opinions/hypotheses

Opinions Regarding the Diagnosis and Management of Venous Thromboembolic Disease

ACCP Consensus Committee on Pulmonary Embolism*

Purpose: **The purpose of this consensus report was to address clinically relevant questions related to the diagnosis and management of acute pulmonary embolism and deep venous thrombosis.**
Background: **Physicians are often forced to make decisions about the diagnosis and management of pulmonary thromboembolism even though there are only limited data to guide them.**
Methods: **We assessed the relevant literature regarding clinical trials according to levels of evidence. The data on which the opinions of the committee were made were sparse. The consensus opinions, therefore, were often based on experience or intuition, rather than firm data.**
Results: **Consensus opinions were given in regard to eight clinically relevant questions.**
Conclusion: **We hope that the consensus opinions of this committee will assist others in making clinical decisions while we all await prospective investigations.**

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Key words: computed tomography; D-dimer; deep venous thrombosis; magnetic resonance imaging; pulmonary angiography; pulmonary embolism; ventilation perfusion scintigraphy

Abbreviations: CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; PE=pulmonary embolism; PIOPED=Prospective Investigation of Pulmonary Embolism Diagnosis; $\dot{V}/\dot{Q}$=ventilation/perfusion

In 1996, a committee of physicians and a clinical epidemiologist experienced in pulmonary thromboembolism explored areas of agreement and unresolved differences of opinion about some aspects of the diagnosis and management of patients with suspected acute pulmonary embolism (PE).[1] Commonly encountered questions were posed about which there were insufficient data on which to reach a recommendation based on rules of evidence.[2]

The present statement is a continuation of this expression of opinions in regard to timely questions frequently faced by physicians. Unresolved issues should be addressed by future clinical trials. In the interim, physicians are forced to make decisions, even though data are lacking. We hope that the consensus opinions of this committee will assist others in making clinical decisions while we all await prospective investigations.

Materials and Methods

We assessed the relevant literature regarding clinical trials according to levels of evidence.[2] For the assessment of diagnostic tests, the essential design features for such studies were reviewed,[3-6] and those that met the minimum criteria were labeled level I, whereas those that did not received no designation. The levels of evidence were indicated in Roman numerals beside the references in the reference list, as well as in the text, a process that has been successfully used in the past.[3]

The essential study design features for studies evaluating diagnostic tests are the following. (1) The study should include a consecutive series of patients. (2) All patients should undergo both the test under evaluation and the diagnostic reference test ("gold standard") to determine the four indexes of diagnostic efficacy: sensitivity, specificity, positive predictive value, and negative predictive value. (3) The test should be evaluated in a broad spectrum of patients, both with and without the disease of

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interest, with varying severity of the disease, and with a variety of comorbid conditions that are commonly confused with the disease of interest. (4) The results of the test under evaluation and the reference test should be interpreted independently and without knowledge of the results of the other test, or of the patient's clinical or ancillary test findings. (5) A sufficient number of patients should be studied to draw valid conclusions, based on 95% confidence intervals (CIs), for the indexes of sensitivity, specificity, and positive and negative predictive values. (6) There should be studies including long-term follow-up to determine the safety of withholding treatment in patients with negative results by the test under evaluation.

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Questions Regarding the Diagnosis and Management of Acute Venous Thromboembolic Disease

Question 1: What is the role of MRI in the diagnosis of deep venous thrombosis?

Background Question 1: MRI for deep venous thrombosis, using venography as a standard, in small numbers of patients showed a sensitivity of 100% (95% CI, 66 to 100%) for deep venous thrombosis of the veins of the pelvis and 100% (95% CI, 79 to 100%) for deep veins of the thigh[7] (Table 1). The specificity was 95% (95% CI, 85 to 99%) for deep veins of the pelvis and 100% (95% CI, 92 to 100%) for deep veins of the thigh.[7] The 95% CIs, particularly of the sensitivities, were wide due to small numbers of patients investigated. Pooled data of MRI for acute deep venous thrombosis of the calves showed a sensitivity of 85% (95% CI, 62 to 97%) and a specificity of 98% (95% CI, 87 to 100%)[7,8] (Table 1).

Consensus Opinion Regarding Question 1: MRI of deep venous thrombosis is still in the early stages of investigation. Available data suggest that it is a very sensitive and specific test for detecting deep venous thrombosis, but only a limited number of investigations comparing results with venography have been performed. Consensus opinion, not supported by data, is that this test is institution specific.

Question 2: Does a ventilation scan need to be performed in all patients, or are there patients in whom the combination of a plain chest radiograph and perfusion scan are sufficient?

Background Question 2: In the collaborative investigation, Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), a high-probability perfusion lung scan in combination with a chest radiograph had no less positive predictive value for acute PE than a high-probability combined ventilation/perfusion ($\dot{V}/\dot{Q}$) lung scan[9(I)] (Table 2). Also, low-probability perfusion lung scans and low-probability $\dot{V}/\dot{Q}$ scans had a comparable negative predictive value. In PIOPED, the positive predictive value of low-probability interpretations of the $\dot{V}/\dot{Q}$ lung scan was 14%.[10(I)] Somewhat more patients who had only perfusion scans had intermediate (indeterminate) probability interpretations than did those with $\dot{V}/\dot{Q}$ scans, but this difference was not statistically significant. The data indicate that useful information can be obtained from the perfusion scan alone. Data from others tend to corroborate this assessment.[11(I)] If the perfusion scan is interpreted as intermediate probability for PE, a subsequent $\dot{V}/\dot{Q}$ scan may change the interpretation to a more definitive probability.[9(I)] A normal perfusion scan can spare patients an unnecessary hospitalization.[12(I)]

Good results have been shown with obtaining perfusion lung scans before ventilation scans when the ventilation scans were obtained with ^{99m}Tc-diethylenetriamine pentaacetate.[13] Performing the perfusion scan prior to the ventilation scan permitted the ventilation study to be tailored for optimal positioning to determine if mismatched defects were present. Direct overlay of the ventilation image on the perfusion image allowed detection of some previously unrecognized perfusion defects. Ventilation scans were unnecessary in patients in whom the perfusion scans were normal and in patients who had matched chest radiographic and perfusion scan defects.

Consensus Opinion Regarding Question 2: If $\dot{V}/\dot{Q}$ scans are obtained with ^{99m}Tc aerosols, a chest radiograph and a perfusion scan can be obtained initially and evaluated by the nuclear medicine physician. If a ventilation scan is deemed necessary, it can be performed by postperfusion techniques. If the perfusion scan is normal, no ventilation scan is needed. If the perfusion scan shows characteristic vascular defects in regions where the chest radiograph is normal, this would indicate a high probability for PE and a ventilation scan is unnecessary. In patients with prior cardiopulmonary disease, in whom matched perfusion and ventilation defects are likely to occur, both a ventilation and perfusion scan are often indicated.

Question 3: What is the utility of the D-dimer in combination with $\dot{V}/\dot{Q}$ scans?

Background Question 3: A diagnostic strategy that combines the use of $\dot{V}/\dot{Q}$ lung scans with measurement of quantitative plasma D-dimer levels has been speculated to be useful in the evaluation of patients with suspected PE.[14] Among 10 patients who had a low-probability interpretation of the $\dot{V}/\dot{Q}$ lung scan and a plasma D-dimer level <500 ng/mL, the negative predictive value for acute PE was 100% (95% CI, 69 to 100%).[14] Decision analyses based on D-dimer and venous ultrasound[15] and based on clinical probability, D-dimer, and ultrasound of the lower extremities also have been proposed.[16]

A D-dimer measured by the enzyme-linked immunosorbent assay (ELISA) below a cutoff of 300 to 500 ng/mL was used by most investigators,[15,17,18(I),19-22,23(I),24(I),25] but one investigator used a cutoff value <1,000 ng/mL.[26] Pooled data from 908 patients with suspected acute PE, among whom 342 had PE, showed a weighted negative predictive value of 91%.[27] The average weighted sensitivity for acute PE was 97% and the

Table 1–*MRI for Acute Deep Venous Thrombosis**

Vein	Sensitivity n/N (%)	Sensitivity (95% CI)	Specificity n′/N′ (%)	Specificity (95% CI)	Reference No.
Pelvic	9/9 (100)	(66-100)	52/55 (95)	(85-99)	7
Thigh	16/16 (100)	(79-100)	43/43 (100)	(92-100)	7
Calf	17/20 (85)	(62-97)	41/42 (98)	(87-100)	7,8

*n=number of patients with abnormal MRI; N=number of patients with deep venous thrombosis; n′=number of patients with normal MRI; N′=number of patients without deep venous thrombosis.

Table 2–*Positive Predictive Values of Perfusion Scans Alone Compared to V̇/Q̇ Scans**

Scan Prob	Perfusion Scan PE/n (%)	Perfusion Scan (95% CI)	V̇/Q̇ Scan PE/n (%)	V̇/Q̇ Scan (95% CI)
High	14/15 (93)	(68-100)	15/16 (94)	(70-100)
Intermediate	14/38 (37)	(22-54)	9/25 (36)	(18-57)
Low	0/12 (0)	(0-26)	5/25 (20)	(7-41)
Near normal/normal	1/2 (50)	(1-99)	0/1 (0)	(0-98)

*All differences between perfusion scans alone and V̇/Q̇ scans were not significant. n=number of patients; Prob=probability. Modified from Stein and associates[9(I)] with permission.

average specificity was 45% when using the ELISA method.[27] Pooled analyses of latex tests for D-dimer suggest that their sensitivity is not sufficient to allow exclusion of deep venous thrombosis or PE, although some commercial assays showed good performance in small trials.[27]

Consensus Opinion Regarding Question 3: The combination of a low D-dimer and low-probability V̇/Q̇ scan was shown in a few patients to be diagnostically useful in assessing possible PE. Using the ELISA with the appropriate cutoff value, a negative D-dimer is strong evidence that the patient does not have a PE. That is, the ELISA for D-dimer has a high negative predictive value for PE. Until D-dimer testing is standardized and more widely validated in prospective outcome studies, however, widespread use of D-dimer measurement is not recommended.

Question 4: Should the technique of pulmonary angiography routinely incorporate adjunctive techniques such as cineangiography, digital subtraction angiography, or superselective injection?

Background Question 4: Techniques that augment standard angiography may be used to enhance the visualization of small PE. Such techniques include cineangiography,[28] balloon-occlusion angiography,[29,30] superselective angiography,[31] and selective intra-arterial digital subtraction angiography.[32(I)] Thromboemboli as small as 1.5- to 2.0-mm diameter can be imaged by wedge arteriography.[33] Experience with some of these techniques is sparse,[29,30,33] and they may be considered experimental.

Reader agreement on the interpretation of pulmonary angiograms depends in part on the quality of the angiogram. Among 1,099 pulmonary angiograms in PIOPED, overall agreement on all three categories of interpretation (both readers agreed that PE was present, PE was absent, or PE was uncertain) was 81%.[34] There was closer agreement on the presence of PE than on the absence of PE.[34] Both agreed PE was present or both agreed that PE could not be diagnosed with certainty in 92%. Both readers agreed that PE was absent or both agreed that PE could not be excluded with certainty in 82%. The quality of the angiograms had a greater impact on the agreement on negativity than on positivity.[34] Agreement on positivity with good-, fair-, and poor-quality angiograms was 93%, 90%, and 98%, respectively. Agreement on negativity was 88%, 77%, and 54%, respectively.

Regarding experience unrelated to PIOPED, Quinn and associates[35] showed a mean interobserver agreement of 86% among three angiographers who retrospectively reviewed the arteriograms of 60 patients. Among 45 pulmonary angiograms, Van Beek and associates[32(I)] showed 64.5% agreement between reader 1 and reader 2, and 80.0% and 84.4% agreement between reader 1 and consensus readings and reader 2 and consensus readings.

In regard to the relation of interobserver agreement to the size of arteries that showed PE, average copositivity (average agreement of reader 1 with reader 2 and of reader 2 with reader 1) among patients with main or lobar, segmental, and subsegmental PE was reported from the data in PIOPED.[34] Average copositivity was 98% with main or lobar PE, 90% with segmental PE, and 66% with subsegmental PE. Quinn and associates[35] reported agreement on interpretation in only 2 of 15 (13%) PE limited to subsegmental pulmonary arteries.[35]

Consensus Opinion Regarding Question 4: In general, the current standard method provides the necessary diagnostic information. When there is an area of concern in small vessels, and a negative reading is being entertained because no PE was identified elsewhere, adjunctive techniques can be diagnostically useful. The choice of these techniques is dependent on the expertise of the angiographer.

Question 5: What is the role of contrast-enhanced helical (spiral) CT?

Background Question 5: Contrast-enhanced helical or electron-beam CT permits visualization of PE following the injection of contrast material into a peripheral vein. The amount used by some is 100 to 140 mL of 30% iodinated contrast material injected at a rate 2 to 5 mL/s.[36] The images may be obtained while holding the breath 15 to 25 sec. The holding of breath may be divided into two parts to permit a pause for breathing.[36]

Pooled data on the results of imaging with contrast-enhanced helical or electron-beam CT with comparison to conventional pulmonary angiography or autopsy as the standard show a sensitivity of 72% (95% CI, 59 to 83%) and a specificity of 95% (95% CI, 89 to 98%) (Table 3).[36-40]

Regarding PE in central pulmonary arteries (main through segmental branches), pooled data show a sensitivity of 94%, specificity of 94%, positive predictive value of 93%, and negative predictive value of 95% (Table 4).[37,38,41-43] Regarding PE in subsegmental pulmonary arteries, the sensitivity was 1 of 8 (13%) (95% CI, 0 to 53%).[37,38] The prevalence of PE involving only subsegmental pulmonary arteries in PIOPED was 6%.[44(I)] The prevalence of PE limited to subsegmental pulmonary arteries that was observed in PIOPED was lower than reported by Oser and associates[45] (30%) and by Goodman and associates[38] (36%), but was comparable to the frequency reported by Quinn and associates[35] (10%). Goodman and associates[38] reported a higher prevalence of low-probability interpretations of the V̇/Q̇ lung scan among patients with PE, 5 of 11 (45%), than observed in PIOPED,[10(I)] 59 of 375 (16%). The patients in PIOPED, therefore, had more severe PE than the patients described by Goodman and associates. The patients evaluated by Goodman and associates, however, were selected and not representative of all patients with PE. Among patients with low-probability V̇/Q̇ lung scans, the prevalence of PE involving only subsegmental pulmonary arteries in PIOPED was 17%.[44(I)]

Consensus Opinion Regarding Question 5: This diagnostic modality is still under investigation and no firm general conclusions can be made without more extensive experience. It appears to be a useful addition to the panel of tests available for the diagnosis of PE, particularly in central arteries. In institutions where experience and skill with this modality are available, it can have value in diagnosing central PE in circumstances wherein

Table 3–*Validity of Contrast-Enhanced Helical or Electron-Beam CT in All Patients With Suspected Acute PE**

Sensitivity		Specificity		Reference
n/N (%)	(95% CI)	n′/N′ (%)	(95% CI)	No.
15/23 (65)	(43-84)	36/37 (97)	(86-100)	37
7/11 (64)	(31-89)	8/9 (89)	(52-100)	38
3/6 (50)	(12-88)	14/15 (93)	(68-100)	36
14/15 (93)	(68-100)	4/5 (80)	(28-99)	39
5/6 (83)	(36-100)	37/38 (97)	(86-100)	40
44/61 (72)	(59-83)	99/104 (95)	(89-98)	Total

*Confirmation by pulmonary angiography or autopsy. n=number of patients with CT showing PE; N=number of patients with PE; n′=number of patients with no PE shown by CT; N′=number of patients without PE.

established diagnostic tests are not immediately available. A normal contrast-enhanced CT scan does not exclude PE, particularly in subsegmental arteries. In patients with renal insufficiency, consideration should be given to the consequences of the load of radiographic contrast material prior to choosing CT or conventional pulmonary angiography. Both contrast-enhanced CT and conventional pulmonary angiography require a substantial load of contrast material. If only a limited amount of contrast material can be given safely to a particular patient, it may be prudent to select the single most definitive test, conventional pulmonary angiography, rather than risk the requirement for a conventional pulmonary angiogram subsequent to a potentially nondiagnostic contrast-enhanced CT scan. Further studies are necessary to delineate the diagnostic role of contrast-enhanced helical CT in patients with suspected acute PE.

Question 6: Should an inferior vena cava filter be used routinely instead of anticoagulation as treatment of deep venous thrombosis or PE in patients with cancer?

Background Question 6: An inferior vena cava filter has been recommended in patients with deep venous thrombosis or PE associated with cancer.[46-49] To our knowledge, however, there are no prospective, randomized trials indicating that patients with cancer should undergo inferior vena cava filter placement as primary treatment for venous thromboembolism. An inferior vena cava filter in patients with deep venous thrombosis or PE who had primary or metastatic brain tumors did not reduce the incidence of intracranial bleeding in comparison to anticoagulants.[50]

Consensus Opinion Regarding Question 6: The routine use of inferior vena cava filters in patients with cancer and deep venous thrombosis or PE is not recommended. Heparin therapy generally can be employed successfully in patients with cancer and deep venous thrombosis or PE. If bleeding occurs, or if the risk of bleeding is substantial, then placement of an inferior vena cava filter becomes appropriate. At the present time, however, routine inferior vena cava filter placement cannot be recommended in cancer patients with deep venous thrombosis or PE in the absence of the usual indications.

Question 7: Can low molecular weight heparin be recommended for the outpatient treatment of deep venous thrombosis or PE at this time?

Background Question 7: Two recent prospective randomized clinical trials compared standard unfractionated heparin administered by continuous infusion in the hospital with low molecular weight heparin administered primarily at home as the initial therapy for proximal deep venous thrombosis.[51(I),52(I)] Among the patients treated with low molecular weight heparin by Levine and associates,[51(I)] 51% spent 2.2±3.8 days (mean±SD) in the hospital. Among the patients treated with low molecular weight heparin by Koopman and associates,[52(I)] 43% spent ≥2 days in the hospital, and an additional 22% were hospitalized <2 days. Patients with concomitant symptomatic PE were excluded from the studies. Those with coexisting conditions, including cancer, infection or stroke, also were excluded. Patients with PE have not received home treatment. In the home therapy model, the patients received low molecular weight heparin, administered subcutaneously twice daily in fixed doses adjusted for the patient's weight without laboratory monitoring. Recurrent thromboembolic events and bleeding complications occurred with similar frequency in the two treatment groups. Life-threatening PE was extremely rare during the initial treatment with either form of heparin.

Consensus Opinion Regarding Question 7: In the United States, use of low molecular weight heparin is not yet approved for the outpatient or inpatient treatment of deep venous thrombosis or PE. At the present time, we caution against the use of low molecular weight heparin in an outpatient setting. The

Table 4–*Validity of Contrast-Enhanced Helical or Electron-Beam CT in Patients With Central PE**

Sensitivity		Specificity		Reference
n/N (%)	(95% CI)	n′/N′ (%)	(95% CI)	No.
6/7 (86)	(42-100)	12/13 (92)	(64-100)	38
7/7 (100)	(54-100)	3/3 (100)	(29-100)	41
15/15 (100)	(78-100)	36/36 (100)	(90-100)	37
18/18 (100)	(74-100)	23/24 (96)	(79-100)	42
39/43 (91)	(78-97)	25/29 (86)	(68-96)	43
85/90 (94)	(86-98)	99/105 (94)	(88-98)	Total

*See Table 3 footnotes.

outcome of investigations now in progress will determine the safety and efficacy of low molecular weight heparin in an outpatient setting.

Question 8: In patients with proven PE, particularly those with adequate cardiopulmonary reserve and no apparent source of deep venous thrombosis, is it ever proper to withhold therapy?

Background Question 8: Autopsy shows deep venous thrombosis as the cause of PE in ≥80% of patients.[53(I),54-56] Impedance plethysmography detects deep venous thrombosis of the thigh in 86 to 94% of patients shown to have deep venous thrombosis by venography.[57(I),58(I)] However, single noninvasive tests for deep venous thrombosis, using impedance plethysmography in patients with documented PE, show abnormal results in only 43 to 57% of the patients.[57(I),59(I)] Two percent to 6% of patients with suspected deep venous thrombosis or suspected PE in whom an initial leg test provided normal results showed deep venous thrombosis with serial noninvasive leg tests.[60(I),61(I),62(I),63(I),64(I)] (Among all patients with deep venous thrombosis, 15 to 16% were identified by serial noninvasive leg test.[60(I),61(I)]) It is apparent, therefore, that approximately 50% of patients with PE will not show deep venous thrombosis with serial plethysmography. Even so, in patients with suspected acute PE who had indeterminate $\dot{V}/\dot{Q}$ lung scans, adequate cardiorespiratory reserve, and normal serial impedance plethysmograms, the recurrence rate of PE and fatal PE, when untreated, is low. Only 0.6% of such patients suffered recurrent PE, and only 0.2% suffered a fatal recurrent PE.[61(I)] This perhaps may reflect a lower morbidity and mortality from recurrent PE than previously thought, particularly among patients with mild PE. The prevalence of death from the initial PE or from recurrent PE within 1 year among patients with relatively mild PE who escaped treatment in the PIOPED was 5% (1/20) (95% CI, 0 to 25%).[65(I)]

Consensus Opinion Regarding Question 8: This issue needs clarification by means of prospective clinical trials. In the absence of further data, consensus opinion at this time is that any patient who has a proven diagnosis of PE needs to be treated unless there are extenuating circumstances such as terminal carcinoma. The Committee recognizes that a few patients with mild PE who escaped treatment in PIOPED had a satisfactory outcome without treatment. Also, calculations from data reported in one level I trial suggest that some patients with serially normal results of noninvasive leg tests and nondiagnostic $\dot{V}/\dot{Q}$ scans may have had PE, but fared well without treatment. However, these data are insufficient to permit withholding treatment of PE at the present time.

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