD. A patient's clinical pretest probability (C-PTP) of pulmonary embolism was assessed with the use of the seven-item Wells score (scores range from 0 to 12.5, with higher scores indicating a higher probability of pulmonary embolism). A low C-PTP was defined as a Wells score of 0 to 4.0[1,2,5,12] (not 0 to 1.5, as was originally proposed for a low C-PTP; a score of 0 to 4.0 also corresponds to pulmonary embolism being "unlikely"),[13] a moderate C-PTP was defined as a Wells score of 4.5 to 6.0, and a high C-PTP was defined as a Wells score of 6.5 or higher. CT denotes computed tomography, DVT deep-vein thrombosis, NA not applicable, and VTE venous thromboembolism.

† Other D-dimer assays included HemosIL HS in 14 patients (the usual threshold level of 230 ng per milliliter D-dimer units was used in patients with a moderate C-PTP, and a level of 460 ng per milliliter D-dimer units was used in patients with a low C-PTP) and Roche Cardiac Reader in 7 patients. The assay type was not recorded for 4 patients.

‡ Patients could undergo both CT pulmonary angiography and ventilation–perfusion scanning.

method was used to obtain 95% confidence intervals for the paired difference in the percentage of patients who would undergo chest imaging and D-dimer testing with the PEGeD strategy as compared with other diagnostic strategies.[14] Data analyses were performed by biostatisticians using SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From December 2015 through May 2018, a total of 3133 patients were assessed by the clinical centers as meeting the inclusion criteria; of those, 941 met one or more exclusion criteria

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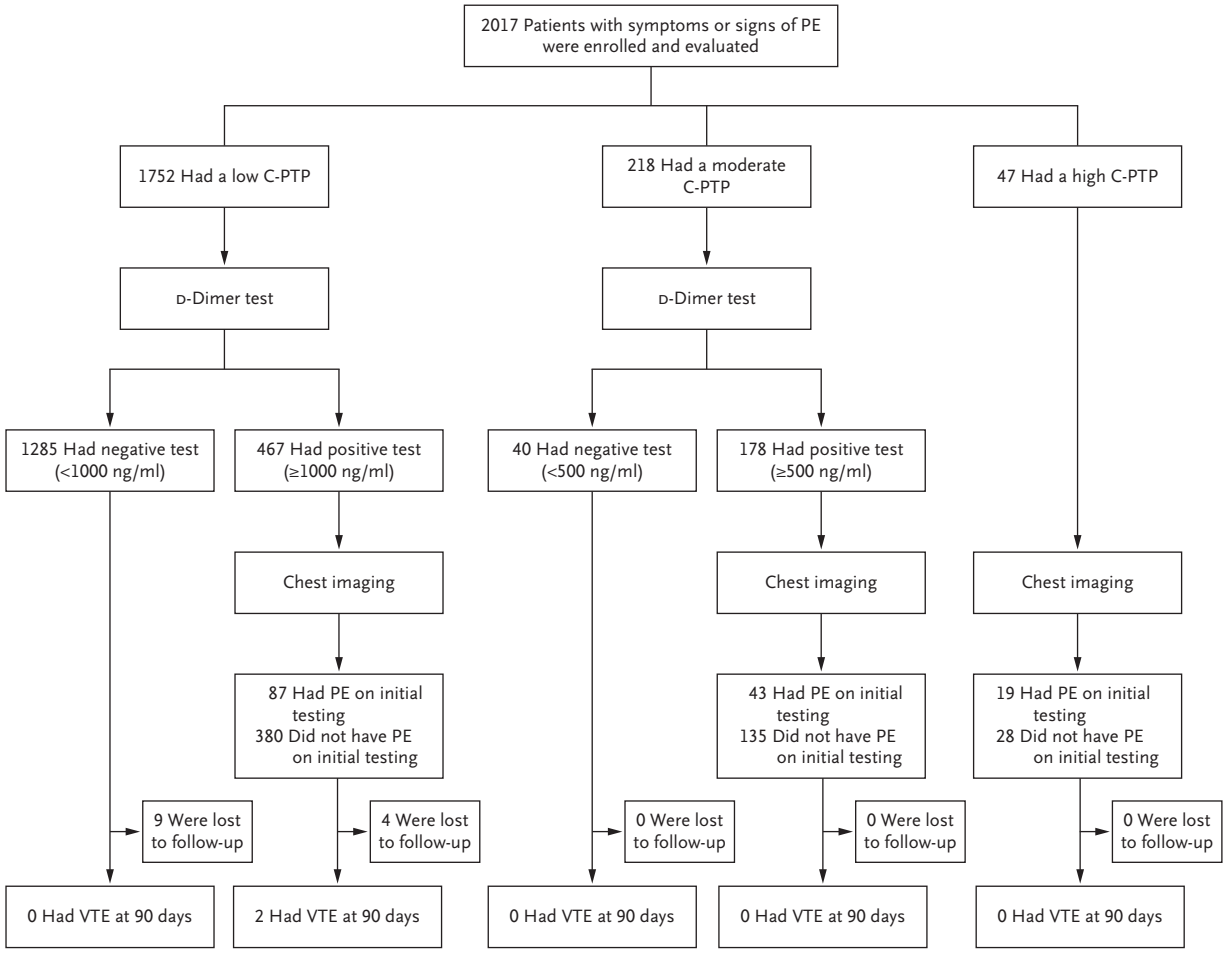

Figure 1. Patient Enrollment, Results of Initial Diagnostic Testing, and Cases of Venous Thromboembolism (VTE) during Follow-up.

A patient's clinical pretest probability (C-PTP) of pulmonary embolism (PE) was assessed with the use of the Wells score (range, 0 to 12.5, with higher scores indicating a higher probability of PE). A low C-PTP was defined as a Wells score of 0 to 4.0, a moderate C-PTP as a Wells score of 4.5 to 6.0, and a high C-PTP as a Wells score of 6.5 or higher. A total of 2 patients who had PE on initial testing did not receive anticoagulant therapy: 1 had a moderate C-PTP, and 1 had a high C-PTP (both had thrombocytopenia). A total of 5 patients who did not have PE on initial testing received anticoagulant therapy: 2 had a low C-PTP (1 had chronic PE and 1 underwent nondiagnostic computed tomographic [CT] pulmonary angiography and declined ventilation–perfusion scanning), 2 had a moderate C-PTP (1 had leg deep-vein thrombosis [DVT] with negative findings on CT pulmonary angiography, and 1 had arm DVT with negative findings on CT pulmonary angiography), and 1 had a high C-PTP (untreated leg DVT 5 months previously [prescription was lost] and negative findings on CT pulmonary angiography). Of the 4 patients with a low C-PTP and a positive D-dimer test who were lost to follow-up, none had PE on initial testing. In the entire study population, 2 patients (both with a low C-PTP and a positive D-dimer test) had VTE during follow-up: a DVT occurred in a patient who did not have PE on initial testing (negative CT and no anticoagulant therapy), and a recurrent PE occurred in a patient who had PE on initial testing (positive CT and anticoagulant therapy).

(Table S1 in the Supplementary Appendix, available at NEJM.org) and 136 did not provide consent, which resulted in the registration of 2056 patients. Shortly after registration and before any study outcomes were suspected, central data monitors identified that 39 of these patients did not meet major eligibility criteria, and they were not included in any analyses (Table S2). Therefore, data from 2017 patients (predominantly from emergency departments; only 1 was an inpatient) were analyzed.

The mean age of the patients was 52 years, and 66.2% were female (Table 1). A total of 86.9% of the patients had a low C-PTP, 10.8%

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Table 2. Venous Thromboembolism (VTE) after Initial Diagnostic Testing.*

Variable	Patients	VTE	Percentage of Patients (95% CI)
	number		
No pulmonary embolism on initial testing and no anticoagulant therapy	1863	1	0.05 (0.01–0.30)
Low or moderate C-PTP and negative D-dimer test	1325	0	0.00 (0.00–0.29)
Low C-PTP and D-dimer <1000 ng/ml	1285	0	0.00 (0.00–0.30)
Low C-PTP and D-dimer <500 ng/ml	970	0	0.00 (0.00–0.39)
Low C-PTP and D-dimer 500–999 ng/ml	315	0	0.00 (0.00–1.20)
Moderate C-PTP and D-dimer <500 ng/ml	40	0	0.00 (0.00–8.76)
Low or moderate C-PTP and positive D-dimer test	511	1	0.20 (0.03–1.10)
Low C-PTP and D-dimer ≥1000 ng/ml	378	1	0.26 (0.05–1.50)
Moderate C-PTP and D-dimer ≥500 ng/ml	133	0	0.00 (0.00–8.76)
High C-PTP	27	0	0.00 (0.00–12.5)
Pulmonary embolism on initial testing and anticoagulant therapy	147	1	0.68 (0.12–3.75)
Low C-PTP	87	1	1.15 (0.20–6.23)
Moderate C-PTP	42	0	0.00 (0.00–8.38)
High C-PTP	18	0	0.00 (0.00–18.6)
Pulmonary embolism on initial testing and no anticoagulant therapy†	2	0	
No pulmonary embolism on initial testing and anticoagulant therapy†	5	0	

* VTE includes proximal DVT and segmental or more proximal pulmonary embolism (no isolated distal DVT or subsegmental episodes of pulmonary embolism occurred during follow-up).
† For details on patients who did not receive anticoagulant therapy despite the presence of pulmonary embolism or who received anticoagulant therapy despite the absence of pulmonary embolism, see Table S5.

had a moderate C-PTP, and 2.3% had a high C-PTP. D-Dimer testing was performed predominantly with the STA-Liatest assay (70.9% of the tests). Despite negative D-dimer testing, 1 patient with a low C-PTP (ventilation–perfusion lung scanning) and 2 with a moderate C-PTP (CT pulmonary angiography) underwent chest imaging after enrollment; none had pulmonary embolism. At initial diagnostic testing, 5 patients without pulmonary embolism received anticoagulant therapy and 2 patients with pulmonary embolism did not receive anticoagulant therapy (Fig. 1 and Table S3). During follow-up, 19 patients without pulmonary embolism at initial diagnostic testing started anticoagulant therapy for reasons other than venous thromboembolism (atrial fibrillation in 13) (Table S4). A total of 13 patients (0.6%) did not complete 3 months of follow-up (Fig. 1).

PRIMARY ANALYSIS

Of 1970 patients (97.7% of the total population) who had a low or moderate C-PTP, 1325 (67.3%) had a negative D-dimer test and did not receive anticoagulant therapy. None of these patients (95% confidence interval [CI], 0.00 to 0.29%) had venous thromboembolism during follow-up (Fig. 1 and Table 2).

SECONDARY ANALYSES

Of 1863 patients (92.4% of the total population) who did not receive a diagnosis of pulmonary embolism at initial presentation and did not receive anticoagulant therapy, 1 patient (0.05%; 95% CI, 0.01 to 0.30), who had a low C-PTP, a positive D-dimer test (1200 ng per milliliter), and negative findings on CT pulmonary angiography, had venous thromboembolism during follow-up (Fig. 1 and Table 2). Of 1285 patients (63.7% of the total population) who had a low C-PTP, a negative D-dimer test (i.e., <1000 ng per milliliter), and did not receive anticoagulant therapy, none (95% CI, 0.00 to 0.30%) had venous thromboembolism during follow-up (Fig. 1 and Table 2). Of these 1285 patients with a low C-PTP, 315

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Table 3. Number of D-Dimer Tests and Chest Imaging Examinations with the PEGeD Strategy as Compared with Other Diagnostic Strategies.*

Diagnostic Strategy	Low C-PTP (N=1752)		Moderate C-PTP (N=218)		High C-PTP (N=47)		All Patients (N=2017)	
	D-Dimer Test	Chest Imaging†	D-Dimer Test	Chest Imaging†	D-Dimer Test	Chest Imaging†	D-Dimer Test	Chest Imaging†
PEGeD	1752	467	218	178	0	47	1970	692
Standard‡	1752	782	0	218	0	47	1752	1047
Difference: PEGeD – standard	0	–315	218	–40	—	0	218	–355
Age-adjusted§	1752	654	218	164	0	47	1970	865
Difference: PEGeD – age-adjusted	0	187	0	14	—	0	0	–173
YEARS¶	1752	520	218	176	47	37	2017	733
Difference: PEGeD – YEARS	0	–53	0	2	–47	10	–47	–41

* PEGeD denotes Pulmonary Embolism Graduated D-Dimer.
† Chest imaging was usually CT pulmonary angiography.
‡ With the standard strategy, pulmonary embolism is considered to be ruled out by a D-dimer level of less than 500 ng per milliliter in patients with a low C-PTP. All other patients undergo chest imaging.
§ With the age-adjusted strategy, pulmonary embolism is considered to be ruled out in patients with a low or moderate C-PTP who are 50 years of age or younger and have a D-dimer level of less than 500 ng per milliliter or who are older than 50 years of age and have a D-dimer level (in nanograms per milliliter) that is less than 10 times the patient's age.
¶ With the YEARS strategy, pulmonary embolism is considered to be ruled out in patients with zero YEARS criteria (i.e., none of the following: clinical signs of DVT; hemoptysis; or pulmonary embolism considered to be the most likely diagnosis) and a D-dimer level of less than 1000 ng per milliliter and in those with one or more YEARS criteria and a D-dimer level of less than 500 ng per milliliter. The D-dimer results in 13 patients with a high C-PTP who did not have D-dimer measured were extrapolated from the D-dimer results in the 34 patients with a high C-PTP who had D-dimer measured.

had a D-dimer level of 500 to 999 ng per milliliter, and none had venous thromboembolism during follow-up (95% CI, 0.00 to 1.20%). Of 40 patients (2.0% of the total population) who had a moderate C-PTP, a negative D-dimer test (i.e., <500 ng per milliliter), and did not receive anticoagulant therapy, none (95% CI, 0.00 to 8.76%) had venous thromboembolism during follow-up (Fig. 1 and Table 2). There were 7 major bleeding episodes, 23 minor bleeding episodes, and 34 deaths during follow-up; no deaths were attributed by the central adjudication committee to pulmonary embolism. (For details on secondary analyses, see Table S5.)

IMAGING TO DETECT PULMONARY EMBOLISM AND USE OF D-DIMER TESTING

The PEGeD diagnostic strategy resulted in the use of chest imaging in 34.3% of patients, whereas the standard strategy in which pulmonary embolism is considered to be ruled out with a low C-PTP and a D-dimer level of less than 500 ng per milliliter would result in the use of chest imaging in 51.9% (difference, –17.6 percentage points; 95% CI, –19.2 to –15.9), corresponding to a relative difference of –33.9% (Table 3). By extending D-dimer testing to patients with a moderate C-PTP, the PEGeD strategy resulted in the use of D-dimer testing in 97.7% of patients, whereas the standard strategy would result in the use of D-dimer testing in 86.9%. Comparisons of the PEGeD strategy with the age-adjusted strategy and with the strategy used in the YEARS study[15] are summarized in Table 3.

DISCUSSION

When we considered pulmonary embolism to be ruled out if outpatients were assessed as having a low C-PTP and had a D-dimer level of less than 1000 ng per milliliter or were assessed as having a moderate C-PTP and had a D-dimer level of less than 500 ng per milliliter and therefore withheld chest imaging and anticoagulant therapy on the basis of these findings, none of the 1325 patients had thromboembolic complications during follow-up. As compared with the use of D-dimer testing to rule out pulmonary embolism only in patients

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with a low C-PTP who have a D-dimer level of less than 500 ng per milliliter, the PEGeD algorithm increased the percentage of patients who had pulmonary embolism ruled out by D-dimer testing and, therefore, did not proceed to chest imaging from 48.1% to 65.7%. This corresponds to a 33.9% relative reduction in chest imaging.

Most of this benefit was from the ruling out of pulmonary embolism with D-dimer levels of 500 to 999 ng per milliliter in patients with a low C-PTP, because only 10.8% of patients had a moderate C-PTP and only 18.3% of these had a D-dimer level of less than 500 ng per milliliter. Because most of the patients who had pulmonary embolism ruled out with the use of D-dimer testing had a low C-PTP, our study provides stronger evidence for ruling out pulmonary embolism with a D-dimer level of less than 1000 ng per milliliter and a low C-PTP than for a D-dimer level of less than 500 ng per milliliter and a moderate C-PTP. However, our results in patients with a moderate C-PTP support the findings of other studies that suggest that a D-dimer level of less than 500 ng per milliliter rules out pulmonary embolism in these patients.[2,3]

Our findings are consistent with those of the YEARS management study, which showed a low incidence of venous thromboembolic complications among patients with suspected pulmonary embolism who had a D-dimer level of less than 1000 ng per milliliter and a low-risk YEARS clinical-assessment score (none of the following: clinical signs of deep-vein thrombosis; hemoptysis; or pulmonary embolism considered to be the most likely diagnosis) or who had a D-dimer level of less than 500 ng per milliliter and did not have a low-risk score (≥1 of these criteria).[15] Our data suggest that the PEGeD strategy results in a modest reduction in the use of chest imaging as compared with the YEARS strategy (difference, −2.0 percentage points; 95% CI, −2.8 to −1.2) (Table 3). Our findings are also consistent with those of a management study from our own group that showed that a D-dimer level of less than 1000 ng per milliliter ruled out thrombosis in patients with a low C-PTP for deep-vein thrombosis.[16]

The age-adjusted D-dimer interpretation strategy considers pulmonary embolism to be ruled out with a D-dimer level of less than 500 ng per milliliter in patients 50 years of age or younger and with a D-dimer level (in nanograms per milliliter) that is less than 10 times the patient's age in those older than 50 years of age, provided that patients have a low or moderate C-PTP.[2,3,17] Our data also suggest that the PEGeD strategy results in a greater reduction in chest imaging as compared with the age-adjusted strategy (difference, −8.6 percentage points; 95% CI, −10.0 to −7.2) (Table 3). An additional disadvantage of the age-adjusted algorithm is that, because it uses a higher D-dimer threshold to rule out pulmonary embolism only in patients older than 50 years of age, it does not reduce the use of chest imaging in younger patients, a subgroup of patients who are at higher risk from radiation exposure and are less likely to have alternative diagnoses identified by chest imaging.

Strengths of our study include the following: it was large enough to provide estimates with reasonable precision in the overall study population and in important subgroups; standardized testing for venous thromboembolism was used during follow-up, with central adjudication of outcomes; very few patients were lost to follow-up; many clinical centers participated; and a number of different D-dimer assays were used, which increases the generalizability of our findings. With regard to patients lost to follow-up, assuming that the percentage with venous thromboembolism among those patients with a low C-PTP and a negative D-dimer test was the same as the prevalence of pulmonary embolism among all patients with a low C-PTP and a positive D-dimer test (i.e., 18.6%; a worst-case scenario), we estimate that two of the nine patients (Fig. 1) may have had venous thromboembolism during follow-up (0.15%; 95% CI, 0.04 to 0.55).

Limitations of the study include that almost all patients who were enrolled were outpatients (only 1 inpatient), so the findings may not apply to inpatients; too few patients had a moderate C-PTP and a D-dimer level of less than 500 ng per milliliter to precisely identify the negative predictive value in this subgroup; and it is possible that physician discretion influenced which patients were enrolled. In relationship to the last point, the study did not capture the total number of patients who were assessed for pulmonary embolism in participating centers. However, among 127 patients from two of the clinical centers who were excluded because chest imaging was performed when it was not indicated by the PEGeD diagnostic algorithm, a post hoc

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analysis showed only two pulmonary embolisms (in 1.6% of the patients), which suggests that selective enrollment did not substantially bias the study findings (Table S1). Additional evidence suggesting that selective enrollment was not prominent includes the observation that the percentage of enrolled patients who had pulmonary embolism on initial diagnostic testing was similar to that in other North American studies involving outpatients[18,19] and that similar percentages of patients had low, moderate, and high C-PTP and negative D-dimer tests as in a recent observational study involving patients with suspected pulmonary embolism from two of the PEGeD clinical centers.[19]

This study used the Wells score to categorize each patient's C-PTP as low, moderate, or high (Table 1).[1,2,5,12,13] Therefore, it is uncertain whether the same approach to D-dimer interpretation can be used if C-PTP is assessed without using a clinical prediction rule or with a different prediction rule. The Wells score achieved good discrimination in the current study, with a prevalence of pulmonary embolism of 5.0% among patients with a low C-PTP and of 19.7% among those with a moderate C-PTP. As long as the prevalence of pulmonary embolism in low and moderate C-PTP groups is similar to these values, we believe that the PEGeD algorithm should be valid when C-PTP is assessed in other ways.

In general, the prevalence of pulmonary embolism among patients who undergo diagnostic testing is substantially higher in Europe than in North America.[18] This difference is expected to result in a lower proportion of patients in Europe than in North America being classified as having a low C-PTP and a higher proportion being classified as having a moderate C-PTP. If the prevalence of pulmonary embolism in the low and moderate C-PTP categories was also higher in a high-prevalence setting, the negative predictive value of the PEGeD algorithm could be lower.

Our findings establish that the risk of considering pulmonary embolism to be ruled out in patients with a low C-PTP who have a D-dimer level of less than 1000 ng per milliliter is low. Our findings also suggest that considering pulmonary embolism to be ruled out in patients with a moderate C-PTP who have a D-dimer level of less than 500 ng per milliliter is appropriate; these findings are consistent with those of previous studies. Use of the PEGeD algorithm substantially reduced the number of chest-imaging studies performed in patients with suspected pulmonary embolism.

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