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Multidetector Computed Tomography for Acute Pulmonary Embolism

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ABSTRACT

BACKGROUND

The accuracy of multidetector computed tomographic angiography (CTA) for the diagnosis of acute pulmonary embolism has not been determined conclusively.

METHODS

The Prospective Investigation of Pulmonary Embolism Diagnosis II trial was a prospective, multicenter investigation of the accuracy of multidetector CTA alone and combined with venous-phase imaging (CTA-CTV) for the diagnosis of acute pulmonary embolism. We used a composite reference test to confirm or rule out the diagnosis of pulmonary embolism.

RESULTS

Among 824 patients with a reference diagnosis and a completed CT study, CTA was inconclusive in 51 because of poor image quality. Excluding such inconclusive studies, the sensitivity of CTA was 83 percent and the specificity was 96 percent. Positive predictive values were 96 percent with a concordantly high or low probability on clinical assessment, 92 percent with an intermediate probability on clinical assessment, and nondiagnostic if clinical probability was discordant. CTA-CTV was inconclusive in 87 of 824 patients because the image quality of either CTA or CTV was poor. The sensitivity of CTA-CTV for pulmonary embolism was 90 percent, and specificity was 95 percent. CTA-CTV was also nondiagnostic with a discordant clinical probability.

CONCLUSIONS

In patients with suspected pulmonary embolism, multidetector CTA-CTV has a higher diagnostic sensitivity than does CTA alone, with similar specificity. The predictive value of either CTA or CTA-CTV is high with a concordant clinical assessment, but additional testing is necessary when the clinical probability is inconsistent with the imaging results.

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UNCERTAINTY PERSISTS ABOUT THE ACCURACY of contrast-enhanced multidetector computed tomographic angiography (CTA) for the diagnosis of pulmonary embolism. The sensitivity of single-slice CTA has ranged from 60¹ to 100² percent, and the specificity has ranged from 81¹ to 100³ percent. A previous review focused on the diagnostic accuracy of single-slice CTA.⁴

Visualization of segmental and subsegmental pulmonary arteries is substantially better with four-slice CTA and thin collimation (1.25 mm) than with single-slice CTA.^{5,6} In two studies of fewer than 100 patients, sensitivities for the detection of pulmonary embolism with four-slice CTA have been reported to be 96 percent⁷ and 100 percent,⁸ with respective specificities of 98 percent and 89 percent.

Pulmonary embolism and deep venous thrombosis are two manifestations of one pathologic process. The majority of patients with pulmonary embolism also have deep venous thrombosis.^{9,10} For this reason, testing for deep venous thrombosis has become an integral part of the diagnosis of pulmonary embolism. Venous-phase multidetector CT venography (CTV) in combination with single-slice CTA (CTA-CTV) improved the detection of pulmonary embolism.^{11,12} The sensitivity of four-slice CTA-CTV appears to be higher than that of four-slice CTA alone.¹³⁻¹⁵

Meta-analyses of outcome, mostly performed after single-slice CTA, showed that imaging of the lower extremities should be normal^{16,17} or the clinical probability of pulmonary embolism should be low or intermediate¹⁸ to rule out disease in patients with normal findings on CTA. Most outcome studies that are performed after normal findings have been obtained on 4-slice or 16-slice CTA have used additional diagnostic tests to rule out pulmonary embolism.^{13,19-21} However, Perrier et al.²² showed a potential ability to rule out pulmonary embolism on the basis of normal findings on multidetector CTA without ultrasonography of the lower limbs. The Christopher Study investigators²³ showed pulmonary embolism during three-month follow-up in only 0.7 percent of untreated patients and deep venous thrombosis in 0.6 percent after normal findings had been obtained on single-row or multidetector CTA alone.

The Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) trial was designed with two primary objectives: to determine

whether multidetector CTA can reliably detect and rule out acute pulmonary embolism and whether the addition of CTV improves the ability to detect and rule out pulmonary embolism. We also determined whether the addition of a validated clinical assessment (the Wells score) (Table 1)²⁴ improves the ability to detect or rule out pulmonary embolism by CTA or CTA-CTV in patients with suspected pulmonary embolism.

METHODS

The PIOPED II trial was a prospective, multicenter study designed by the authors and sponsored by the National Heart, Lung, and Blood Institute. The protocol and consent forms were approved by the institutional review board of each center and by a data safety monitoring board appointed by the institute. All recruited patients gave written informed consent. All the criteria of the Standards for Reporting of Diagnostic Accuracy were met.^{25,26}

STUDY POPULATION AND ENROLLMENT

All patients who were at least 18 years of age and had clinically suspected acute pulmonary embolism were seen on either an inpatient or outpatient basis at the eight participating clinical centers between September 2001 and July 2003. Patients who were referred for diagnostic imaging for suspected pulmonary embolism were identified for recruitment, as well as patients for whom the study nurse was aware of a consultation request for suspected pulmonary embolism. Patients were recruited consecutively during periods of staff availability, usually during the daytime on weekdays. Exclusion criteria are shown in Figure 1.

DIAGNOSTIC EVALUATION

All patients who were enrolled in the study underwent a clinical assessment of the probability of pulmonary embolism, including a Wells score (Table 1).²⁴ In addition, all patients consented to undergo diagnostic testing, including CTA-CTV, ventilation-perfusion scanning, venous compression ultrasonography of the lower extremities, and if necessary, pulmonary digital-subtraction angiography (DSA).²⁷ For ethical reasons, conventional pulmonary DSA was restricted to patients in whom pulmonary embolism was not conclusively diagnosed or ruled out by the noninvasive tests.

A composite reference standard was used to diagnose or rule out pulmonary embolism. The

diagnosis of pulmonary embolism according to the composite reference standard required one of the following conditions: ventilation–perfusion lung scanning showing a high probability of pulmonary embolism in a patient with no history of pulmonary embolism, abnormal findings on pulmonary DSA, or abnormal findings on venous ultrasonography in a patient without previous deep venous thrombosis at that site and nondiagnostic results on ventilation–perfusion scanning (not normal and not high probability without previous pulmonary embolism). Abnormal venous ultrasonography in such a patient was interpreted as a surrogate for the diagnosis of pulmonary embolism.

Exclusion of pulmonary embolism according to the composite reference standard required one of the following conditions: normal findings on DSA, normal findings on ventilation–perfusion scanning, ventilation–perfusion scanning showing either a low or very low probability of pulmonary embolism, a clinical Wells score of less than 2 (Table 1),²⁴ and normal findings on venous ultrasonography.

To confirm the accuracy of the exclusion of pulmonary embolism according to the composite reference standard, patients in whom pulmonary embolism was ruled out by the reference test underwent telephone interviews three and six months after enrollment. Deaths and new evaluations for venous thromboembolic disease were reviewed by an outcome committee.

CTA AND CTV

The study was performed with 4-row, 8-row, or 16-row multidetector scanners, as described in the Supplementary Appendix (available with the full text of this article at www.nejm.org). Diagnostic criteria for acute pulmonary embolism by CTA were as follows: failure of contrast material to fill the entire lumen because of a central filling defect (the artery may be enlarged, as compared with similar arteries; a partial filling defect surrounded by contrast material on a cross-sectional image; contrast material between the central filling defect and the artery wall on an in-plane, longitudinal image; and a peripheral intraluminal filling defect that forms an acute angle with the artery wall. The criterion for acute deep venous thrombosis on CTV was a complete or partial central filling defect.

Table 1. Model for Determining the Clinical Probability of Pulmonary Embolism, According to the Wells Score.*

Clinical Feature	Score
Clinical signs and symptoms of DVT (objectively measured leg swelling and pain with palpation in the deep-vein system)	3.0
Heart rate >100 beats/min	1.5
Immobilization for ≥3 consecutive days (bed rest except to go to bathroom) or surgery in previous 4 weeks	1.5
Previous objectively diagnosed pulmonary embolism or DVT	1.5
Hemoptysis	1.0
Cancer (with treatment within past 6 mo or palliative treatment)	1.0
Pulmonary embolism likely or more likely than alternative diagnoses (on the basis of history, physical examination, chest radiography, ECG, and blood tests)	3.0

* Data are from Wells et al.²⁴ The condition of patients is scored according to the following criteria: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability. DVT denotes deep venous thrombosis, and ECG electrocardiography.

CENTRAL READINGS

Image interpretations for all diagnostic tests except venous ultrasonography were based on agreement of two certified readers in the PIOPED II trial who were from centers other than that at which the image was obtained. Additional readers were used until agreement of two was obtained. Readers were unaware of all clinical information and of the results of other imaging tests except chest radiographs, which were included with ventilation–perfusion scans. Local readings of venous ultrasonography were accepted after site visits to validate technique and interpretation. The reading of multidetector CTA and conventional DSA required agreement regarding at least one lobe for a diagnosis of pulmonary embolism, and pulmonary embolism was ruled out if two readers agreed that the condition was absent. In interpreting CTV results, two readers had to agree on the leg that was affected by deep venous thrombosis. Separate consensus of readers was required for both CTA and CTV. For CTA–CTV, pulmonary embolism was diagnosed if there was consensus that either test showed abnormal findings. Pulmonary embolism was ruled out if there was consensus that both CTA and CTV showed normal findings.

STATISTICAL ANALYSIS

We used standard methods to calculate the sensitivity, specificity, and positive and negative pre-

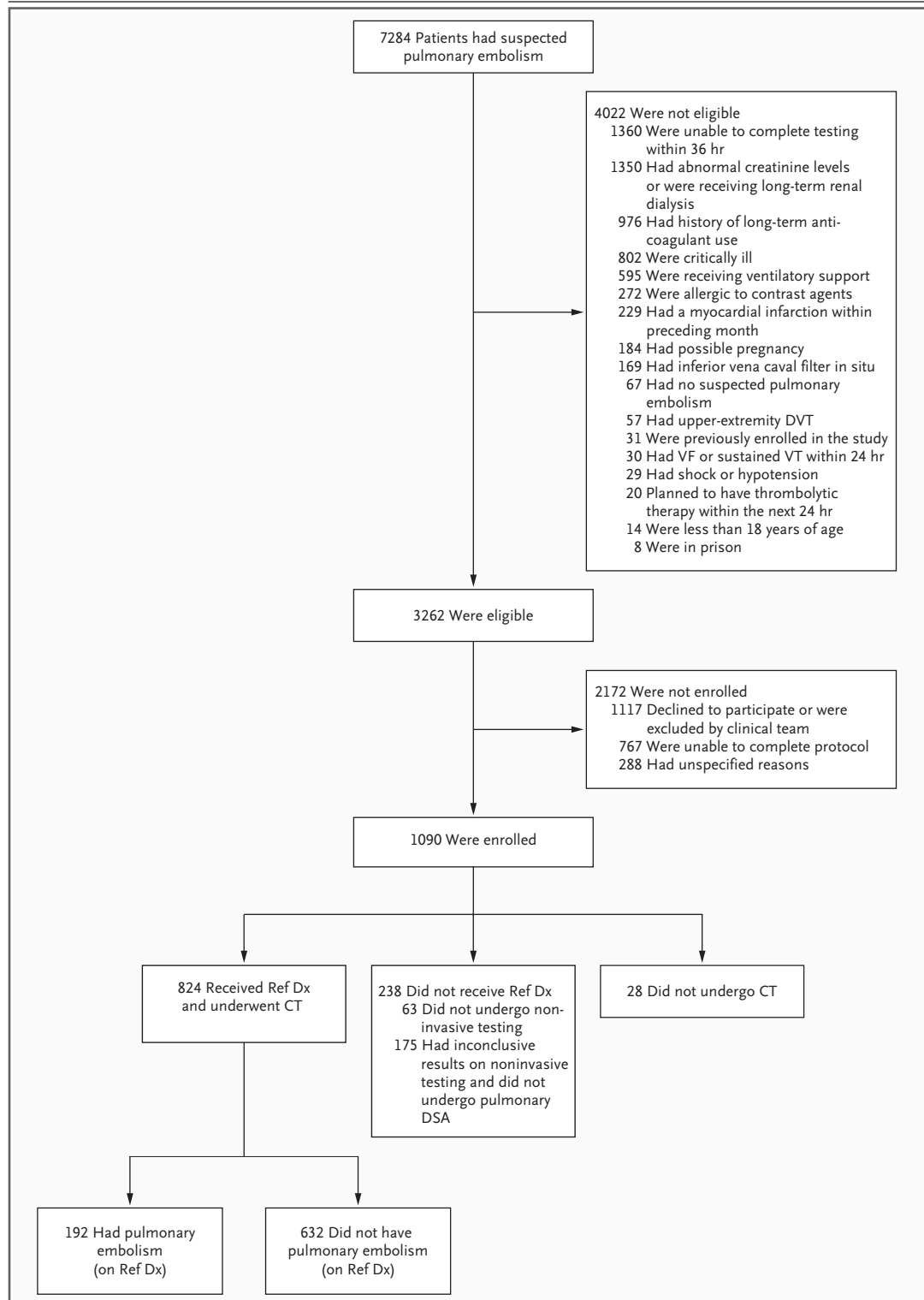


Figure 1. Enrollment and Outcomes.

Some patients had more than one reason for exclusion from the study. Patients receiving long-term renal dialysis were excluded from the study only during the first 14 months of recruitment. DVT denotes deep venous thrombosis, VF ventricular fibrillation, VT ventricular tachycardia, and Ref Dx diagnosis obtained with the use of the composite reference standard.

dictive values.²⁸ Patients for whom results on CTA or CTA-CTV were unclassified were excluded from these calculations. For the calculation of the negative predictive value of CTA among patients who were deemed to have a low probability of disease, we included only patients with a reference test diagnosis obtained by ventilation-perfusion scanning or conventional pulmonary DSA. We calculated exact 95 percent confidence intervals for sensitivity, specificity, and unadjusted positive and unadjusted negative predictive values from the binomial distribution with the use of StatXact5 software, release 5.0.3 (Cytel Software). Values for likelihood ratios for a positive test were calculated as the sensitivity, divided by 1 minus the specificity; and likelihood ratios for a negative test were calculated as 1 minus the sensitivity, divided by the specificity.²⁹⁻³¹

In a separate analysis, values for the sensitivity and specificity of CTA were adjusted for possible inaccuracy of the composite reference standard with the use of the lowest reported false positive and false negative rates for the tests that make up that standard.³²⁻³⁶ Calculations were also performed with the use of the highest reported false positive and false negative rates for the composite reference standard tests.^{24,32-34,37}

RESULTS

During the 23-month recruitment period, 7284 patients were screened, 3262 were eligible for study, and 1090 were enrolled (Fig. 1). A majority of the 1090 enrolled patients were women; the mean age was 51.7 years. Most patients were deemed to have a low or moderate probability of pulmonary embolism on the basis of the Wells score (Tables 1 and 2). Of the 1090 patients enrolled, 28 did not undergo CT and 238 did not receive a reference test diagnosis. The remaining 824 patients underwent subsequent analysis. Demographic and clinical features of the 238 patients without a reference diagnosis and the 824 patients who received a diagnosis are shown in Table 2.

REFERENCE DIAGNOSIS

On the basis of the composite reference standard, pulmonary embolism was diagnosed in 192 of the 824 patients who received a reference diagnosis (23 percent) (Table 3). Among the 632 in whom pulmonary embolism was ruled out, the 592 pa-

tients who also had an interpretable CTA were followed for six months; 590 patients did not receive anticoagulants. Clinical courses in 2 of 590 patients (<1 percent) suggested an initially unrecognized pulmonary embolism.

RESULTS OF CTA AND CTA-CTV

Of the 824 patients with a reference diagnosis and a completed CT study, the quality of the CTA was insufficient for conclusive interpretation in 51 (Table 4). Of the 773 patients with an adequate CTA (94 percent), the sensitivity of CTA for the diagnosis of pulmonary embolism was 83 percent (150 of 181 patients; 95 percent confidence interval, 76 to 92 percent), and the specificity was 96 percent (567 of 592 patients; 95 percent confidence interval, 93 to 97 percent). The likelihood ratio for a positive test was 19.6 (95 percent confidence interval, 13.3 to 29.0), and the likelihood ratio for a negative test was 0.18 (95 percent confidence interval, 0.13 to 0.24). The positive predictive value was 86 percent (150 of 175 patients; 95 percent confidence interval, 79 to 90 percent), and the negative predictive value was 95 percent (567 of 598 patients; 95 percent confidence interval, 92 to 96 percent). Positive predictive values were 97 percent (116 of 120 patients) for pulmonary embolism in a main or lobar artery, 68 percent (32 of 47 patients) for a segmental vessel, and 25 percent (2 of 8 patients) for a subsegmental branch.

Of the 824 patients with a reference diagnosis and a completed CT study, the quality of results on CTA-CTV was insufficient for conclusive interpretation for 87 patients (Table 4). Among the 737 patients with adequate results on CTA-CTV (89 percent), the sensitivity of results on CTA-CTV for the diagnosis of pulmonary embolism was 90 percent (164 of 183 patients; 95 percent confidence interval, 84 to 93 percent), and the specificity was 95 percent (524 of 554 patients; 95 percent confidence interval, 92 to 96 percent). The likelihood ratio for a positive test was 16.5 (95 percent confidence interval, 11.6 to 23.5), and the likelihood ratio for a negative test was 0.11 (95 percent confidence interval, 0.07 to 0.16). The positive predictive value was 85 percent (164 of 194 patients; 95 percent confidence interval, 78 to 89 percent), and the negative predictive value was 97 percent (524 of 543 patients; 95 percent confidence interval, 94 to 97 percent). Among 105 patients with positive results on CTV, thrombi were

Table 2. Demographic Characteristics, Coexisting Illnesses, Presenting Signs and Symptoms, and Clinical Probability of Pulmonary Embolism.*

Characteristic	All Patients (N=1090)	Standard Diagnosis Obtained and CT Performed (N=824)	No Standard Diagnosis Obtained (N=238)
Demographic characteristic			
Female sex — no./total no. (%)	676/1090 (62)	507/824 (62)	150/238 (63)
Age (yr)	51.7±17.1	51.4±16.9	53.2±17.7
Race — no./total no. (%)†			
White	699/1089 (64)	535/823 (65)	148/238 (62)
Black	337/1089 (31)	244/823 (30)	83/238 (35)
Outpatient (including nursing homes and rehabilitation centers) — no./total no. (%)	971/1085 (89)	754/822 (92)	198/236 (84)
Coexisting condition — no./total no. (%)			
Smoking history	567/1085 (52)	411/822 (50)	143/235 (61)
Congestive heart failure	99/1074 (9)	127/823 (15)	42/237 (18)
Current asthma	178/1078 (17)	125/814 (15)	46/236 (19)
Chronic obstructive pulmonary disease	102/1084 (9)	68/821 (8)	30/235 (13)
Current pneumonia	65/1014 (6)	39/773 (5)	25/214 (12)
Surgery within past 3 mo	188/1087 (17)	124/824 (15)	57/236 (24)
Cancer	191/1079 (18)	132/816 (16)	56/235 (24)
Central venous instrumentation	94/1082 (9)	57/819 (7)	36/235 (15)
Symptom — no./total no. (%)‡			
Dyspnea	821/1085 (76)	610/821 (74)	189/236 (80)
Pleuritic pain	613/807 (76)	465/619 (75)	133/170 (78)
Cough	473/1083 (44)	330/820 (40)	131/235 (56)
Calf pain	282/1080 (26)	203/817 (25)	72/235 (31)
Sign — no./total no. (%)			
Hemoptysis	63/1080 (6)	37/816 (5)	23/236 (10)
Tachypnea (≥20 breaths/min)	560/1074 (52)	404/815 (50)	142/233 (61)
Crackles	221/1077 (21)	151/817 (18)	65/234 (28)
Tachycardia (>100 beats/min)	221/1079 (20)	147/818 (18)	64/234 (27)
Calf tender to palpation	109/287 (38)	71/218 (33)	34/62 (55)§
Swollen calf (>1 cm)	322/890 (36)	234/646 (36)	83/218 (38)
Clinical probability — no./total no. (%)¶			
Low	587/1048 (56)	500/796 (63)	72/226 (32)
Moderate	396/1048 (38)	252/796 (32)	135/226 (60)
High	65/1048 (6)	44/796 (6)	19/226 (8)
PaO₂ — no./total no. (%)			
≥80 mm Hg	114/335 (34)	83/230 (36)	28/94 (30)
70–79 mm Hg	62/335 (19)	39/230 (17)	22/94 (23)
60–69 mm Hg	64/335 (19)	44/230 (19)	18/94 (19)
50–59 mm Hg	63/335 (19)	41/230 (18)	19/94 (20)
<50 mm Hg	32/335 (10)	23/230 (10)	7/94 (7)
PaCO₂ — no./total no. (%)			
≥40 mm Hg	127/332 (38)	87/228 (38)	35/93 (38)
36–39 mm Hg	81/332 (24)	50/228 (22)	29/93 (31)
<36 mm Hg	124/332 (37)	91/228 (40)	29/93 (31)

* Plus-minus values are means ±SD. Standard diagnosis refers to the diagnosis of pulmonary embolism on the basis of a composite reference standard. PaO₂ denotes partial pressure of oxygen in arterial blood while patient is breathing ambient air, and PaCO₂ partial pressure of carbon dioxide in arterial blood while patient is breathing ambient air.

† Racial or ethnic background was self-reported. No more than 4 percent of patients in any group were listed as Asian or Pacific Islander, Hispanic, or Native American, Eskimo, or Inuit.

‡ Less than 10 percent of patients in any group had hemiparesis, diaphoresis, pleural friction, or a history of trauma.

§ The presence or absence of calf tenderness was not reported for 803 patients.

¶ The condition of patients was graded according to the Wells score²⁴: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability.

Table 3. Basis for the Diagnosis or Exclusion of Pulmonary Embolism among 824 Patients Evaluated by CTA.*

Variable	Pulmonary Embolism (N = 192)	No Pulmonary Embolism (N = 632)
	<i>no. of patients (%)</i>	
DSA	33 (17)	192 (30)
Ventilation–perfusion scanning†	109 (57)	146 (23)
Ultrasonography of lower extremities with abnormal findings, no previous DVT at same site, and nondiagnostic ventilation–perfusion scanning	50 (26)	NA
Ventilation–perfusion scanning indicating low or very low probability of disease, low clinical probability, and normal findings on ultrasonography‡	NA	294 (47)

* DVT denotes deep venous thrombosis, and NA not applicable.

† Abnormal findings on ventilation–perfusion scanning indicate a high probability of pulmonary embolism in a patient with no previous pulmonary embolism. Normal findings rule out pulmonary embolism.

‡ The clinical probability was determined by a Wells score of less than 2.²⁴

shown in the inferior vena cava or pelvic veins alone in 3 patients (3 percent), thigh veins alone in 89 (85 percent), and both in 13 (12 percent).

If the composite reference standard is not assumed to be an absolute standard for the diagnosis of pulmonary embolism but is considered to have its own false positive and false negative rates, the diagnostic accuracy of CTA and CTA–CTV is altered slightly. Sensitivity analysis using the lowest reported false positive and false negative rates of the components of the composite reference test gave an adjusted sensitivity of CTA of 84 percent (150 of 178 patients) and adjusted sensitivity of CTA–CTV of 92 percent (164 of 179 patients). The use of the highest reported false positive and false negative rates resulted in an adjusted value of the sensitivity of CTA of 82 percent (150 of 182 patients); the adjusted sensitivity of CTA–CTV was unchanged at 90 percent (164 of 183 patients). Specificities changed 1 percent or less.

CT RESULTS AND CLINICAL ASSESSMENT

As would be anticipated, the predictive value of CTA and CTA–CTV varied substantially when the clinical assessment was taken into account. Among patients with a previous clinical assessment of high or intermediate probability of pulmonary embolism, the respective positive predictive values for pulmonary embolism were 96 percent (22 of 23 patients) and 92 percent (93 of 101 patients) for CTA (Table 5). Among patients with a low clinical probability of pulmonary embolism, 42 percent of the CTA readings were false positive. Similar positive predictive values were obtained for CTA–CTV (Table 5).

Among patients with a low clinical probability, the negative predictive value for CTA for the exclusion of pulmonary embolism was 96 percent (158 of 164 patients); the negative predictive value for CTA–CTV was 97 percent (146 of 151 patients). Among patients with a high clinical probability, 40 percent of results on CTA and 18 percent of results on CTA–CTV were false negative (Table 5). To avoid bias,³⁸ negative predictive values among patients with a low clinical probability were based entirely on DSA or ventilation–perfusion scanning as the reference test.

COMPLICATIONS

Complications associated with 1095 CTA procedures were a mild allergic reaction (itching, swollen eyelid, or vomiting) in four patients (<1 percent), urticaria in one patient (<1 percent), and moderately severe extravasation of contrast material into the antecubital fossa in two patients (<1 percent). One patient with diabetes mellitus had a transient episode of acute renal failure characterized by an increase in the serum creatinine level from 1.3 to 2.9 mg per deciliter (115 to 256 μ mol per liter) after CTA–CTV, which was followed 22 hours later by DSA. The elevated creatinine level returned to normal after the administration of intravenous fluids. No other complications were reported with 209 DSA procedures or with any other reference tests. No other elevations in creatinine levels were attributed to the procedures. Serum creatinine levels were typically checked daily in hospitalized patients, but the test results were not required by protocol and typically were not obtained from outpatients after CTA and DSA.

Table 4. Results on CTA and CTA–CTV among Patients with a Confirmed Diagnosis of Pulmonary Embolism, According to the Composite Reference Standard.

Variable	Abnormal Findings on Composite Reference Standard	Normal Findings on Composite Reference Standard	Total
<i>number of patients</i>			
Findings on CTA			
Abnormal findings	150	25	175
Normal findings	31	567	598
Indeterminate findings	11	40	51
Total	192	632	824
Findings on CTA–CTV			
Abnormal findings on either CTA or CTV	164	30	194
Normal findings on both CTA and CTV	19	524	543
Indeterminate findings*	9	78	87
Total	192	632	824

* Findings were normal on either CTA or CTV and the alternative CT method was not performed, or findings were of insufficient quality for conclusive interpretation.

DISCUSSION

Our data show that multidetector CTA–CTV had a higher sensitivity (90 percent) than CTA alone (83 percent), with similar specificity (about 95 percent for both testing techniques). Positive results on CTA in combination with a high probability or intermediate probability of pulmonary embolism on the basis of clinical assessment or normal findings on CTA with a low clinical probability had a predictive value (positive or negative) of 92 to 96 percent. Such values are consistent with those generally considered adequate to confirm or rule out the diagnosis of pulmonary embolism.

We report sensitivity based on the number of patients who had conclusive interpretations of CTA or CTA–CTV. The sensitivity of diagnostic imaging with CTA and CTA–CTV would be lower if patients with inconclusive interpretations owing to poor image quality were included. However, since patients with inconclusive findings on CTA or CTA–CTV in clinical practice would probably undergo additional testing, we regard the values for diagnostic accuracy given here to be appropriate for clinical use and for comparison with other techniques. The data we report were primarily obtained with four-slice CT. We did not study enough patients with 8-slice or 16-slice scanners to determine whether accuracy improved with the use of more advanced scanners.

Both multidetector CTA–CTV and multidetector CTA alone would require additional testing to diagnose or rule out pulmonary embolism if the previous assessment of clinical probability did not agree with the imaging results. It has been suggested that the clinical probability of pulmonary embolism should be considered in combination with CTA because of false positive or false negative results of CTA in patients with discordant clinical findings.³⁹

Other studies have examined a variety of approaches to the use of CTA in the evaluation of patients with suspected pulmonary embolism; the findings of these studies have been generally consistent with ours. In a meta-analysis, Quiroz et al.¹⁸ showed that pulmonary embolism could be ruled out safely with primarily single-detector CTA in cases in which the clinical probability was low or intermediate. On the basis of a meta-analysis of primarily single-detector CTA, Moores et al.^{16,17} concluded that lower-extremity imaging should be normal before anticoagulation is withheld in patients with suspected pulmonary embolism and normal findings on CTA. Perrier et al.²² showed that normal findings on D-dimer testing among patients with a low or intermediate clinical probability of pulmonary embolism safely eliminated the need for further diagnostic testing. In this alternative strategy, such patients do not appear to require CTA.

Strengths of this investigation include incor-

Table 5. Positive and Negative Predictive Values of CTA, as Compared with Previous Clinical Assessment.*

Variable	High Clinical Probability		Intermediate Clinical Probability		Low Clinical Probability	
	No./Total No.	Value (95% CI)	No./Total No.	Value (95% CI)	No./Total No.	Value (95% CI)
Positive predictive value of CTA	22/23	96 (78–99)	93/101	92 (84–96)	22/38	58 (40–73)
Positive predictive value of CTA or CTV	27/28	96 (81–99)	100/111	90 (82–94)	24/42	57 (40–72)
Negative predictive value of CTA	9/15	60 (32–83)	121/136	89 (82–93)	158/164†	96 (92–98)
Negative predictive value of both CTA and CTV	9/11	82 (48–97)	114/124	92 (85–96)	146/151†	97 (92–98)

* The clinical probability of pulmonary embolism was based on the Wells score: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability. CI denotes confidence interval.

† To avoid bias for the calculation of the negative predictive value in patients deemed to have a low probability of pulmonary embolism on previous clinical assessment, only patients with a reference test diagnosis by ventilation–perfusion scanning or conventional pulmonary DSA were included.

poration of all the criteria of the Standards for Reporting of Diagnostic Accuracy.^{25,26} Recruited patients were inpatients and outpatients of both sexes with a wide range of ages and associated illnesses. The composite reference test was shown to be robust by sensitivity analysis and by the generally benign outcome among patients with a negative reference test.

Weaknesses of the investigation include the use of noninvasive diagnostic tests as part of the reference standard. This was necessary, since it was deemed to be unethical to require DSA in all recruited patients. With the use of data from previous reports,^{24,32–37} the composite reference standard overall is estimated to have had false positive rates of no more than 9.3 percent and false negative rates of no more than 2.4 percent. In patients with pulmonary embolism diagnosed by the composite reference test, demonstration of deep venous thrombosis by CTV was interpreted as a surrogate for pulmonary embolism. The validity of this approach is supported by the literature.^{9,10} Patients with suspected pulmonary embolism in whom the diagnosis is confirmed by diagnostic imaging generally have deep venous thrombosis of the lower extremities, particularly if patients with deep venous thrombosis of the upper extremities are excluded, as we did in the PLOPED II trial.

Other weaknesses of the study include the restriction of recruitment to patients who could safely undergo the extra tests within 36 hours after the reference test. The reported values of

diagnostic accuracy may not apply to pregnant women, patients with renal failure, and patients who are critically ill, in shock, or receiving ventilatory support. Among 1090 recruited patients, 238 did not complete the diagnostic reference testing, primarily because the diagnosis was inconclusive on noninvasive testing and patients or their clinical team declined DSA. A smaller proportion of these patients had a low clinical probability of pulmonary embolism. It is not apparent whether this affected the results. It is also not apparent whether a lack of screening and recruiting of patients during night and weekend shifts affected the results. Patients who presented on weekdays may have had generally milder symptoms than those who presented at night or on weekends.

In conclusion, among patients with suspected pulmonary embolism, multidetector CTA–CTV has a higher sensitivity for the diagnosis than does CTA alone, with similar specificity. The false negative rate of 17 percent for CTA alone indicates the need for additional information to rule out pulmonary embolism. The predictive value of either CTA or CTA–CTV is high with a concordant clinical assessment, but additional testing is necessary when clinical probability is inconsistent with the imaging results.

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APPENDIX

The following people participated in the PLOPED II trial: *Cornell University, New York* — H. Sostman (principal investigator), A. Fisher, S. Goldsmith, C. Henschke, K. Kandarpa, A. Ng, A. Sanders, T. Sos, R. Sullivan, D. Trost, D. Yankelevitz; *Duke University, Durham, N.C.* — V. Tapson (principal investigator), T. Carmon, R. Coleman, L. Heyneman, A. Krichman, H. McAdams, T. Smith, C. Yetsko; *Emory University, Atlanta* — K. Leeper (principal investigator), P. Dean, D. Entzian, B. Hatfield, L. Herridon, K. Horlander, K. Scheidt, M. Sheline, G. Skardasis, R. Woodcock; *Henry Ford Hospital, Detroit* — J. Popovich (principal investigator), R. Almaro, M. Brown, J. Buckley, A. Fogel, M. Ford, K. Karvelis, M. Major, K. McHugh, D. McVinnie, A. Shepard, D. Spizarny, D. Simmons-Villanueva, L. Willcock; *Massachusetts General Hospital, Boston* — C. Hales (principal investigator), J. Cahill, A. Greenfield, T. McLoud, E. Palmer, D. Quinn, J. Scott, J. Shepard, A. Waltman, C. Wittram; *University of Calgary, Calgary, Alta., Canada* — R. Hull (principal investigator), B. Behan, D. Bradley, W. Brunet, P. Burrowes, M. Carson, P. Elliott, L. Hoddinott, R. Kloiber, J. MacGregor, C. Molnar, G. Pineo, M. Sheldon, B. So, K. Weber, C. Wrona; *University of Michigan, Ann Arbor* — J. Weg (principal investigator), L. Sawyer, E. Alahmad, K. Cho, B. Fex, K. Frey, S. Gay, E. Kazerooni, V. Lama, M. Lowell, T. Ojo, S. Patel, P. Shreve, T. Wakefield, D. Schmidtke; *Washington University, St. Louis* — P. Woodard (principal investigator), J. Battaile, S. Bhalla, D. Brown, L. Crouch, R. Gropler, R. Hachem, J. Heiken, A. Lamb, L. Lewis, M. Mohrman, G. Polites, H. Royal, B. Rubin, D. Wehrle, R. Yussen; *Consultants* — A. Gottschalk, Michigan State University, East Lansing; L. Goodman, Medical College of Wisconsin, Milwaukee; *Data and Coordinating Center, George Washington University, Rockville, Md.* — S. Fowler (principal investigator), J. Bamdad, S. Bergman, C. Christophi, S. Grau, M. Hanson, K. Hirst, K. Jablonski, L. Pyle, A. Sapozhnikova, G. Styles, F. Walker-Murray; *Administrative Center, St. Joseph Mercy Oakland Hospital, Pontiac, Mich.* — P. Stein (principal investigator), A. Beemath, F. Kayali; *Project Office, National Heart, Lung, and Blood Institute, Bethesda, Md.* — C. Vreim, M. Wu, G. Zheng; *Data Safety Monitoring Board* — J. Dalen (chair), C. Freund, B. Hillman, T. Hyers, R. Matthay, F. Miller, D. Naidich, M. Schluchter, B. Thompson, H. Peavy (executive secretary); *Steering Committee* — P. Stein (chair), S. Fowler, L. Goodman, A. Gottschalk, C. Hales, R. Hull, K. Leeper, J. Popovich, H. Sostman, V. Tapson, C. Vreim, J. Weg, P. Woodard; *Operations Committee* — P. Stein (chair), S. Fowler, C. Hales, R. Hull, H. Sostman, V. Tapson, C. Vreim, J. Weg; *Writing Committee* — P. Stein (chair), S. Fowler, C. Hales, R. Hull, H. Sostman, J. Weg; *Outcome Committee* — D. Quinn (chair), J. Buckley, K. Leeper, G. Pineo, J. Popovich, A. Sanders, H. Sostman, V.F. Tapson, T. Wakefield, J. Weg, P. Woodard, R. Yussen; *Ethics Committee* — J. Weg (chair), S. Fowler, A. Greenfield, H. Royal, A. Shepard, C. Vreim, D. Yankelevitz; *Ancillary Studies Committee* — G. Pineo (chair), C. Hales, S. Fowler, P. Stein; *DSA Working Group* — T. Sos (chair), D. Brown, K. Cho, C. Fan, K. Kandarpa, D. McVinnie, M. Sheline, T. Smith, B. So, D. Trost, A. Waltman; *CT Working Group* — L. Goodman (chair), P. Burrowes, B. Hatfield, J. Heiken, C. Henschke, L. Heyneman, E. Kazerooni, J. MacGregor, H. McAdams, T. McLoud, S. Patel, J. Shepard, D. Spizarny, C. Wittram, P. Woodard, R. Woodcock, D. Yankelevitz; *Ventilation-Perfusion Scan Working Group* — A. Gottschalk (chair), M. Brown, R. Coleman, S. Goldsmith, C. Molnar, E. Palmer, H. Royal, J. Scott; *Venous Ultrasound Working Group* — T. Wakefield (chair), G. Brunet, B. Fex, A. Fisher, K. Fiest, M. McPharlin, B. Rubin, A. Shepard, G. Skardasis, A. Waltman, P. Woodard; *Clinical Science Working Group* — R. Hull (chair), C. Hales, K. Leeper, G. Pineo, J. Popovich, D. Quinn, P. Stein, V. Tapson, J. Weg, J. Buckley, R. Yussen; *Publications Committee* — C. Hales, H. Sostman (cochairs), S. Fowler, G. Pineo, P. Stein, V. Tapson, P. Woodard.

REFERENCES

1. Drucker EA, Rivitz SM, Shepard JA, et al. Acute pulmonary embolism: assessment of helical CT for diagnosis. *Radiology* 1998;209:235-41.
2. Pruszczyk P, Torbicki A, Pacho R, et al. Noninvasive diagnosis of suspected severe pulmonary embolism: transesophageal echocardiography vs spiral CT. *Chest* 1997; 112:722-8.
3. Otmani A, Tribouilloy C, Leborgne L, et al. Valeur diagnostique de l'échographie cardiaque et de l'angioscanner thoracique hélicoïdal pour le diagnostic de l'embolie pulmonaire aiguë. *Ann Cardiol Angeiol (Paris)* 1998;47:707-15.
4. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. *Ann Intern Med* 2000;132:227-32.
5. Raptopoulos V, Boiselle PM. Multi-detector row spiral CT pulmonary angiography: comparison with single-detector row spiral CT. *Radiology* 2001;221:606-13.
6. Patel S, Kazerooni EA, Cascade PN. Pulmonary embolism: optimization of small pulmonary artery visualization at multi-detector row CT. *Radiology* 2003; 227:445-60.
7. Coche E, Verschuren F, Keyeux A, et al. Diagnosis of acute pulmonary embolism in outpatients: comparison of thin-collimation multi-detector row spiral CT and planar ventilation-perfusion scintigraphy. *Radiology* 2003;229:757-65. [Erratum, *Radiology* 2004;232:627-8.]
8. Winer-Muram HT, Rydberg J, Johnson MS, et al. Suspected acute pulmonary embolism: evaluation with multi-detector row CT versus digital subtraction pulmonary arteriography. *Radiology* 2004;233:806-15.
9. Hull RD, Hirsh J, Carter CJ, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med* 1983; 98:891-9.
10. Hull RD, Hirsh J, Carter CJ, et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. *Chest* 1985;88:819-28.
11. Loud PA, Katz DS, Bruce DA, Klippenstein DL, Grossman ZD. Deep venous thrombosis with suspected pulmonary embolism: detection with combined CT venography and pulmonary angiography. *Radiology* 2001;219:498-502.
12. Cham MD, Yankelevitz DF, Henschke CI. Thromboembolic disease detection at indirect CT venography versus CT pulmonary angiography. *Radiology* 2005;234: 591-4.
13. Revel MP, Petrover D, Hernigou A, Lefort C, Meyer G, Friaia G. Diagnosing pulmonary embolism with four-detector row helical CT: prospective evaluation of 216 outpatients and inpatients. *Radiology* 2005; 234:265-73.
14. Richman PB, Wood J, Kasper DM, et al. Contribution of indirect computed tomography venography to computed tomography angiography of the chest for the diagnosis of thromboembolic disease in two United States emergency departments. *J Thromb Haemost* 2003;1:652-7.
15. Ghaye B, Szapiro D, Willems V, Dondelinger RF. Combined CT venography of the lower limbs and spiral CT angiography of pulmonary arteries in acute pulmonary embolism: preliminary results of a prospective study. *JBR-BTR* 2000;83:271-8.
16. Moores LK, Jackson WL Jr, Shorr AF, Jackson JL. Meta-analysis: outcomes in patients with suspected pulmonary embolism managed with computed tomographic pulmonary angiography. *Ann Intern Med* 2004;141:866-74.
17. Moores LK, Jackson WL Jr. Defining the role of computed tomographic pulmonary angiography in suspected pulmonary embolism. *Ann Intern Med* 2005;142: 802.
18. Quiroz R, Kucher N, Zou KH, et al. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review. *JAMA* 2005;293:2012-7.
19. Kavanagh EC, O'Hare A, Hargaden G,

- Murray JG. Risk of pulmonary embolism after negative MDCT pulmonary angiography findings. *AJR Am J Roentgenol* 2004;182:499-504.
20. Perrier A, Roy P-M, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. *Am J Med* 2004;116:291-9.
21. Remy-Jardin M, Tille-Leblond I, Szapiro D, et al. CT angiography of pulmonary embolism in patients with underlying respiratory disease: impact of multislice CT on image quality and negative predictive value. *Eur Radiol* 2002;12:1971-8.
22. Perrier A, Roy P-M, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. *N Engl J Med* 2005;352:1760-8.
23. Van Belle A, Buller HR, Huisman MV, et al., for the Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 2006;295:172-9.
24. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med* 2001;135:98-107.
25. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003;138:W1-W12.
26. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD Initiative. *Ann Intern Med* 2003;138:40-4.
27. Gottschalk A, Stein PD, Goodman LR, Sostman HD. Overview of Prospective Investigation of Pulmonary Embolism Diagnosis II. *Semin Nucl Med* 2002;32:173-82.
28. Fisher L, van Belle G. *Biostatistics: a methodology for the health sciences*. New York: Wiley, 1993:206.
29. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* 1999;282:1061-6. [Erratum, *JAMA* 2000;283:1963.]
30. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA* 1994;271:703-7.
31. Sox HC. Commentary. *Ann Intern Med* 2004;140:602.
32. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA* 1990;263:2753-9.
33. Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. *Ann Intern Med* 1997;126:775-81.
34. Henry JW, Relyea B, Stein PD. Continuing risk of thromboemboli among patients with normal pulmonary angiograms. *Chest* 1995;107:1375-8.
35. Kipper MS, Moser KM, Kortman KE, Ashbrun WL. Longterm follow-up of patients with suspected pulmonary embolism and a normal lung scan: perfusion scans in embolic suspects. *Chest* 1982;82:411-5.
36. Perrier A, Miron MJ, Desmarais S, et al. Using clinical evaluation and lung scan to rule out suspected pulmonary embolism: is it a valid option in patients with normal results of lower-limb venous compression ultrasonography? *Arch Intern Med* 2000;160:512-6.
37. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998;129:997-1005.
38. Sackett DL. Bias in analytic research. *J Chronic Dis* 1979;32:51-63.
39. Eisner MD. Before diagnostic testing for pulmonary embolism: estimating the prior probability of disease. *Am J Med* 2003;114:232-4.

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