The state of the art, gaps in knowledge, and issues of study design are reviewed and assessed to improve the safe and effective diagnostic evaluation of hemodynamically stable patients with suspected acute pulmonary embolism.
measured by rapid enzyme-linked immunosorbent assay\(^1,2\) or, in the opinion of some, a quantitative latex agglutination test.\(^2\) Exclusion by clinical probability assessment and D-dimer spares the cost and radiation of an imaging evaluation. The 3-month risk of venous thromboembolism in untreated patients with a negative D-dimer measurement and an unlikely\(^4\) or low or intermediate clinical probability\(^6\) was only 0% to 0.5%. If clinical assessment is high probability, a negative D-dimer test result does not exclude pulmonary embolism.\(^3\)

The sensitivity of D-dimer testing for pulmonary embolism increases with the extent of the pulmonary embolism.\(^7,8\) D-dimer concentrations are highest in patients with pulmonary embolism in the pulmonary trunk\(^7\) and with perfusion scan defects involving more than 50% of the lung.\(^8\)

Hospitalized patients often have disorders that cause a positive D-dimer test result.\(^9\) D-dimer tests are less likely to be negative in patients with a history of deep venous thrombosis or pulmonary embolism.\(^10\) In pregnancy, D-dimer levels increase with the gestational period.\(^11\) However, during the early weeks of pregnancy (<20 weeks) D-dimer remains a useful test.\(^11\) Normal D-dimer levels are uncommon in patients aged more than 80 years.\(^12,13\) D-dimer levels might be elevated in patients with cancer.\(^14-16\) In these various populations, measurement of D-dimer might not be useful.

There has been a progressive decrease in the proportion of confirmed cases of acute pulmonary embolism among suspected cases, especially in North America.\(^17\) Also, the proportion of patients with a positive D-dimer test result but without pulmonary embolism has increased dramatically.\(^17\) This has resulted in an important cost-efficacy imbalance in the diagnostic strategies based on D-dimer testing. We might question whether implementing a costly diagnostic workup in a population with a prevalence of pulmonary embolism of only 5% or 10% is reasonable. Thus, the question may not be how should we investigate pulmonary embolism, but rather in whom?\(^17\)

**Further Investigations Needed in Laboratory Diagnosis**

Further investigation of laboratory diagnosis is needed regarding the cost-effectiveness and appropriate cut-points for using D-dimer measurements in patients in whom the diagnostic yield is low (eg, elderly, those with cancer, inpatients, and pregnant women).

**CLINICAL SIGNIFICANCE**

- Diagnostic evaluation should begin with clinical assessment using a prediction rule plus measurement of D-dimer.
- Radiation exposure of CT venography can be reduced by imaging only the proximal leg veins (excluding the pelvis) and obtaining discontinuous images.
- Compression ultrasound may be used instead of CT venography.
- To reduce radiation exposure, ventilation-perfusion lung scans may be preferred in women aged less than 50 years who are outpatients.

**CLINICAL DIAGNOSIS AND PREDICTION RULES**

There is suggestive evidence that there is an enormous failure to suspect pulmonary embolism. Major pulmonary embolism is often undiagnosed ante-mortem.\(^18-21\) Approximately 70% of major pulmonary embolism diagnosed at autopsy had been overlooked.\(^22\) Clinical findings, such as unexplained dyspnea, tachypnea, and chest pain, are useful for the selection of patients for further diagnostic testing.\(^23-25\) Diagnostic methods are completely negated by failure to suspect the diagnosis.

Recent guidelines\(^3,26-28\) recommend that before any tests are performed, the clinical probability of acute pulmonary embolism should be assessed if the diagnosis is suspected. From Bayes’ theorem, the probability of pulmonary embolism after testing depends not only on the sensitivity and specificity of the test but also on the clinical probability before testing.\(^26\) When the clinical probability and results of objective testing are discordant, the post-test probability of pulmonary embolism is neither sufficiently high nor sufficiently low to permit therapeutic decisions. Under these circumstances, further objective testing is mandatory.\(^3\)

Estimates of the clinical probability of pulmonary embolism, based on intuitive assessment by experienced physicians, have a reasonably good predictive value.\(^30,31\) In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), 9% of patients who were assigned a low clinical probability had pulmonary embolism, compared with 30% of those with intermediate clinical probability and 68% of those with high clinical probability.\(^30\) In the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis, pulmonary embolism was present in 9% of patients with a low clinical probability, in 47% with an intermediate probability, and in 91% with a high clinical probability.\(^31\) There is no evidence that the predictive value of such probability assessments can be achieved by less experienced clinicians.\(^32\) The interobserver consistency of pre-test probability assessment is higher with objective assessment than with a physician’s intuitive impression.\(^33\)

Three scoring systems have been tested prospectively and validated in large clinical trials: the Wells’ score,\(^34-38\) Geneva score,\(^39,40\) and Pisa score.\(^31,42\) All 3 scoring systems perform reasonably well in outpatients and emergency departments.\(^4,6,39,41-44\) The Pisa score might be more optimized for use in inpatients.\(^45\)

Other similar scoring systems were proposed more recently.\(^46\) A prediction rule for pulmonary embolism was
introduced that is unique in that it includes the D-dimer level as one factor in the rule.\textsuperscript{47} It had a negative predictive value of 97.8%.\textsuperscript{47}

Clinical prediction rules have numerous variables, variables with positive and negative value predictors,\textsuperscript{48} and variables with varying weights. This makes them difficult to memorize and apply. To address this concern, the Amsterdam Simplified Model scored all Wells criteria with 1 point.\textsuperscript{49} On the basis of data from the Christopher study,\textsuperscript{4} if the score was less than 4 and the D-dimer was normal, 30\% of patients were safely excluded from further testing, with a rate of venous thromboembolism in untreated patients of only 0.5\% during follow-up.\textsuperscript{49}

Our consensus opinion is that clinical probability should be recorded in the admission notes and included on every request form for computed tomography (CT) angiography.\textsuperscript{50} The appropriate and consistent use of scoring systems should be considered as a measure of health care quality.

Further investigation of clinical diagnosis is needed regarding the following.

- Clinical hallmarks of acute pulmonary embolism should be identified. Such hallmarks could prompt further clinical assessment with a prediction rule for probability of pulmonary embolism.
- Newer, more simplified prediction rules need validation, although the need for simplicity might not be the limiting factor.
- Prediction rules are needed for patients who are severely ill and for patients whose clinical picture might be changing rapidly.
- The role of D-dimer measurement combined with clinical parameters into a prediction rule should be tested.

**IMAGING DIAGNOSIS**

**Role of Computed Tomography Angiography and Venography**

Multidetector contrast-enhanced CT angiography, in combination with a concordant clinical assessment, has a high positive and negative predictive value.\textsuperscript{51} The sensitivity and specificity of CT angiography have been reviewed.\textsuperscript{52} Outcome studies\textsuperscript{6,4} have shown that the diagnosis of pulmonary embolism can be safely excluded by a negative multislice CT angiogram.

The role of CT venography is less well established than CT angiography. Thromboembolic risk is low in those with a negative single-detector CT angiogram combined with a negative compression ultrasound,\textsuperscript{53} or a negative compression ultrasound with a moderate or low probability clinical assessment.\textsuperscript{5,4} The sensitivity of 4-slice CT angiography was increased from 83\% to 90\% by use of CT venography in combination,\textsuperscript{51} albeit the increase was not statistically significant. With 16-slice CT, 16\% of patients with suspected pulmonary embolism who were shown to have venous thromboembolism were diagnosed by a positive CT venogram, although the CT angiogram was negative.\textsuperscript{55} However, with either a single-slice or multislice CT\textsuperscript{4} or 4-slice or 16-slice CT,\textsuperscript{6} outcome studies after a negative CT angiogram showed pulmonary embolism on follow-up of untreated patients in only 1.3\%\textsuperscript{4} or 1.7\%\textsuperscript{4} of patients.\textsuperscript{6} Non-invasive leg tests added little to the outcome in these studies.\textsuperscript{6} This outcome may reflect a low rate of symptomatic recurrent pulmonary embolism in patients with undiagnosed small pulmonary embolism.\textsuperscript{56}

Whether CT venography is necessary in patients with suspected pulmonary embolism who are evaluated with 64-slice CT angiography is not known. We also do not know whether there is an increased sensitivity of 64-slice CT angiography compared with 4-slice CT for the detection of acute pulmonary embolism.

With increasing use\textsuperscript{57} of 16-slice and 64-slice CT angiography as a quasi-screening technique, there is a potential for false-positive diagnoses.\textsuperscript{29} Bayes’ theorem predicts that with an assumed sensitivity of 90\% and specificity of 95\% for CT angiography, patients who have a low (12\%) pretest probability for pulmonary embolism will have a false-positive rate of 58\% and patients who have a moderate (22\%) pretest probability will have a 9.5\% false-positive rate.\textsuperscript{29} Furthermore, in a large accuracy study of CT angiography,\textsuperscript{51} it was reported that the positive predictive values for pulmonary embolism detected by CT angiography in the lobar, segmental, and subsegmental vessels were 97\%, 68\%, and 25\%, respectively, albeit with some doubt about the validity of the reference standard for isolated small pulmonary embolism. Whether 64-slice scanners will alleviate or amplify this problem is not known.

Dangers of radiation require that protocols for CT angiography be optimized.\textsuperscript{58} In regard to CT venography, it was found in PIOPED II that no patient with pulmonary embolism or deep venous thrombosis would have been undiagnosed if imaging of the pelvic veins had not been done.\textsuperscript{58} Patients with pelvic vein thrombosis also had proximal leg deep venous thrombosis or pulmonary embolism,\textsuperscript{58} so CT venography of only the thighs (excluding the pelvic veins) would reduce the radiation exposure at no loss of diagnostic sensitivity.\textsuperscript{55,58} The results of discontinuous axial imaging of the proximal leg veins showed good, but not perfect, agreement with continuous helical imaging.\textsuperscript{58} Adopting discontinuous imaging and other dose-reduction strategies can reduce pelvic radiation by more than 75\%.\textsuperscript{58} Finally, it also has been shown that CT venography and compression ultrasonography are diagnostically equivalent.\textsuperscript{59}

It seems that CT angiography is being used excessively, with CT angiography showing pulmonary embolism in less than 10\% of patients in some emergency departments.\textsuperscript{17} The increasing use of CT may result in an increased incidence of radiation-related cancer in the not-too-distant future.\textsuperscript{26,57,60} Breast irradiation with CT angiography in an average 60-kg woman is 20 mGy per breast,\textsuperscript{61} 50 to 80 mGy based on CT coronary angiography,\textsuperscript{62} and as much as 190 mGy with CT angiography in a woman with large breasts.\textsuperscript{63} The estimated risk of cancer from CT coronary angiography may be as
Role of pulmonary scintigraphy

Because of the risk of radiation with CT angiography, particularly radiation of the breasts, scintigraphy may be the imaging test of choice in women aged less than 50 years. Breast irradiation with ventilation-perfusion scintigraphy is approximately 0.28 to 0.9 mGy,64 which is not more than 0.5% to 5% of the radiation dose to the breasts resulting from CT angiography. In PIOPED I (32% outpatients), ventilation-perfusion scans gave a definitive diagnosis in only 28% of patients.30 More recently, in a mixed population of inpatients and outpatients, 46% had a definitive diagnosis by ventilation-perfusion scans.65 Retrospective analysis of data from PIOPED II (75% outpatients) showed a definitive ventilation-perfusion lung scan in 74% of patients.66 If the chest radiograph was normal or nearly normal, a definitive reading of the ventilation-perfusion scan was shown in 89%67 and 91%68 of patients. However, without the low probability interpretation, and considering a very low probability interpretation as nondiagnostic, some found a definitive diagnosis by ventilation-perfusion in patients with a normal chest radiograph of only 22%69 and 52%.70 A low probability interpretation of the ventilation-perfusion scan is as reliable as CT angiography in excluding pulmonary embolism when the clinical probability is low or moderate.71 A randomized trial showed equivalent outcomes comparing patients evaluated with a clinical prediction rule and either CT angiography or ventilation-perfusion scintigraphy, although more patients had pulmonary embolism that was detected by CT angiography.65

If scintigraphy includes only a perfusion scan, elimination of the ventilation scan could reduce cost and radiation exposure.28 A normal perfusion scan excludes pulmonary embolism with a negative predictive value close to 100%.30,72,73 The ventilation scan can be eliminated in most patients without reducing diagnostic accuracy.31,72-74 If outcome studies confirm its efficacy, perfusion scintigraphy could be beneficial in young women and in other patients in whom reduced radiation exposure is preferred. It is arguable that the benefits of more comprehensive imaging with CT angiography would outweigh the smaller risks of radiation in an older population and in men of all ages.

Role of Magnetic Resonance Angiography

Gadolinium-enhanced magnetic resonance angiography is a potentially useful imaging modality for patients with suspected acute pulmonary embolism, in whom it is important to avoid exposure to ionizing radiation, or patients allergic to iodinated contrast material. Investigations in a few patients showed sensitivity for the detection of pulmonary embolism with gadolinium-enhanced magnetic resonance angiography of 77% to 100% and specificity of 95% to 98%.75-77 More recently, however, sensitivities of 31% and 71% (reader 1 and reader 2, respectively) and specificities of 85% and 92% were reported.78 Analogous to CT venography, venous phase imaging of the proximal veins of the lower extremity in combination with gadolinium-enhanced magnetic resonance angiography of the chest has been recommended.79 The sensitivity and specificity of magnetic resonance angiography combined with magnetic resonance venography are being investigated in PIOPED III.

There is concern about nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy, which occurs rarely in patients with poor renal function who receive gadolinium-containing contrast material.80,81 The American College of Radiology 2007 recommendations were that no special treatment or handling is needed for patients with kidney disease with a glomerular filtration rate (GFR) greater than or equal to 60 mL/min/1.73 m².82 Patients with any level of renal disease, however, should not receive gadodiamide (Omniscan, Amersham Health, AS, Oslo, Norway).82 Patients with moderate kidney disease (GFR 30-59 mL/min/1.73 m²), severe kidney disease (GFR 15-29 mL/min/1.73 m²), end-stage kidney disease (GFR < 15 mL/min/1.73 m²), on dialysis, or with acute kidney injury should be imaged with the lowest dose that would provide a diagnostic benefit. The radiologist should order the dose and type of gadolinium-containing contrast agent, and informed consent should be obtained.82 In the future, magnetic resonance angiography of the pulmonary arteries without contrast material may be possible, as it is already for the aorta.83 However, to date, non–contrast-enhanced magnetic resonance angiography for acute pulmonary embolism in small case series showed a high sensitivity but suboptimal specificity,84-86 or vice versa.87

Further investigation of imaging diagnosis is needed regarding the following:

- Outcome should be assessed in untreated patients evaluated with 64-slice CT angiography alone versus those evaluated with 64-slice CT angiography and lower-extremity imaging with ultrasound or CT venography.
- In young women with suspected acute pulmonary embolism who are outpatients and have a normal chest radiograph, outcome should be compared in those evaluated with ventilation-perfusion scans versus CT angiography.
- The accuracy of an abnormal perfusion scan alone (without ventilation imaging) should be assessed in patients with either a normal or abnormal chest radiograph.
- The significance of asymptomatic pulmonary embolism, detected on CT angiography performed for another indication, should be assessed.
- The significance of subsegmental emboli in symptomatic patients should be assessed.
- Methods for making or excluding the diagnosis of pulmonary embolism in critically ill patients and those in intensive care units who cannot be safely moved to the radiology department should be assessed.
RESEARCH METHODOLOGY

Imaging is useful for investigation of topics, such as prevalence of disease in different populations, clinical prediction rules, and new laboratory tests. Accordingly, we recommend the adoption of imaging as a diagnostic reference standard that would enable studies of such studies to be performed, rather than relying on outcome studies. This leads to a conundrum of establishing a reference test for determining the accuracy of the most up-to-date imaging modalities. Previous reference standards for evaluation of the most advanced imaging modalities now are outdated and inapplicable, so imaging research is going to be limited to outcome designs. Such approaches carry much uncertainty. Conventional pulmonary angiography, being invasive, is now considered to be inappropriate for use in research as a reference standard. Many consider CT angiography to be the new diagnostic reference standard for pulmonary embolism. An accuracy study comparing multidetector row CT angiography with conventional pulmonary angiography demonstrated a false-positive CT angiography rate of 11% with most false positives in isolated segmental vessels or subsegmental vessels. However, the validity of the assumption that discordance with pulmonary angiography means CT angiography is wrong has been questioned. Wittram and associates examined 20 discrepant CT pulmonary angiograms and conventional pulmonary angiograms from PIOPED II. Most discrepancies were at the segmental or subsegmental level. The use of composite reference criteria, as was adopted in PIOPED II, can be used for noninferiority evaluation of new technologies, but these do not serve the need, for example, to demonstrate a difference between 16-slice and 64-slice CT angiography. Prospective outcome studies or studies comparing different diagnostic tools or strategies with a randomized design are preferred.

References


