

# Computed Tomographic Pulmonary Angiography vs Ventilation-Perfusion Lung Scanning in Patients With Suspected Pulmonary Embolism

## A Randomized Controlled Trial

David R. Anderson, MD

Susan R. Kahn, MD

Marc A. Rodger, MD

Michael J. Kovacs, MD

Tim Morris, MD

Andrew Hirsch, MD

Eddy Lang, MD

Ian Stiell, MD

George Kovacs, MD

Jon Dreyer, MD

Carol Dennie, MD

Yannick Cartier, MD

David Barnes, MD

Erica Burton, BSc

Susan Pleasance, BScN

Chris Skedgel, MSc

Keith O'Rourke, PhD

Philip S. Wells, MD

**P**ULMONARY EMBOLISM IS A COMMON and serious medical condition leading to the hospitalization or death of more than 250 000 people in the United States each year.<sup>1</sup> It is the third leading cause of cardiovascular mortality and is estimated to result in 5% to 10% of all deaths in US hospitals.<sup>2</sup> Despite the potentially lethal nature of this condition, pulmonary embolism remains one of the most difficult conditions for clinicians to diagnose accurately.<sup>3</sup> Given

For editorial comment see p 2788.

**Context** Ventilation-perfusion ( $\dot{V}/\dot{Q}$ ) lung scanning and computed tomographic pulmonary angiography (CTPA) are widely used imaging procedures for the evaluation of patients with suspected pulmonary embolism. Ventilation-perfusion scanning has been largely replaced by CTPA in many centers despite limited comparative formal evaluations and concerns about CTPA's low sensitivity (ie, chance of missing clinically important pulmonary emboli).

**Objectives** To determine whether CTPA may be relied upon as a safe alternative to  $\dot{V}/\dot{Q}$  scanning as the initial pulmonary imaging procedure for excluding the diagnosis of pulmonary embolism in acutely symptomatic patients.

**Design, Setting, and Participants** Randomized, single-blinded noninferiority clinical trial performed at 4 Canadian and 1 US tertiary care centers between May 2001 and April 2005 and involving 1417 patients considered likely to have acute pulmonary embolism based on a Wells clinical model score of 4.5 or greater or a positive D-dimer assay result.

**Intervention** Patients were randomized to undergo either  $\dot{V}/\dot{Q}$  scanning or CTPA. Patients in whom pulmonary embolism was considered excluded did not receive antithrombotic therapy and were followed up for a 3-month period.

**Main Outcome Measure** The primary outcome was the subsequent development of symptomatic pulmonary embolism or proximal deep vein thrombosis in patients in whom pulmonary embolism had initially been excluded.

**Results** Seven hundred one patients were randomized to CTPA and 716 to  $\dot{V}/\dot{Q}$  scanning. Of these, 133 patients (19.2%) in the CTPA group vs 101 (14.2%) in the  $\dot{V}/\dot{Q}$  scan group were diagnosed as having pulmonary embolism in the initial evaluation period (difference, 5.0%; 95% confidence interval [CI], 1.1% to 8.9%) and were treated with anticoagulant therapy. Of those in whom pulmonary embolism was considered excluded, 2 of 561 patients (0.4%) randomized to CTPA vs 6 of 611 patients (1.0%) undergoing  $\dot{V}/\dot{Q}$  scanning developed venous thromboembolism in follow-up (difference, -0.6%; 95% CI, -1.6% to 0.3%) including one patient with fatal pulmonary embolism in the  $\dot{V}/\dot{Q}$  group.

**Conclusions** In this study, CTPA was not inferior to  $\dot{V}/\dot{Q}$  scanning in ruling out pulmonary embolism. However, significantly more patients were diagnosed with pulmonary embolism using the CTPA approach. Further research is required to determine whether all pulmonary emboli detected by CTPA should be managed with anticoagulant therapy.

**Trial Registration** [isrctn.org](http://isrctn.org) Identifier: ISRCTN65486961

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the high mortality of untreated pulmonary embolism, timely accurate diagnostic tests are essential to enable the

**Author Affiliations** are listed at the end of this article.  
**Corresponding Author:** David R. Anderson, MD, Room 430, Bethune Bldg, 1278 Tower Rd, Queen Elizabeth II Health Sciences Centre, VGH Site, Halifax, Nova Scotia B3H 2Y9, Canada ([david.anderson@dal.ca](mailto:david.anderson@dal.ca)).

**Box. Variables Used to Determine Patient Pretest Probability for Pulmonary Embolism (Wells Criteria)<sup>a</sup>**

Clinical signs and symptoms of deep vein thrombosis (minimum of leg swelling and pain with palpation of the deep veins): 3.0 points

Pulmonary embolism as or more likely than an alternative diagnosis: 3.0 points

Heart rate greater than 100/min: 1.5 points

Immobilization or surgery in the previous 4 weeks: 1.5 points

Previous deep vein thrombosis or pulmonary embolism: 1.5 points

Hemoptysis: 1.0 points

Maligancy (on treatment in the last 6 months or palliative): 1.0 points

<sup>a</sup>Pulmonary embolism unlikely, score <4.5 pulmonary embolism likely, score ≥4.5.

initiation of antithrombotic therapy for patients proven to have pulmonary embolism while avoiding its risks to patients in whom this diagnosis is excluded.<sup>4,6</sup>

For 30 years, ventilation-perfusion ( $\dot{V}/\dot{Q}$ ) lung scanning has been the noninvasive imaging procedure of choice in patients with suspected pulmonary embolism. A normal  $\dot{V}/\dot{Q}$  scan essentially excludes the diagnosis of pulmonary embolism while a high probability scan has an 85% to 90% positive predictive value in a patient population with a prevalence of pulmonary embolism of 25% to 30%.<sup>3,7</sup> However, in most patients for whom pulmonary embolism is suspected,  $\dot{V}/\dot{Q}$  scans are either of low or intermediate probability, and the actual incidence of pulmonary embolism in these individuals ranges from 10% and 40%.<sup>3,7</sup> The diagnostic uncertainty in these situations is a major limitation of  $\dot{V}/\dot{Q}$  scanning.

In the last decade, computed tomographic pulmonary angiography (CTPA) was introduced as an alternative noninvasive test to diagnose pulmonary embolism.<sup>8,9</sup> Despite concerns about low sensitivity of CTPA (reported between 53% and 100%), its adoption has been rapid.<sup>10,11</sup> Clinicians have been attracted to CTPA use because it provides a clear result (either positive or negative) and because it may detect alternative nonthrombotic causes of patients' symp-

oms. To date a direct comparison of the utility of CTPA with  $\dot{V}/\dot{Q}$  scanning for the investigation of patients with suspected pulmonary embolism has not been performed. We report the results of a randomized controlled, investigator-blinded, diagnostic management study to determine whether CTPA is a reliable safe alternative to  $\dot{V}/\dot{Q}$  scanning as an initial noninvasive imaging procedure for evaluating the diagnosis of pulmonary embolism. This study was designed as a noninferiority study to determine whether the widely adopted new technology of uncertain sensitivity (CTPA) was at least as safe as the standard technology ( $\dot{V}/\dot{Q}$  scanning) at not missing the detection of clinically important pulmonary embolism.

**METHODS****Study Participants**

Consecutive patients presenting with symptoms or signs suspected by a physician to be caused by acute pulmonary embolism (acute onset of new or worsening shortness of breath, chest pain, hemoptysis, presyncope, or syncope) with or without signs of deep vein thrombosis were potentially eligible for this study. Exclusion criteria included deep vein thrombosis or pulmonary embolism diagnosed within the previous 3 months, no change in severity of pulmonary symptoms within the previous 2 weeks, use of therapeutic doses of parenteral anticoagulants for greater

than 48 hours, comorbid condition making life expectancy less than 3 months, contraindication to contrast media (including renal insufficiency), a need for long-term use of anticoagulants, pregnancy, age younger than 18 years, refusal to provide informed consent, and geographic inaccessibility to follow-up.

**Setting and Locations**

Patients were recruited from the outpatient clinics, emergency departments, and inpatient units of 5 academic health centers: the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia; the Ottawa Hospital in Ottawa, Ontario; the Victoria Hospital in London, Ontario; the Jewish General Hospital in Montreal, Quebec; and the University of California at San Diego Medical Centre in San Diego. Approval of the research ethics committees was obtained at all institutions and written informed consent was obtained from all participating patients.

**Interventions**

Consecutive patients were evaluated by physicians for suspected pulmonary embolism using the Wells model (BOX) to assign clinical pretest probability and by D-dimer testing.<sup>12</sup> Patients with a model score of less than 4.5 were considered unlikely to have pulmonary embolism, and those with a score of 4.5 or greater were considered likely to have pulmonary embolism. Patients underwent automated D-dimer testing from plasma samples according to local practice. D-dimer testing was performed in coagulation laboratories by individuals who were unaware of the clinical probability assessment of the participating patients. Subsequent management was based on the patient's clinical pretest probability and D-dimer test result as described below. Patients considered clinically unlikely to have pulmonary embolism and who had a negative D-dimer test result did not undergo further testing and were considered to have pulmonary embolism excluded. They were not randomized into the study.

### Randomization

Patients considered more likely to have pulmonary embolism based on either a clinical probability score of 4.5 or greater or a positive D-dimer test result were randomized to undergo either  $\dot{V}/\dot{Q}$  scanning or CTPA. Randomization lists were generated by computer in variable blocks ranging from 4 to 6. Randomization was stratified by center and by patient location (inpatient vs outpatient). Randomization assignments were kept locally, concealed in consecutively numbered opaque sealed envelopes distributed to each center. The next consecutively numbered allocation envelope was opened by an experienced research coordinator otherwise not involved in the study.

### Computed Tomographic Pulmonary Angiography

Patients randomized to CTPA were evaluated using either a single-detector or a multidetector row system. First, a high-resolution CT scan of the entire thorax was performed using 1-mm thick images (140 kilovolt [peak] kV[p] 280 mA, bone reconstruction algorithm) at 10-mm intervals. The initial examination was performed without contrast to detect alternative findings that may have accounted for a patient's symptoms. Subsequent images were obtained during the injection of Omnipaque 240 contrast (Nycomed Ingenor, Paris, France) via a vein in the antecubital fossa. For single-detector scans, 150 mL of contrast was injected at a rate of 5 mL/s. The scan was started 12 seconds after the beginning of the injection and 3-mm images were obtained at 3-mm intervals from the bottom of the aortic arch to 2 cm below the inferior pulmonary veins in a cranial-caudal fashion using a pitch of 1.7:1.0 during a single-breath hold over 15 to 25 seconds. For multidetector scans, 100 mL of contrast was injected at 4 mm/s and 1.25-mm images were obtained at 1.2-mm intervals using a pitch of 1.0:1.0. Computed tomographic pulmonary angiographic results were categorized as positive for pulmonary embolism if an intraluminal filling de-

fect was seen within a pulmonary arterial vessel and were considered negative if no filling defect was observed. Scans were considered technically inadequate only if main or lobar pulmonary vessels were not visualized. Single-detector CTPA studies were performed in 195 patients and 499 patients underwent a multidetector CTPA procedure. All CTPA studies were interpreted by experienced chest radiologists unaware of patient clinical probability or D-dimer results.

### $\dot{V}/\dot{Q}$ Scanning

Patients randomized to  $\dot{V}/\dot{Q}$  scanning underwent procedures performed using previously described methods.<sup>7</sup> Lung scan results were categorized as high probability if there were 1 or more segmental perfusion defect(s) with normal ventilation or 2 or more large subsegmental perfusion defects (>75% of a segment) with normal ventilation.<sup>7</sup> Lung scans were categorized as normal if there were no perfusion defects. All other combinations of  $\dot{V}/\dot{Q}$  scan results were categorized as nondiagnostic (nonhigh probability). All scans were interpreted by experienced nuclear medicine physicians unaware of the clinical probability or D-dimer result.

### CTPA and $\dot{V}/\dot{Q}$ Scan Algorithms

Patients randomized to CTPA or  $\dot{V}/\dot{Q}$  scanning underwent diagnostic imaging as outlined in the FIGURE 1. Patients with high-probability  $\dot{V}/\dot{Q}$  scans or positive CTPA were considered to have pulmonary embolism. Patients with normal  $\dot{V}/\dot{Q}$  scans were considered to have pulmonary embolism excluded. All other patients underwent leg ultrasound imaging of the proximal venous system from the common femoral to the trifurcation of the popliteal vein using previously described techniques.<sup>13</sup> Deep vein thrombosis was diagnosed if any venous segment was consistently noncompressible.

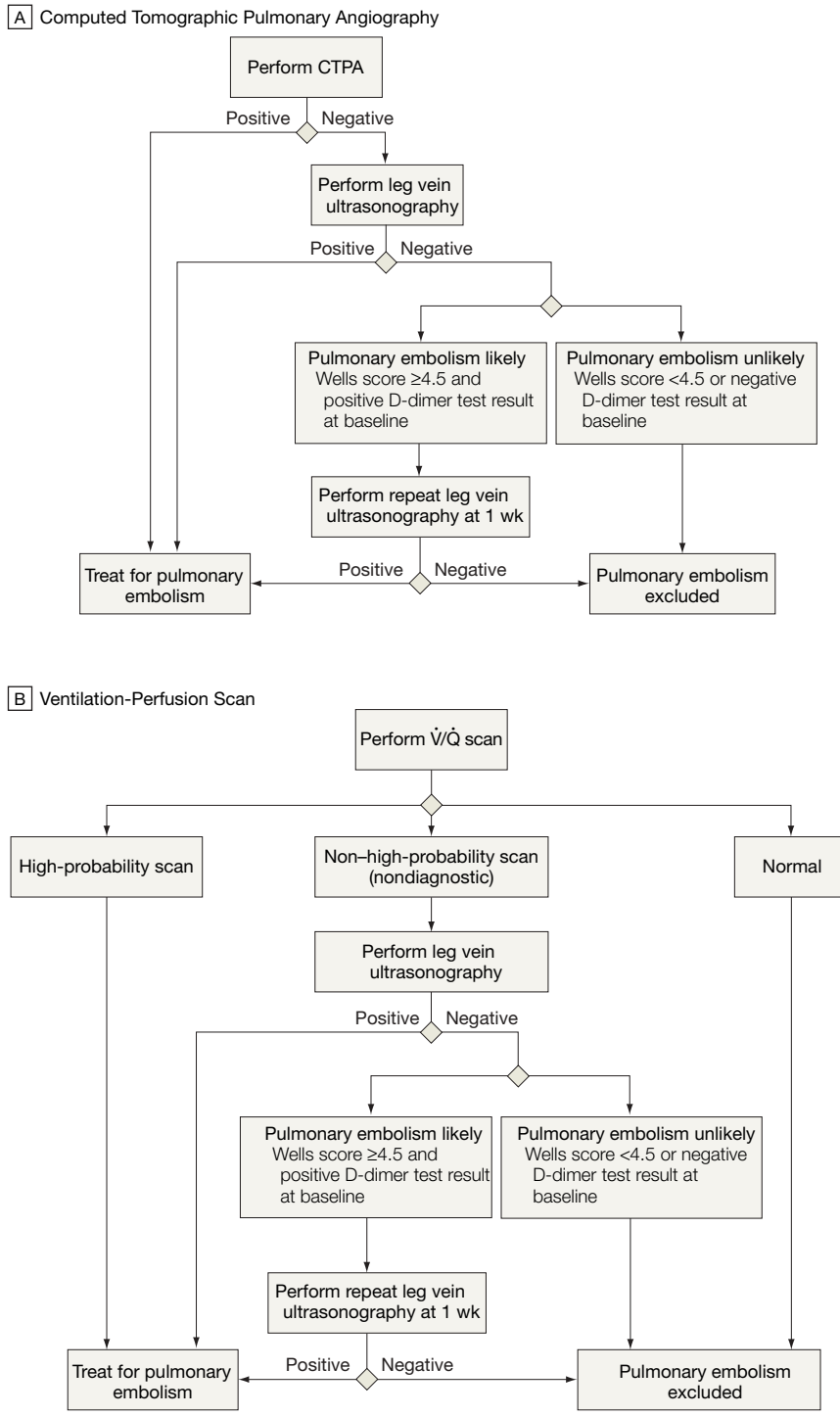
Physicians (study and attending) were blinded to the initial diagnostic test allocation group. Generic pulmonary imaging reports were issued that indicated 1 of the following: *positive for*

*pulmonary embolism* (high probability  $\dot{V}/\dot{Q}$  scan or positive CTPA), *nondiagnostic study* (non-high-probability  $\dot{V}/\dot{Q}$  scan or negative CTPA), or *no evidence of pulmonary embolism* (normal  $\dot{V}/\dot{Q}$  scan). Patients with negative leg vein ultrasonographic and nondiagnostic scan results (negative CTPA or non-high probability  $\dot{V}/\dot{Q}$  scans) were considered to have pulmonary embolism excluded if the D-dimer result was negative or the clinical probability of pulmonary embolism was unlikely. Patients considered likely to have pulmonary embolism with positive D-dimer and nondiagnostic scan results did not receive anticoagulant therapy and were scheduled to undergo a single repeat venous ultrasound assessment of the lower extremities a week later. Physicians were also given the option of performing classical pulmonary angiography in patients considered highly likely to have pulmonary embolism despite nondiagnostic pulmonary imaging testing and negative ultrasonography. However, crossover from CTPA to  $\dot{V}/\dot{Q}$  scanning or vice versa was not permitted by the protocol. Once the initial diagnostic phase was completed and pulmonary embolism was considered excluded, physicians were permitted to know which examination strategy was used to facilitate making an appropriate alternative diagnosis. Physicians were also made aware of which group the patients were assigned to if the assigned test could not be performed or was not a technically adequate study.

Patients with a previous history of venous thromboembolism were investigated for suspected pulmonary embolism using the algorithms outlined above with the following exceptions. For patients with previous pulmonary embolism, a diagnosis of recurrent pulmonary embolism was made only in the presence of one or more new high-probability abnormalities on  $\dot{V}/\dot{Q}$  scanning or by a new intraluminal filling defect on CTPA seen in a different anatomical location than on the most recent scan. For patients with a previous history of deep vein thrombosis, a diagnosis of

recurrence required the presence of a new area noncompressibility not observed on the initial ultrasound or an increase of larger than 4.0 mm of compressed vein diameter in an area of previous thrombosis.<sup>14</sup>

**Figure 1.** Diagnostic Algorithms for Initial Investigations of Suspected Pulmonary Embolism Using Computed Tomographic Pulmonary Angiography and Perfusion Scan



CTPA indicates computed tomographic pulmonary angiography;  $\dot{V}/\dot{Q}$ , ventilation-perfusion.

**Management and Follow-up**

Patients diagnosed with pulmonary embolism or isolated deep vein thrombosis as part of the diagnostic algorithms (initial testing period) were treated with conventional anticoagulant therapy. Anticoagulant therapy was withheld in all other patients who were followed up for 3 months for development of symptomatic venous thromboembolism. Patients were asked to report to their local emergency department or to call the study center as soon as possible if they developed symptoms of pulmonary embolism or deep vein thrombosis. All patients were reassessed for symptoms of venous thromboembolism at a clinic visit or by telephone a week and 3 months after initial presentation. All efforts were made to document causes of death by review of medical records and by contacting patients' families or physicians.

**Outcomes**

The primary outcome of the study was the development of venous thromboembolism (composite of proximal deep vein thrombosis or pulmonary embolism) in the 3-month follow-up period in patients in whom pulmonary embolism was considered excluded during the initial testing period. If pulmonary embolism was suspected during follow-up, patients were investigated using either CTPA or  $\dot{V}/\dot{Q}$  scanning and had venous ultrasonography of the proximal leg veins of the lower extremities. A newly positive CTPA or a high-probability  $\dot{V}/\dot{Q}$  scan confirmed the diagnosis of pulmonary embolism. For patients with a previous history of pulmonary embolism, a diagnosis of recurrence required the presence of a new intraluminal filling defect in an anatomic location not seen on the initial CTPA study or a new high-probability defect on  $\dot{V}/\dot{Q}$  scan. A noncompressible segment of the proximal venous system confirmed the diagnosis of deep vein thrombosis on ultrasonography. For patients with previous deep vein thrombosis, an ultrasound abnormality was only considered diagnostic of deep vein thrombosis if it was located

in a new anatomical location from that noted on the most recent study. The clinical details and diagnostic imaging studies from patients with suspected outcome events and deaths were reviewed by an expert adjudication committee blinded to scan allocation. Causes of death were classified as being due to pulmonary embolism, being due to an alternative disorder, or as sudden death or unexplained sudden cardiorespiratory deterioration (both therefore potentially due to pulmonary embolism).

### Sample Size and Statistical Analysis

This protocol was designed as a non-inferiority trial<sup>15</sup> with  $\dot{V}/\dot{Q}$  scanning representing the standard of care. Previously published  $\dot{V}/\dot{Q}$  scan-based algorithms to exclude pulmonary embolism resulted in 3-month rates of venous thromboembolic events of about 1.4%.<sup>16</sup> The primary objective of this study was to determine whether a CTPA-based algorithm to exclude pulmonary embolism was not clinically inferior to a  $\dot{V}/\dot{Q}$  scan-based approach. To determine the required sample size, we considered that a minimal clinically important difference (MCID) of venous thromboembolic events during the 3-month follow-up period was 2.5%. If the MCID was exceeded, CTPA would be judged to be clinically inferior to  $\dot{V}/\dot{Q}$  scanning; otherwise, CTPA would be considered to be an acceptable alternative. The clinical rationale for the choice of the MCID was—as less than 15% of recurrent venous thromboembolic events would be expected to be fatal—fatalities associated with this MCID (15% of 2.5%) would be less than fatal complications expected if all patients with nondiagnostic  $\dot{V}/\dot{Q}$  scans underwent conventional pulmonary angiography (given the 0.45% mortality of this procedure).<sup>17</sup>

Using these rates, we carried out a Monte-Carlo simulation based on 1000 replications and determined that we required a sample size of 1148 patients in whom a diagnosis of pulmonary embolism would be considered excluded

to determine that the 95% 1-sided confidence interval (CI) ruled out the MCID in the cases of the true excess equaled the MCID 5.0401% of the time (false-acceptable error rate) and 94.27% of the time when the true excess equaled 0 (1 minus the false-inferiority rate).<sup>18</sup> We projected that 22% of patients would be diagnosed with pulmonary embolism upon initial presentation and that 3% of scans would be technically inadequate; hence, the total number of patients initially projected to be randomized was 1530. However, after a period of enrollment, it was determined that our overall rate of pulmonary embolism diagnosed at initial presentation was 16% and we decreased our final target sample size of randomized patients to 1380.

The primary outcome was compared between the 2 groups using Fisher exact test with a *P* value of <.05 being regarded as statistically significant. All analyses conducted were by intention to treat. The absolute difference and the 95% CI surrounding this difference were also determined. Rates of secondary outcomes were compared using  $\chi^2$  testing. The statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

## RESULTS

### Study Patients

A total of 3886 patients were approached between May 2001 and April 2005. Of these, 1907 were excluded for reasons outlined in FIGURE 2. Of the remaining 1979 patients, 402 refused consent and 160 were unable to provide consent due to sedation, dementia, or a language barrier. One hundred seventy-eight patients were excluded on the basis of being in the pulmonary embolism unlikely category with negative D-dimer test result. None of these patients received further investigation and none experienced thromboembolic events in the 3-month follow-up period.

Of the 1417 eligible, consenting patients, 701 were randomized to the CTPA group and 716 to the  $\dot{V}/\dot{Q}$  group.

The baseline characteristics of the 2 treatment groups were similar with the exception that cancer (as defined as active malignancy or treatment with chemotherapy in the previous 6 months) was present in 9.7% of the CTPA group and in 12.2% of the  $\dot{V}/\dot{Q}$  group (TABLE 1). Eleven patients (0.8%) were lost to follow-up (7 in the CTPA group and 4 in the  $\dot{V}/\dot{Q}$  scan group) with none of these patients experiencing venous thromboembolism prior to being lost to follow-up. The remaining patients make up the groups analyzed for the study.

### Patient Outcomes

**Initial Outcomes of Pulmonary Embolism.** Of the 694 evaluable patients randomized to CTPA, 133 (19.2%) were diagnosed with pulmonary embolism or deep vein thrombosis in the initial evaluation period (TABLE 2 and FIGURE 3); 94 isolated pulmonary embolism, 29 pulmonary embolism and deep vein thrombosis and 10 isolated deep vein thrombosis (7 proximal). Of the 712 evaluable patients in the  $\dot{V}/\dot{Q}$  scanning group, 101 (14.2%) were diagnosed with pulmonary embolism or deep vein thrombosis in the initial evaluation period (Table 2 and FIGURE 4); 64 isolated pulmonary embolism, 19 pulmonary embolism and deep vein thrombosis, and 18 isolated deep vein thrombosis (11 proximal). The overall rate of venous thromboembolism (composite of deep vein thrombosis and pulmonary embolism) found in the initial diagnostic period was significantly greater in patients randomized to the CTPA strategy (difference, 5.0%; 95% CI; 1.1%-8.9% *P* = .01).

Six hundred sixteen of the randomized patients were considered likely to have pulmonary embolism and 790 were considered unlikely to have pulmonary embolism by the Wells clinical model. After the completion of the 3 months' follow-up, 160 (difference, 26%; 95% CI, 22.6%-29.6%) of the likely group and 82 (difference, 10.0%; 95% CI, 8.3%-12.7%) of the unlikely group were confirmed to have pulmonary embolism by objective testing.

**Primary Outcome**

The primary outcome compared the rates of symptomatic pulmonary embolism or proximal deep vein thrombosis events occurring during the 3-month follow-up in patients in whom

venous thromboembolism was initially considered excluded (Table 2). In the CTPA group, 2 of 561 patients (0.4%) developed symptomatic venous thromboembolic events compared with 6 of 611 (1.0%) of the pa-

tients in the V/Q scanning group (difference, -0.6%; 95% CI, -1.6% to 0.3%; P=.29). The 2 events in the CTPA group were both nonfatal pulmonary embolism that occurred on days 8 and 39 following enrollment. In the V/Q scanning group, 2 patients developed proximal deep vein thrombosis on days 13 and 36 and 4 patients pulmonary embolism on days 3, 11, 49, and 66 following enrollment. One of the pulmonary emboli that occurred in the V/Q scan group (day 49) was fatal.

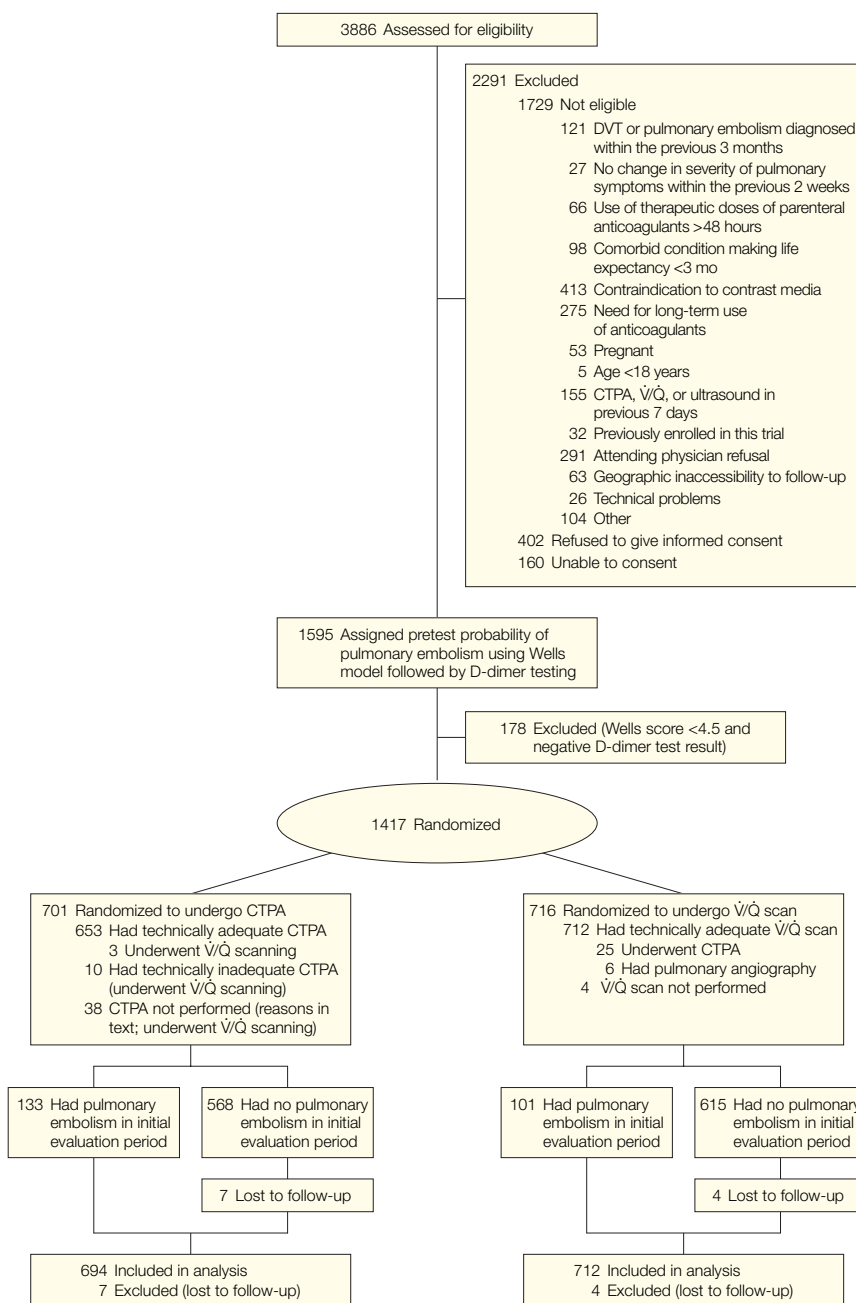
**Deaths**

Fifty-eight patients died during the 3-month follow-up period. Among patients confirmed to have pulmonary embolism on initial testing, 5 patients in the CTPA group and 6 patients in the V/Q scanning group died. Among the patients in whom venous thromboembolism was initially ruled out 17 of 561 (3.0%) in the CTPA group died during the 3-month follow-up period compared with 30 of 611 (4.9%) in the V/Q group (difference, 1.9%; 95% CI, -0.3% to 4.1%; P=.12). Two patients in each group (0.3%) died from pulmonary embolism, sudden death, or unknown cardiopulmonary compromise as shown in TABLE 3. Most of the deaths occurred as complications of underlying malignancy, 11 of 17 (65%) in the CTPA group and 20 of 30 (67%) in the V/Q scanning group.

**Crossover**

The protocol was designed to prevent crossover from one test group to the other. Nevertheless, crossover was observed in the study. Fifty-one patients randomized to the CTPA group underwent V/Q scanning. Three patients underwent V/Q scanning despite technically satisfactory CTPA. None of these patients had pulmonary embolism diagnosed initially or during follow-up. In 38 patients, CTPA could not be performed (scan contraindicated in 16; physician refusal, 8; technical problems, 8; patient refusal, 3; and unknown reason, 3). In addition, in 10 patients, the CTPA was considered technically inadequate and an addi-

**Figure 2.** Trial Flow Diagram



CTPA indicates computed tomographic pulmonary angiography; DVT, deep vein thrombosis; V/Q, ventilation-perfusion.

tional test was recommended. Eleven of these 48 patients were diagnosed with pulmonary embolism (22.9%) on the basis of  $\dot{V}/\dot{Q}$  scanning, ultrasonography, or both.

A total of 25 patients randomized to the  $\dot{V}/\dot{Q}$  scanning group underwent CTPA and 6 had conventional pulmonary angiography performed. In 29 patients this occurred because there continued to be a high clinical suspicion for pulmonary embolism despite nondiagnostic  $\dot{V}/\dot{Q}$  scans and negative bilateral ultrasonography. In the other 2 patients,  $\dot{V}/\dot{Q}$  scanning could not be performed for technical reasons. Nine of these 31 patients (29.0%) were found to have pulmonary embolism. Each of these 9 patients had a positive D-dimer test result. Using the prospective investigation of pulmonary embolism diagnosis criteria,<sup>7</sup> 7 patients had intermediate-probability and 2 low-probability  $\dot{V}/\dot{Q}$  scans.

### Predictive Accuracy of Initial Imaging Tests

Of 712 patients in the  $\dot{V}/\dot{Q}$  scan group, 247 (35.0%) had normal scan results. Of these, 2 patients (0.8%) had proximal deep vein thrombosis on ultrasound. Three-hundred eighty-six (54.2%) had nondiagnostic  $\dot{V}/\dot{Q}$  scans. Of these, 16 (4.1%) were found to have deep vein thrombosis on ultrasonography, with 1 of these being detected on the 1-week follow-up ultrasound. Ten additional patients (2.6%) were also diagnosed with pulmonary embolism (6 by CTPA, 3 by conventional pulmonary angiography, and 1 by the clinical decision of attending physician). Hence, of the 386 patients with nondiagnostic  $\dot{V}/\dot{Q}$  scans, 26 (7.0%) were found to have venous thromboembolism upon initial testing. Six additional patients (1.0%) with nondiagnostic  $\dot{V}/\dot{Q}$  scans and a negative ultrasonography result for their legs developed venous thromboembolism in the follow-up period.

Seventy-three of 75 patients (97.3%) with high-probability  $\dot{V}/\dot{Q}$  scans were treated with anticoagulation therapy. The remaining 2 patients were consid-

ered not to have pulmonary embolism (false-positive  $\dot{V}/\dot{Q}$  scan) by their physicians, and they did not receive anticoagulation therapy. Neither patient experienced a venous thromboembolic complication in follow-up.

All 115 patients with positive CTPA for pulmonary embolism were treated with anticoagulation. Of the remaining 531 patients with technically adequate scan results, 7 (1.3%) were found to have deep vein thrombosis on ultrasonography and were treated with anticoagulation. Two of the remaining 524 patients developed symptomatic pulmonary embolism in the follow-up period. For the patients who had a technically adequate CTPA performed, of those undergoing single-slice CTPA, pulmonary embolism was detected in 26 of 174 patients (14.9%) compared with 89 of 472 patients (18.9%) diagnosed using the multidetector row CT ( $P=.25$ ). The 2 patients with negative CTPA who had pulmonary emboli found in the 3-month follow-up period were initially tested using the multidetector row CT scanner.

### Pulmonary Embolism Number and Location on CTPA

Details of location and quantification of extent of pulmonary embolism were available for 111 of 115 patients with positive CTPA scans. Of these 91 patients (82.0%) were reported to have scans involving multiple vessels, whereas 20 patients (18%) had thrombi involving single vessels only. The most proximal location of the thrombi was the main pulmonary artery in 23 patients (20.7%), a lobar artery in 21 patients (18.9%), segmental arteries in 34 patients (30.6%), and subsegmental arteries in 8 patients (7.3%).

### COMMENT

This is, to our knowledge, the first randomized controlled trial that has directly compared the utility of CTPA with  $\dot{V}/\dot{Q}$  scanning for the management of patients with suspected pulmonary embolism. We have demonstrated that a diagnostic-management strategy using CTPA in combination

with consideration of clinical probability, D-dimer testing, and leg venous ultrasonography was not inferior to one using  $\dot{V}/\dot{Q}$  scanning in excluding the diagnosis of pulmonary embolism. With either strategy, the rates of patients returning with confirmed venous thromboembolism during 3 months of follow-up in whom the diagnosis of pulmonary embolism was considered excluded in the initial evaluation period were low (0.4% with CTPA vs 1.0% with  $\dot{V}/\dot{Q}$  scanning) and not clinically or statis-

**Table 1.** Demographic and Clinical Characteristics for Each Pretest Group

	No. (%) of Patients	
	CTPA (n = 694)	$\dot{V}/\dot{Q}$ (n = 712)
Age, mean (SD), y	53.3 (18.8)	53.1 (18.9)
Men	259 (37.3)	271 (38.1)
Outpatients	619 (90.0)	637 (89.5)
Risk factors		
Prior VTE	64 (9.2)	70 (9.9)
Cancer	67 (9.7)	87 (12.2)
Recent surgery	161 (23.2)	169 (23.8)

Abbreviations: CTPA, computed tomographic pulmonary angiography;  $\dot{V}/\dot{Q}$ , ventilation-perfusion scan; VTE, venous thromboembolism.

**Table 2.** Rates of Pulmonary Embolism and Deep Vein Thrombosis at Baseline and at 3 Months of Follow-up

	No. (%) of Baseline Patients	
	CTPA (n = 694)	$\dot{V}/\dot{Q}$ (n = 712)
PE alone	94 (13.5)	64 (9.0)
PE and DVT	29 (4.2)	19 (2.7)
DVT		
Total	10 (1.4)	18 (2.5)
Proximal	7 (1.0)	11 (1.5)
Total VTE <sup>a</sup>	<b>133</b> (19.2)	<b>101</b> (14.2)
Three-Month Follow-up		
	(n = 561)	(n = 611)
PE total	2 (0.4)	4 (0.7)
Fatal PE	0	1 (0.2)
DVT	0	2 (0.3)
Total VTE <sup>b</sup>	<b>2</b> (0.4)	<b>6</b> (1.0)

Abbreviations: CTPA, computed tomographic pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism;  $\dot{V}/\dot{Q}$ , ventilation-perfusion scan; VTE, venous thromboembolism.

<sup>a</sup>Absolute difference, 5.0%; 95% confidence interval [CI], 1.1% to 8.9%;  $P=.01$ .

<sup>b</sup>Absolute difference, -0.63%; 95% CI, -1.6% to 0.34%;  $P=.20$ .

tically different between the 2 groups (absolute difference, -0.6%; 95% CI, -1.6% to 0.3%). The 95% CI around this difference excluded a 2.5% variance in follow-up event rates (our a priori defined MCID) supporting that we have demonstrated the strategy using CTPA was not inferior to one based on  $\dot{V}/\dot{Q}$  scanning.

In spite of the similar rates of thromboembolic complications in patients in whom pulmonary embolism was considered excluded, an unanticipated finding in our study was that CTPA resulted in a significantly greater number of venous thromboembolism diagnoses than

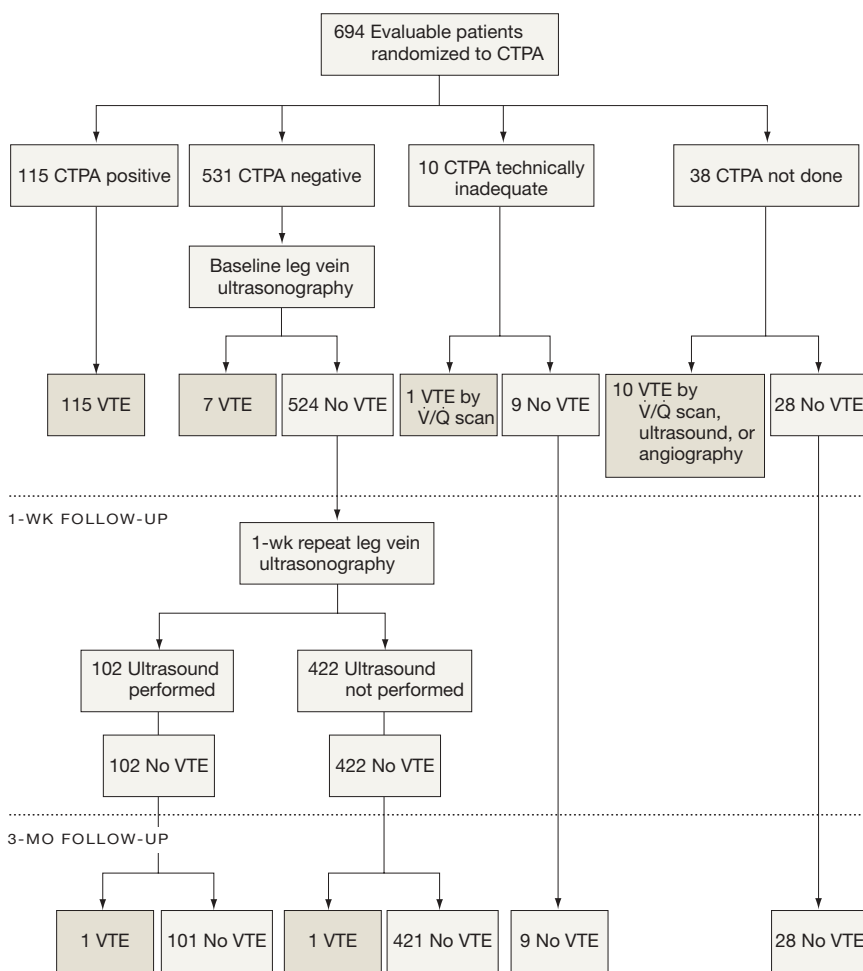
did  $\dot{V}/\dot{Q}$  scanning (19.2% vs 14.2%; absolute difference, 5.0%; 95% CI, 1.1% to 8.9%;  $P = .01$ ). This difference was accounted for by the higher rate of pulmonary embolism diagnosed in patients undergoing CTPA compared with  $\dot{V}/\dot{Q}$  scanning. This important finding requires further exploration and elaboration. The likely explanations may be that CTPA finds more true cases of pulmonary embolism than  $\dot{V}/\dot{Q}$  scanning or CTPA has a higher false-positive rate. Previous studies have demonstrated CTPA is a more specific test for pulmonary embolism than  $\dot{V}/\dot{Q}$  scanning.<sup>7,10,11,19,20</sup> However, the Pro-

spective Investigation of Pulmonary Embolism Diagnosis II trial reported that false-positive CTPA studies were identified particularly for thrombus involving peripheral pulmonary arterial vessels.<sup>21</sup> The positive predictive values of CTPA for segmental and subsegmental pulmonary embolism were only 68% and 25%.<sup>21</sup> In our study, 30% of pulmonary emboli involved the segmental and 7% subsegmental vessels, raising the potential that some of them may have been false-positive studies.

Given that our study found similar rates of thromboembolic complications in the 2 groups in whom pulmonary embolism was excluded suggests that many of the incremental thrombi detected by CTPA were clinically unimportant. Having CTPA diagnosing about 30% more patients with pulmonary embolism than  $\dot{V}/\dot{Q}$  scanning may have substantive undesired consequences. First, it would result in increased numbers of patients being exposed to anticoagulant therapy. It would be expected that at least 2% of patients receiving anticoagulation for pulmonary embolism would experience major bleeding complications that could be life threatening.<sup>22,23</sup> In addition, the resource consequences of hospitalization, anticoagulant therapy, and potential major bleeding complications would almost certainly make management with CTPA more costly than with  $\dot{V}/\dot{Q}$  scanning for patients with suspected pulmonary embolism.

There was no difference observed in mortality between the 2 groups. Only one patient in the  $\dot{V}/\dot{Q}$  group was confirmed to have died from a pulmonary embolism. Three other patients (1 in the  $\dot{V}/\dot{Q}$  group, 2 in the CTPA group) died of sudden death (1 patient) and unexplained respiratory deterioration (2 patients) that could have been due to pulmonary embolism. All patients who died in the study had significant underlying comorbidities identified prior to death. Most of the deaths were due to metastatic cancer. There were 87 patients with cancer in the  $\dot{V}/\dot{Q}$  group

**Figure 3.** Outcomes of Patients Randomized to Computed Tomographic Pulmonary Angiography



CTPA indicates computed tomographic pulmonary angiography;  $\dot{V}/\dot{Q}$ , ventilation-perfusion; VTE, venous thromboembolism.

compared with 67 in the CTPA; the majority of these patients had advanced disease and poor prognosis.

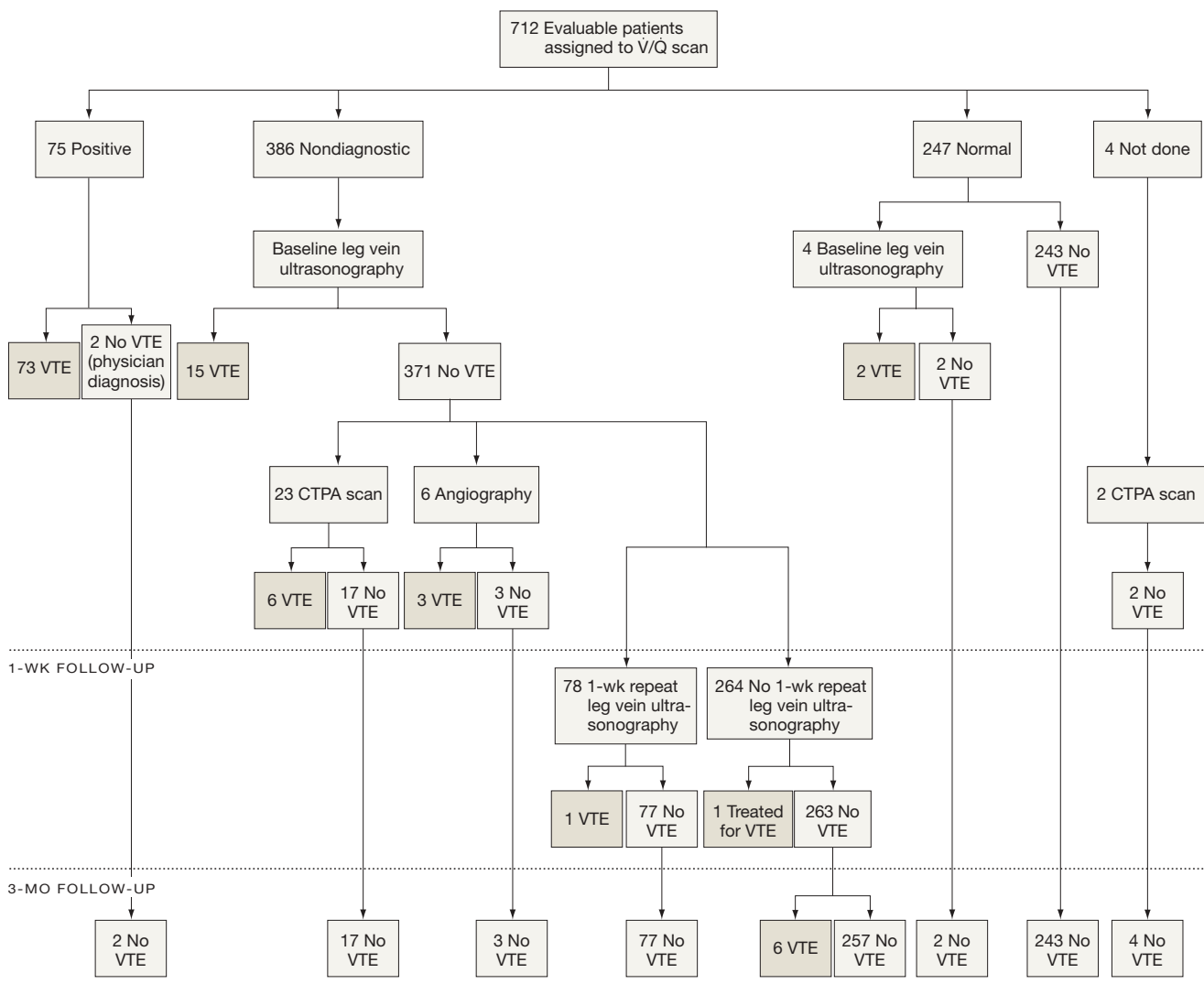
In this study we evaluated a novel simplified scoring system using the Wells Clinical Model, dividing patients into 2 categories, pulmonary embolism likely (score  $\geq 4.5$ ) and pulmonary embolism unlikely (score  $< 4.5$ ). Previous evaluation of the Wells scoring system separated patients into high-, moderate-, and low-probability categories. Dividing patients into 2 categories retained the discriminatory value of the model as

26% of patients in the likely category were confirmed to have pulmonary embolism compared with only 10% in the unlikely category ( $P < .05$ ). In addition, the diagnosis of pulmonary embolism was safely excluded in patients in the unlikely category with a negative D-dimer test result without the need to perform additional diagnostic tests.

Our study has several limitations. The first is that clinicians in the study appeared less comfortable in excluding the diagnosis of pulmonary embolism in patients with nondiagnostic

$\dot{V}/\dot{Q}$  scans than with negative CTPA studies. In 31 of 604 patients in whom  $\dot{V}/\dot{Q}$  scans, bilateral ultrasonography, or both excluded the diagnosis of pulmonary embolism according to our algorithm, either pulmonary angiography (6 patients) or CTPA was ordered (25 patients) and pulmonary embolism was detected in 9 of these patients (1.5%). In these patients, the clinical probability of pulmonary embolism remained high on the basis of a positive D-dimer test result for 9 patients and an intermediate probability lung scan for 7 patients. In con-

**Figure 4.** Outcomes of Patients Randomized to the Ventilation-Perfusion Scan Group



CTPA indicates computed tomographic pulmonary angiography;  $\dot{V}/\dot{Q}$ , ventilation-perfusion; VTE, venous thromboembolism.

**Table 3.** Causes of Death in Patients in Whom Diagnosis of Pulmonary Embolism Was Excluded in the Initial Evaluation Period

	No. (%) of Patients	
	CTPA (n = 694)	$\dot{V}/\dot{Q}$ (n = 712)
Total deaths	22 (3.2)	36 (5.1)
PE excluded at baseline	561	611
Deaths in follow-up	17 (3.0)	30 (4.9)
Cancer	11	20
Sudden death	1	0
Unexplained respiratory deterioration	1	1
COPD	1	0
Congestive heart failure	1	2
Cirrhosis	1	1
Stroke	1	1
Pulmonary embolism	0	1
Acute abdomen	0	1
Interstitial lung disease	0	1
Abdominal aortic aneurysm	0	2

Abbreviations: COPD, chronic obstructive pulmonary disease; CTPA, computed tomographic pulmonary angiography;  $\dot{V}/\dot{Q}$ , ventilation-perfusion scan.

trast, in the CTPA group, a  $\dot{V}/\dot{Q}$  scan was only requested in 3 patients because the physician was concerned that a high clinical suspicion for pulmonary embolism remained after negative CTPA result and none of these patients were found to have pulmonary embolism. Crossover did not alter the primary study conclusion that CTPA was not inferior to  $\dot{V}/\dot{Q}$  scanning for ruling out the diagnosis of pulmonary embolism. However, we cannot exclude the possibility that CTPA was superior to  $\dot{V}/\dot{Q}$  scanning given that up to 9 patients whose pulmonary emboli were detected by CTPA or pulmonary angiography could have had outcome events in the follow-up period.

Another limitation of our study was that the majority of patients enrolled were outpatients (89%). We analyzed our data separately for inpatients and outpatients and found no differences but the small proportion of inpatients precluded definite conclusions regarding the comparative advantages of the 2 strategies in the inpatient population. Two different CT technologies were used in the study with 72% of our patients undergoing multidetector CTPA and 28% having single-detector scans.

However, even if all patients had undergone multidetector CTPA, it is unlikely CTPA would have proven to be clinically superior to the  $\dot{V}/\dot{Q}$  scan strategy given the low rate (1%) of thromboembolic events during follow-up in the latter group. Finally, 11 patients were lost to follow-up. Although unlikely, if a high proportion of these patients had experienced an outcome event in one group compared with the other this could have altered our findings.

Despite these limitations, the findings of our study are likely robust. This was a large randomized trial powered to exclude small clinical differences. Consecutive patients were screened at 5 large centers. Bias was minimized by the adjudication process. The findings should be generalizable to other similar centers.

The results of our study are reassuring given previous reports of relatively low sensitivity of CTPA for the diagnosis of pulmonary embolism.<sup>10,11</sup> Our trial confirms findings from the cohort studies of our group and others that the combination of a negative CTPA and normal ultrasonography safely excludes the diagnosis of pulmonary embolism and that such patients do not require anticoagulant

therapy.<sup>24-29</sup> Two recent cohort studies have evaluated whether a negative CTPA alone can safely rule out pulmonary embolism. Ghanima et al<sup>30</sup> performed a management study in 221 patients in which a negative CTPA was used as a single test to rule out pulmonary embolism. The follow-up venous thromboembolic event rate was 0.6% with 2 patients dying of possible pulmonary embolism. In the Christopher Study,<sup>31</sup> 1.3% of 1436 patients with suspected pulmonary embolism and normal CTPA developed thromboembolic complications in 3 months of follow-up including 7 (0.5%) with suspected fatal pulmonary embolism. In our study, 1.4% of patients in the CTPA group were diagnosed with venous thromboembolism on the basis of ultrasonography after having a negative CTPA.

Ventilation-perfusion lung scanning should still have a role to play for the investigation of pulmonary embolism. This test involves much less radiation exposure and has fewer adverse effects and contraindications than CTPA. A normal  $\dot{V}/\dot{Q}$  scan essentially excludes a diagnosis of pulmonary embolism. This study and another have demonstrated that a nondiagnostic  $\dot{V}/\dot{Q}$  scan in combination with negative venous ultrasonographic results essentially excludes the diagnosis of pulmonary embolism if the clinical suspicion is not high.<sup>16</sup> Consideration should be given to performing CTPA for patients with nondiagnostic  $\dot{V}/\dot{Q}$  scans at high clinical likelihood for pulmonary embolism.

Results of our randomized diagnostic management trial indicated that a strategy to rule out pulmonary embolism that used clinical probability assessment, D-dimer, and lower-extremity ultrasound in conjunction with either CTPA or  $\dot{V}/\dot{Q}$  scanning resulted in low and similar rates of venous thromboembolic events in 3 months follow-up in the 2 groups. However significantly more patients were diagnosed and treated for pulmonary embolism with CTPA than  $\dot{V}/\dot{Q}$

scanning. Further research is required to confirm whether some pulmonary emboli detected by CTPA may be clinically unimportant, the equivalent of deep vein thrombosis isolated to the calf veins, and not require anticoagulant therapy.

**Author Affiliations:** Departments of Medicine (Drs Anderson, Mss Burton and Pleasance, and Mr Skedgel), Emergency Medicine (Dr G. Kovacs), and Radiology (Drs Cartier and Barnes), Dalhousie University, Halifax, Nova Scotia, Canada; Departments of Medicine (Drs Kahn and Hirsch) and Emergency Medicine (Dr Lang), McGill University, Montreal, Quebec, Canada; Departments of Medicine (Dr M. J. Kovacs) and Emergency Medicine (Dr Dreyer), University of Western Ontario, London, Ontario, Canada; Departments of Medicine (Drs Rodger, O'Rourke, and Wells), Emergency Medicine (Dr Stiell), and Radiology (Dr Dennie), Ottawa University, Ottawa, Ontario; and Department of Medicine, University of California at San Diego, San Diego (Dr Morris).

**Author Contributions:** Dr Anderson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Anderson, Kahn, Rodger, M. J. Kovacs, Hirsch, Cartier, Barnes, O'Rourke, Wells.

**Acquisition of data:** Anderson, Kahn, Rodger, M. J. Kovacs, Morris, Hirsch, Lang, Stiell, G. Kovacs, Dreyer, Dennie, Cartier, Barnes, Burton, Pleasance, Skedgel, Wells.

**Analysis and interpretation of data:** Anderson, Kahn, Rodger, M. J. Kovacs, Burton, Pleasance, Skedgel, Wells.

**Drafting of the manuscript:** Anderson, Kahn, Rodger, M. J. Kovacs, Wells.

**Critical revision of the manuscript for important intellectual content:** Anderson, Kahn, Rodger, M. J. Kovacs, Morris, Hirsch, Lang, Stiell, G. Kovacs, Dreyer, Dennie, Cartier, Barnes, Burton, Pleasance, Skedgel, O'Rourke, Wells.

**Statistical analysis:** Anderson, Burton, Skedgel, O'Rourke.

**Obtained funding:** Anderson, Kahn, Rodger, M. J. Kovacs, Morris, Cartier, Barnes.

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**Study supervision:** Anderson, Rodger, M. J. Kovacs, Hirsch, Stiell, G. Kovacs, Dreyer, Pleasance, Wells.

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