CLINICAL PRACTICE

# The Evaluation of Suspected Pulmonary Embolism

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

**An otherwise healthy 51-year-old woman presents to her physician with pleuritic right posterior chest pain, without dyspnea or hemoptysis. Her temperature is 38.2°C, and her pulse is 102 beats per minute. Physical examination discloses a pleural friction rub over the posterior right hemithorax but is otherwise unremarkable. A chest radiograph is normal. She is treated with an antiinflammatory agent for presumed viral pleurisy. Three days later, she returns, reporting dyspnea. How should she be evaluated?**

## THE CLINICAL PROBLEM

Although the exact incidence of pulmonary embolism is uncertain, it is estimated that 600,000 episodes occur each year in the United States, resulting in 100,000 to 200,000 deaths.[1] When the diagnosis of embolism is confirmed and effective therapy is initiated, recurrence of embolism is rare and death is uncommon — with the exception of patients who initially present with hemodynamic impairment, among whom the mortality rate approaches 20 to 30 percent.[2,3] The majority of preventable deaths associated with pulmonary embolism can be ascribed to a missed diagnosis rather than to a failure of existing therapies.

The diagnosis of pulmonary embolism is confounded by a clinical presentation that may be subtle, atypical, or obscured by another coexisting disease.[4] Several noninvasive diagnostic techniques have been developed to improve the accuracy of diagnosis and limit the number of patients who require angiography, a procedure that is associated with some risk and is underutilized in traditional diagnostic strategies.[5,6] However, no single noninvasive diagnostic test is sufficiently sensitive or specific for the diagnosis in all patients.

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## STRATEGIES AND EVIDENCE

### CLINICAL DIAGNOSIS

The clinical presentation and routinely available laboratory data, such as results on electrocardiography, chest radiography, and analysis of arterial blood gases, cannot be relied on to confirm or rule out pulmonary embolism. Although symptoms and signs such as dyspnea, pleuritic chest pain, tachypnea, and tachycardia can raise the suspicion of embolism and indicate a need for further evaluation, these findings are inconsistent in patients with embolism and are nonspecific.[4,7] The presence of one or more risk factors for venous thromboembolism (Table 1) may lower the threshold for the consideration of a diagnostic evaluation. As a means of providing an objective basis for the clinical assessment of the probability of embolism, several sets of standardized prediction rules have been evaluated and published; these range widely in complexity.[8-11] Simple pre-

**Table 1. Risk Factors for Venous Thromboembolism.**

| |
|---|
| Age >40 yr |
| History of venous thromboembolism |
| Surgery requiring >30 min of anesthesia |
| Prolonged immobilization |
| Cerebrovascular accident |
| Congestive heart failure |
| Cancer |
| Fracture of pelvis, femur, or tibia |
| Obesity |
| Pregnancy or recent delivery |
| Estrogen therapy |
| Inflammatory bowel disease |
| Genetic or acquired thrombophilia |
| Antithrombin III deficiency |
| Protein C deficiency |
| Protein S deficiency |
| Prothrombin G20210A mutation |
| Factor V Leiden |
| Anticardiolipin antibody syndrome |
| Lupus anticoagulant |

diction rules (Table 2) involve information that can be acquired easily in the outpatient setting or the emergency room.[9,10] More complicated prediction rules involve a larger number of clinical variables and require the interpretation of radiographic and electrocardiographic data by experts.[11]

The use of empirical or standardized assessments of probability allows patients to be classified into three groups on the basis of the approximate prevalence of pulmonary embolism: low clinical probability (a subgroup with a prevalence of 10 percent or less), intermediate clinical probability (a prevalence of approximately 30 percent), and high clinical probability (a prevalence of approximately 70 percent or higher).[8-11] The combined use of the estimated clinical probability and the results of one or more noninvasive tests substantially increases the accuracy in confirming or ruling out embolism, as compared with either assessment alone.

### D-DIMER TESTING

The measurement of the degradation products of cross-linked fibrin (D-dimer) circulating in plasma is a highly sensitive but nonspecific screening test for suspected venous thromboembolism. Elevated levels are present in nearly all patients with embolism but are also associated with many other circumstances, including advancing age, pregnancy, trauma, the postoperative period, inflammatory states, and cancer.[12] The role of D-dimer testing is therefore limited to the ruling out of embolism.

Multiple D-dimer assays have been developed, with sensitivities that range from almost 100 percent to as low as 80 percent. Highly sensitive assays, such as standard or rapid enzyme-linked immunosorbent assays, have high false positive rates but safely rule out thromboembolism in outpatients presenting with a low clinical probability of embolism.[13-16] Less sensitive assays (e.g., latex agglutination or red-cell agglutination) cannot be used in isolation to rule out thromboembolism. The generalized application of D-dimer testing has been limited by a burgeoning number of available assays and a lack of standardization that has resulted in uncertainty among clinicians regarding the predictive value of the particular assays available to them.

### VENTILATION–PERFUSION SCANNING

Ventilation–perfusion scanning has had a central role in the diagnosis of embolism for almost three decades and is a valuable tool when the results are definitive.[17] A normal ventilation–perfusion scan essentially rules out the diagnosis of embolism, and a scan deemed to indicate a high probability of embolism is strongly associated with the presence of embolism. However, large trials have demonstrated that most patients with suspected embolism who undergo ventilation–perfusion scanning do not have findings that are considered definitive. The majority of patients with embolism do not have findings on scanning that indicate a high probability of embolism, and the overwhelming majority of patients without embolism do not have normal findings on scanning.[7]

### COMPUTED TOMOGRAPHY

The use of computed tomography (CT) has been a major advance in the diagnosis of embolism. Unlike ventilation–perfusion scanning, it allows the direct visualization of emboli as well as the detection of parenchymal abnormalities that may support the diagnosis of embolism or provide an alternative explanation for the patient's symptoms. The reported sensitivity of helical CT scanning for the diagnosis of embolism ranges from 57 to 100 percent, and its reported specificity ranges from 78 to 100 percent.[18,19] These wide ranges are explained in part by differences in the technology used, since newer scanners allow higher resolution, dramatically faster scanning times, better peripheral visualization, and less motion artifact than earlier-generation scanners. The sensitivity and specificity also vary with the location of the emboli, ranging from

90 percent (for both measures) for emboli involving the main and lobar pulmonary arteries to much lower rates for emboli that are confined to segmental or subsegmental pulmonary vessels. In a recent series, the sensitivity of helical CT for the detection of emboli in subsegmental arteries, based on reports by two readers, ranged from 71 to 84 percent even after scans that could not be read because of motion artifact or poor opacification had been excluded[20]; moreover, more than half of subsegmental vessels could not be evaluated by each of two readers.

Isolated thromboembolism of the subsegmental pulmonary arteries is not unusual, occurring in 6 to 30 percent of patients with embolism in different series.[21,22] Thus, filling defects involving the main or lobar pulmonary arteries can be considered diagnostic of embolism, whereas a normal CT scan may indicate a substantially reduced likelihood of embolism but cannot be used to rule out the possibility of embolism with the same degree of certainty that a negative ventilation–perfusion scan provides.[23,24] Outcome studies have demonstrated that withholding anticoagulant therapy in patients with a negative CT scan coupled with a negative ultrasonographic study of the legs is a safe strategy, except in those patients who present with a high clinical probability of embolism.[23-26]

**Table 2. Rules for Predicting the Probability of Embolism.***

| Variable | No. of Points |
|---|---|
| **Risk factors** | |
| Clinical signs and symptoms of deep venous thrombosis | 3.0 |
| An alternative diagnosis deemed less likely than pulmonary embolism | 3.0 |
| Heart rate >100 beats/min | 1.5 |
| Immobilization or surgery in the previous 4 wk | 1.5 |
| Previous deep venous thrombosis or pulmonary embolism | 1.5 |
| Hemoptysis | 1.0 |
| Cancer (receiving treatment, treated in the past 6 mo, or palliative care) | 1.0 |
| **Clinical probability** | |
| Low | <2.0 |
| Intermediate | 2.0–6.0 |
| High | >6.0 |

* Adapted from Wells et al.[9]

### EVALUATION OF THE LEG VEINS

Most pulmonary emboli arise from the deep veins of the legs. Ultrasonography is positive in 10 to 20 percent of all patients without leg symptoms or signs who undergo evaluation and in approximately 50 percent of patients with proven embolism.[27,28] Therefore, the possibility of embolism cannot be ruled out on the basis of negative results on ultrasonography. Moreover, positive ultrasonographic findings in a patient without symptoms or signs referable to the legs should be interpreted with caution.[29] Because ultrasonographic studies may be falsely positive or may detect residual abnormalities related to previous venous thrombosis, only definitely positive studies under appropriate clinical circumstances (e.g., in a patient without a history of venous thrombosis who has a high clinical probability of pulmonary embolism) should serve as a basis for the initiation of therapy.

### CONVENTIONAL PULMONARY ANGIOGRAPHY

Pulmonary angiography is the gold standard for the diagnosis of pulmonary embolism, but it has limitations. It requires expertise in performance and interpretation, is invasive, and has associated risks, although modern techniques and contrast materials have reduced the risks substantially.[29-32] Among patients undergoing angiography in the Prospective Investigation of Pulmonary Embolism Diagnosis trial, 0.5 percent died, and major nonfatal complications (respiratory failure, renal failure, or hematoma necessitating transfusion) occurred in 0.8 percent. Angiography is reserved for the small subgroup of patients in whom the diagnosis of embolism cannot be established by less invasive means. Even under these circumstances, angiography appears to be underutilized.[16,17]

### APPROACHES TO TESTING

The initiating point for any diagnostic approach is clinical suspicion; the degree of suspicion should guide the choice of the initial test. Given current variations in practice, strategies that incorporate either ventilation–perfusion scanning or helical CT as the lung-imaging technique should be considered.

This discussion assumes that the patient with suspected embolism does not have signs or symptoms of acute venous thrombosis. If such signs or symptoms are present, duplex ultrasonography of the legs might be the initial diagnostic choice, given its availability, sensitivity, specificity, and cost.[33]

#### *High Clinical Probability of Pulmonary Embolism*

Depending on the clinical setting and the tool used for clinical assessment, approximately 10 to 30 per-

cent of patients with suspected embolism are categorized as having a high clinical probability of embolism; in this subgroup, the prevalence of pulmonary embolism ranges from 70 to 90 percent.[5,34-36] A positive helical CT scan or a result on ventilation–perfusion scanning that indicates a high probability of embolism would be considered diagnostic of embolism with more than 95 percent certainty. For the remaining patients, the diagnostic strategies outlined in Figure 1 would be appropriate.

*Low Clinical Probability of Pulmonary Embolism*

Twenty-five to 65 percent of patients with suspected embolism are categorized as having a low clinical probability of embolism; in this subgroup, the prevalence of pulmonary embolism ranges from 5 to 10 percent.[5,13,34-36] Several approaches are effective in patients with a low clinical probability of embolism, and outcome data have suggested that they are safe. Pulmonary embolism can be ruled out in outpatients in this category on the basis of negative

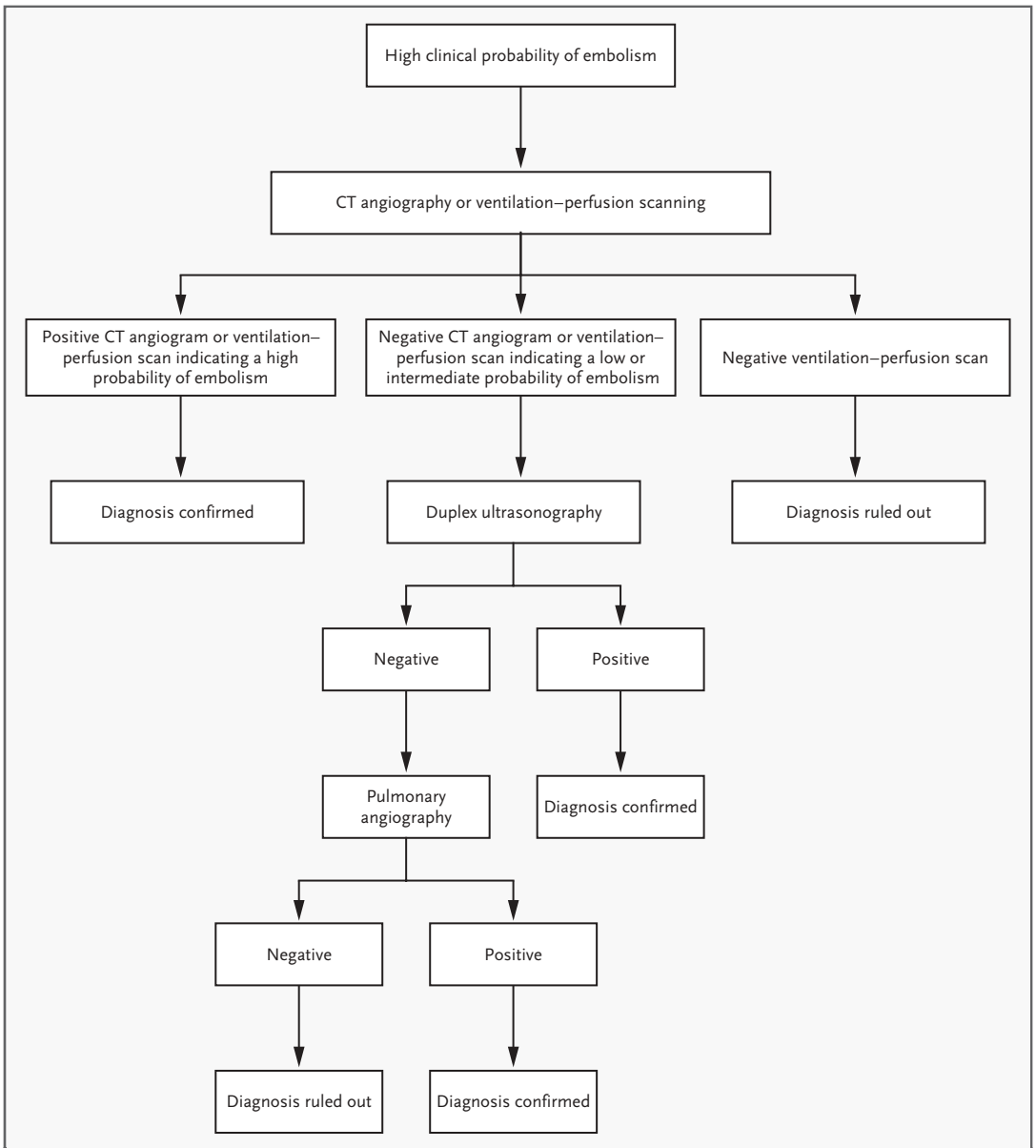


**Figure 1. Diagnostic Approach to a Patient with a High Clinical Probability of Embolism, Using Helical CT Scanning or Ventilation–Perfusion Scanning as the Initial Diagnostic Study.**

results on a validated, standardized, highly sensitive D-dimer assay (Fig. 2). Embolism can also be ruled out in such patients on the basis of a result on ventilation–perfusion scanning that indicates a low or intermediate probability of embolism, or a negative result on helical CT scanning coupled with a negative result on compression ultrasonography. For the remaining patients, the diagnostic strategies outlined in Figure 3 would be appropriate.

*Intermediate Clinical Probability of Pulmonary Embolism*

Another 25 to 65 percent of patients with suspected embolism are categorized as having an intermediate clinical probability of embolism; in this subgroup, the prevalence of pulmonary embolism ranges from 25 to 45 percent.[5,34-36] A result on ventilation–perfusion scanning that indicates a high probability of embolism is associated with a likelihood of pulmonary embolism of 88 to 93 percent among patients in this category. The risks associated with anticoagulant therapy and the long-term health and financial factors that must be considered are not inconsequential, and thus the diagnosis should be substantiated. The diagnostic strategies outlined in Figure 4 would be appropriate.

## SPECIAL CIRCUMSTANCES

The choice of tests will vary in certain clinical circumstances. In patients with severe preexisting pulmonary parenchymal or airway disease, ventilation–perfusion scanning is of limited usefulness, given the high likelihood that the result will be nondiagnostic.[37] In these circumstances, an approach involving the use of helical CT scanning as the initial diagnostic study would be appropriate. An added advantage of helical CT scanning in this population of patients is the information it may provide about the lung parenchyma and other structures that might help to establish an alternative diagnosis.

Patients with a history of pulmonary embolism represent a particular diagnostic challenge. Although follow-up data are limited, residual defects have been detected on perfusion scanning in 66 percent of patients three months after acute embolism.[38] In the absence of a study in patients who have completed therapy, it is uncertain whether abnormalities detected by ventilation–perfusion scanning or CT scanning represent residua of the initial event or recurrent thromboembolism. The angiographic appearance of acute embolism differs from that of chronic thromboembolism, and pulmonary angiography may be required in patients with previous embolism.[39]

The use of contrast medium in the amounts required for CT scanning (100 to 150 ml) poses a substantial risk of nephropathy in patients with preexisting renal insufficiency, especially those with diabetes mellitus.[40] In such patients, it is reasonable to pursue a strategy involving the initial use of duplex ultrasonography and ventilation–perfusion scanning, followed by selective conventional pulmonary angiography if the diagnosis remains unclear.

For patients in intensive care settings, notably those receiving mechanical ventilatory support, the need to transport the patient elsewhere for testing often becomes a major factor in the selection of the diagnostic approach, and bedside duplex ultrasonography is a reasonable initial test. Ventilation–perfusion scanning, although logistically difficult to perform in patients receiving mechanical ventilation, appears to retain its diagnostic usefulness.[41] Helical CT scanning is a reasonable approach, although a preliminary report has questioned its accuracy in this population of patients.[42]

Venous thromboembolism is a leading cause of

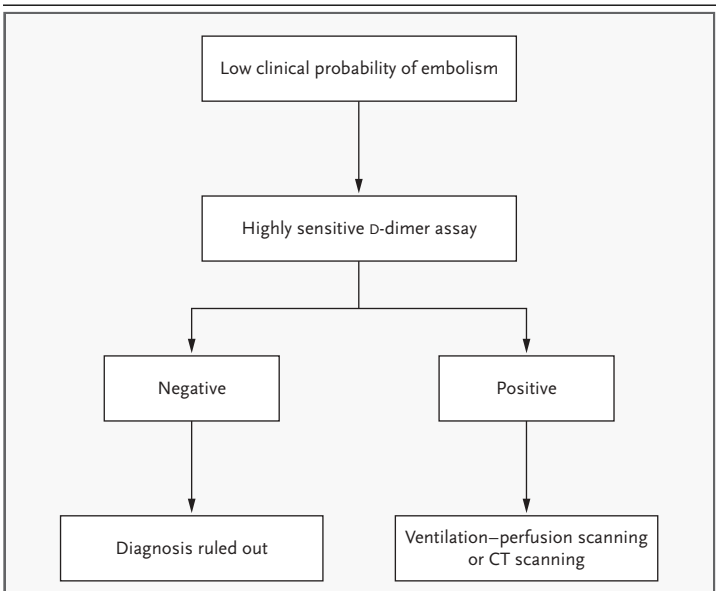


**Figure 2. Diagnostic Approach to an Outpatient with a Low Clinical Probability of Pulmonary Embolism, Using a D-Dimer Assay as the Initial Diagnostic Assay.**

If ventilation–perfusion scanning or CT scanning is performed, the subsequent diagnostic steps should be determined according to the clinical probability of embolism.

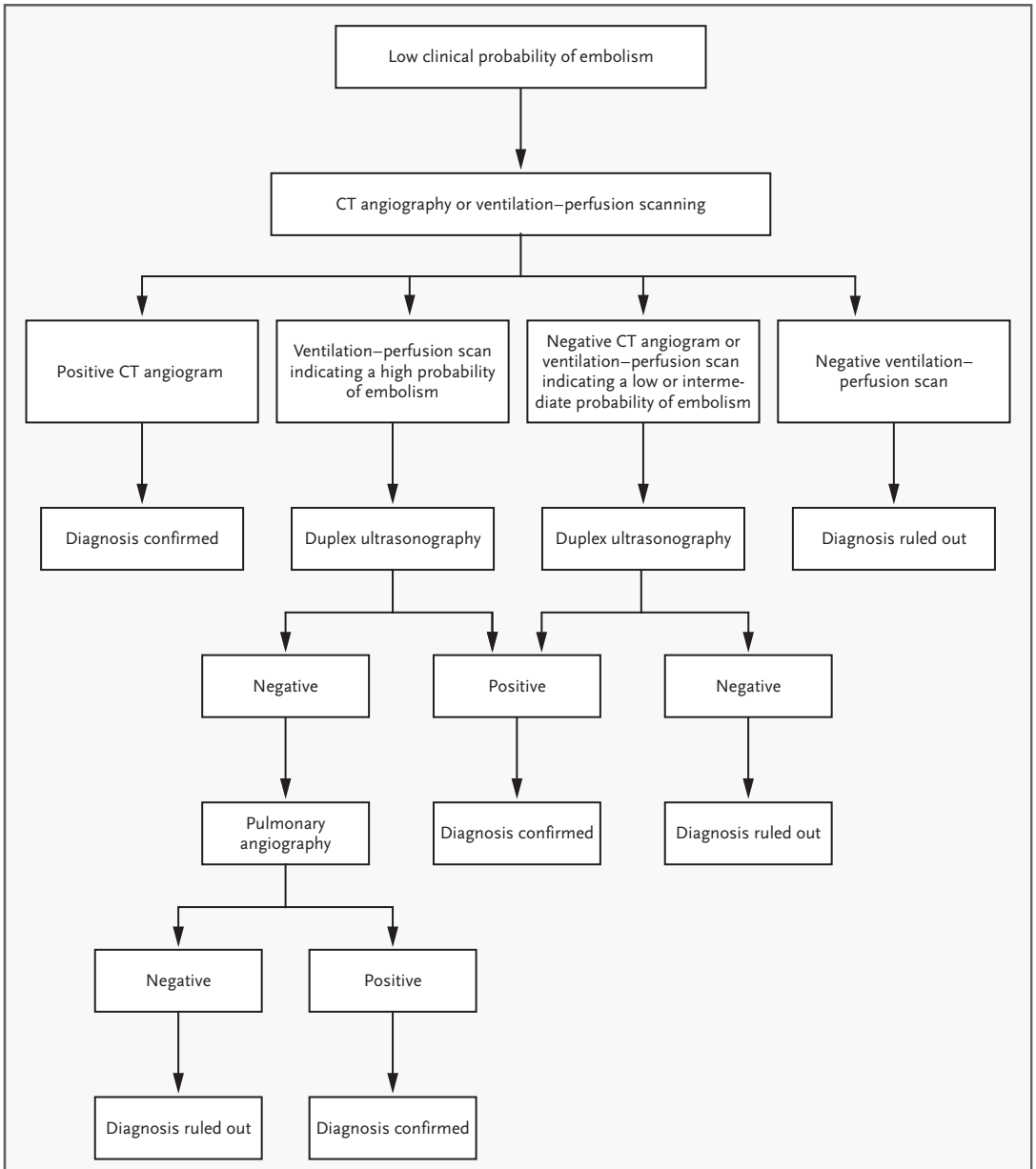


**Figure 3. Diagnostic Approach to a Patient with a Low Clinical Probability of Embolism, Using Helical CT Scanning or Ventilation–Perfusion Scanning as the Initial Diagnostic Study.**

death during pregnancy. Given the risk to the fetus associated with exposure to radiation, a diagnostic approach that limits such exposure is warranted, although objective diagnostic testing should not be withheld solely because of this risk. Duplex ultrasonography is an appropriate initial diagnostic approach. If the findings on ultrasonography are negative, the diagnostic evaluation should proceed, as described, on the basis of the clinical probability of embolism.[43]

## AREAS OF UNCERTAINTY

The yield and cost effectiveness of different diagnostic strategies have not been directly compared in a clinical trial. The optimal role of CT scanning in

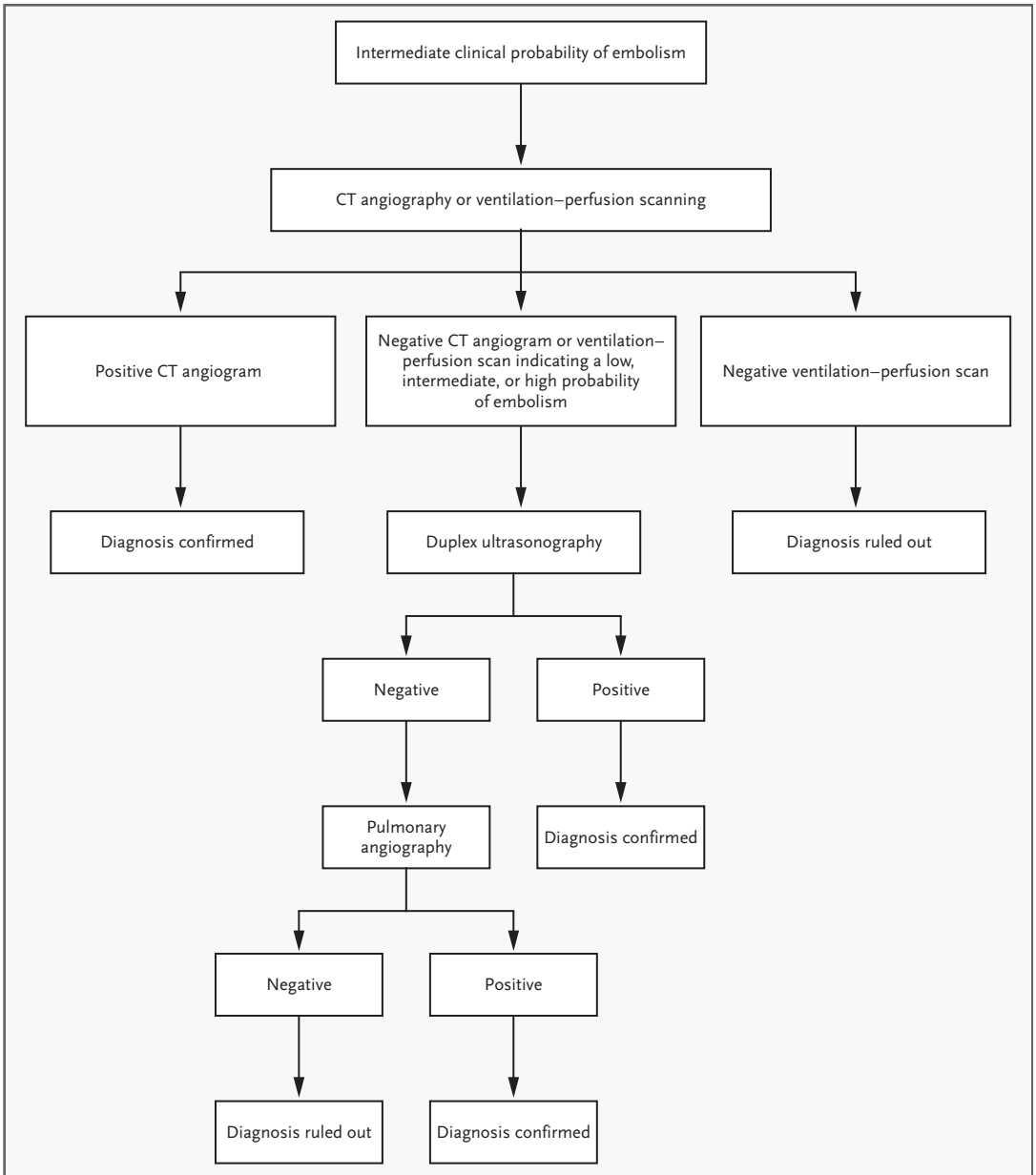


**Figure 4. Diagnostic Approach to a Patient with an Intermediate Clinical Probability of Embolism, Using Helical CT Scanning or Ventilation–Perfusion Scanning as the Initial Diagnostic Study.**

the diagnosis of pulmonary embolism is still evolving. CT scanning has substantial diagnostic value when it is used in conjunction with a tool for assessing the clinical probability of embolism, ultrasonography of the legs, D-dimer testing, or some combination of these techniques. However, the results of published studies do not support the use of helical CT scanning as an isolated test for the ruling out of embolism and have demonstrated that, as a single test, it is not cost effective.[44,45]

The short-term risk of death due to pulmonary embolism is related to the presence of systemic hypotension, a late and potentially fatal manifestation of right ventricular dysfunction at the time of diagnosis. Preliminary studies suggest that the use of transthoracic echocardiography and biochemical

markers such as serum troponin levels or serum brain natriuretic hormone levels to evaluate right ventricular function may improve the assessment of short-term risk by identifying patients who are at high risk for adverse events, including death.[46-49]

The potential long-term consequences of embolism include recurrence, incomplete resolution, and — in 0.1 to 1.0 percent of patients — the development of chronic thromboembolic pulmonary hypertension.[38,50] Testing after completion of therapy has been suggested, but it is not the current standard of care.[38,51] Although such testing is expensive, its results would be useful in the evaluation of patients with a suspected recurrence. Testing after therapy might also assist in the identification of patients with pulmonary vascular obstruction that is sufficient to place them at risk for chronic thromboembolic pulmonary hypertension or to warrant consideration of a more prolonged course of anticoagulant therapy than is usual.

## GUIDELINES

Clinical guidelines issued by the American Thoracic Society[52] and the European Society of Cardiology[53] recommend approaches to suspected acute pulmonary embolism that use the assessment of the clinical probability of embolism in decision making and are in general agreement with those outlined here. However, two distinctions should be noted. First, D-dimer testing is not included in the American Thoracic Society guidelines, since these guidelines were issued in 1999, before clinical studies had demonstrated the value of such testing in the context of clinical-probability rules.[52] In addition, the Congress of the European Society of Cardiology recommends that D-dimer testing followed by ultrasonography of the legs be performed before a lung-imaging study is considered in outpatients with suspected pulmonary embolism that is judged not to be massive,[53] whereas we recommend compression ultrasonography after a nondiagnostic lung study.

## CONCLUSIONS AND RECOMMENDATIONS

In the evaluation of a patient with suspected pulmonary embolism, it should be understood that a sequential diagnostic approach might be necessary and that the optimal use of noninvasive techniques will substantially decrease the need for angiography but not eliminate it. The recommendations provided here are intended not as rigid criteria but rather as guidelines that can be adapted according to the clinical circumstances, available facilities, local practices and expertise, and anticipated advances in the diagnosis of embolism.

The diagnosis of embolism should have been suspected in the patient in the vignette at the time of her initial presentation.[54] Pleuritic chest pain in the absence of dyspnea is a well-recognized presentation of embolism.[4] A low-grade fever may also occur, especially with pulmonary infarction.[55] At her initial presentation, the patient would have been categorized as having a low clinical probability of embolism, according to the criteria of Wells et al.[9] (Table 2). Under this circumstance and depending on local practices, a standardized, highly sensitive D-dimer assay could be performed; negative results would rule out the diagnosis. When dyspnea developed, the patient would have been considered to have an intermediate clinical probability of embolism. Under this circumstance she could be referred directly for ventilation–perfusion scanning or CT scanning. A positive CT scan would confirm the diagnosis, and a negative ventilation–perfusion scan would rule it out. A negative CT scan or a ventilation–perfusion scan that was nondiagnostic or that indicated a high probability of embolism would call for duplex ultrasonography of the legs. Positive results would confirm the diagnosis, whereas negative results, coupled with a negative CT scan, would rule it out.

Dr. Tapson reports having received honorariums from Aventis.

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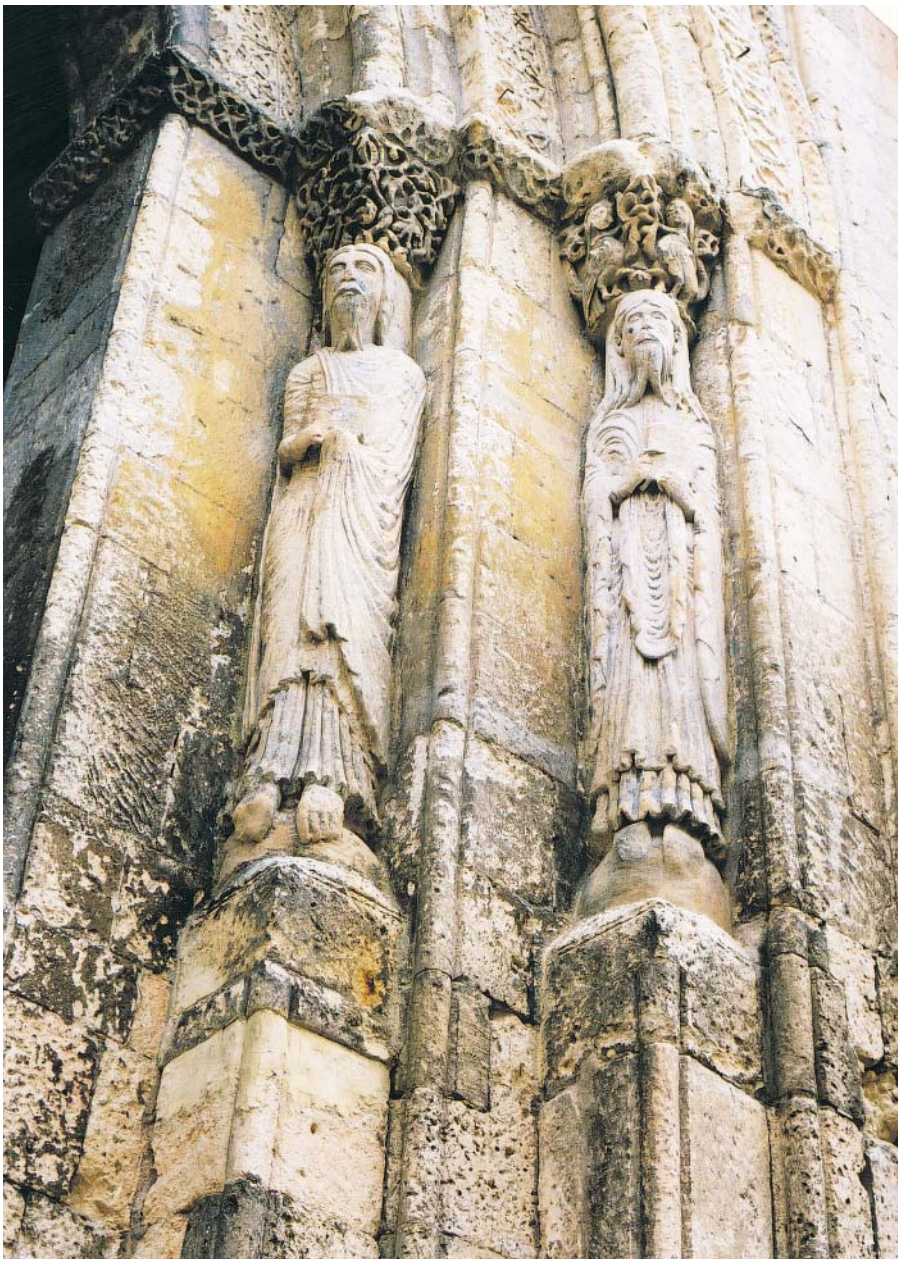

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