Acute Thromboscintigraphy with ^{99m}Tc-Apcitide: Results of the Phase 3 Multicenter Clinical Trial Comparing ^{99m}Tc-Apcitide Scintigraphy with Contrast Venography for Imaging Acute DVT

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^{99m}Tc-apcitide (formerly known as ^{99m}Tc-P280) is a radiolabeled peptide that binds with high affinity and specificity to the glycoprotein IIb/IIIa receptors expressed on the activated platelets that are involved in acute thrombosis. The purpose of the phase 3 multicenter clinical trials was to compare ^{99m}Tc-apcitide scintigraphy with contrast venography for imaging acute deep venous thrombosis (DVT). **Methods:** A total of 280 patients were enrolled in 2 clinical trials conducted in North America and Europe. Patients were to be within 10 d of onset of signs and symptoms of acute DVT or within 10 d of surgery associated with a high risk of DVT. ^{99m}Tc-apcitide scintigraphy and contrast venography were to be performed within 36 h. Planar scintigraphic images were obtained at 10, 60, and 120–180 min after injection. ^{99m}Tc-apcitide scintigrams and contrast venograms were read with masking and also by the institutional investigators. **Results:** Of a total of 243 patients who were evaluable, 61.7% were receiving heparin at the time of imaging. Masked reading of ^{99m}Tc-apcitide scintigraphy, compared with masked reading of contrast venography, had a sensitivity, specificity, and agreement of 73.4%, 67.5%, and 69.1%, respectively, which met the prospectively defined target efficacy endpoint in both trials. Institutional reading of ^{99m}Tc-apcitide scintigraphy, compared with institutional reading of contrast venography, had a sensitivity, specificity, and agreement of 75.5%, 72.8%, and 74.0%, respectively. However, the entire trial population included patients with a history of DVT who may have had old, nonacute venous thrombi that could confound the venography results. Therefore, data from patients having no history of DVT or pulmonary embolism and who presented within 3 d of onset of signs and symptoms (n = 63), i.e., patients for whom a venogram would be expected to be positive only if acute DVT were present, also were analyzed as a subset. In these patients, institutional reading of ^{99m}Tc-apcitide scintigraphy, compared with institutional reading of contrast venography, had a sensitivity, specificity, and agreement of 90.6%, 83.9%, and 87.3%, respectively. **Conclusion:** ^{99m}Tc-apcitide scintigraphy is a new diagnostic modality that is highly sensitive for imaging acute DVT.

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The prevalence of acute deep venous thrombosis (DVT) has been estimated to be as high as 2–5 million cases per year in the United States (*1,2*), and the prevalence of its life-threatening complication, pulmonary embolism (PE), has been estimated to be 500,000–600,000 cases per year (*2,3*). PE has been estimated to result in 50,000–200,000 deaths per year in the United States (*2,3*), and PE is the most common cause of death associated with childbirth (*4*). In approximately one third of cases, death from PE occurs so quickly that there is little opportunity for diagnosis and treatment (*3*). Therefore, the primary goal of treating PE is to prevent subsequent emboli from converting a nonfatal episode of PE into a fatal one (*2,3*). Of the approximately two thirds of patients who survive their first episode of PE, an estimated 30% will die if untreated, whereas 8% will die despite treatment (*3*). Between 70% and 90% of PE cases derive from acute DVT in the lower extremities (*2,5*). Therefore, prompt diagnosis to allow prompt treatment of acute DVT is important. In addition, acute DVT leads to postphlebitic syndrome in 25%–65% of patients (*6,7*). Postphlebitic syndrome is characterized by venous hypertension in the lower extremities, leading to edema, pigmentation, and ulceration (*8*). Prevention of this morbid condition through accurate and timely diagnosis of acute DVT is clearly desirable.

However, the usual treatment for acute DVT and PE—anticoagulation—also is associated with risk. Major bleeding occurs in 2%–7% of patients (*1,9*), and intravenously administered heparin leads to thrombocytopenia in 1% of patients (*10*). Therefore, accurate diagnosis of acute DVT also is needed to avoid inappropriate anticoagulation. Unfortunately, the clinical diagnosis of DVT is inaccurate. Only 20%–50% of patients presenting with signs and symptoms

consistent with DVT are confirmed to have acute DVT (*11,12*). A clear medical need exists for an objective method of accurately diagnosing acute DVT.

The gold standard for detecting DVT has been contrast venography, whereas the diagnostic imaging method used most frequently in the United States is sonography (*13*). Both methods have their shortcomings. Contrast venography is decreasingly used because it is often painful for the patient, can cause side effects, is relatively expensive, and is time-consuming. The test may be technically inadequate or its findings difficult to interpret in 10%–30% of patients (*1,14*), and it cannot reliably differentiate acute recurrent DVT from old, nonacute DVT in patients with a history of disease (*1,15*). Real-time B-mode sonography with compression and pulsed-wave Doppler flow analysis (Duplex sonography), increasingly used in combination with color Doppler flow imaging, is accepted to be highly sensitive and specific between the pelvis and knees in patients with localizing signs and symptoms and no history of DVT in the affected extremity (*16*). However, this method is less accurate below the knee (*16,17*), in patients without localizing signs and symptoms (*18,19*), and in patients with a history of DVT (*20*). The presence of duplicate veins may lead to false-negative results (*21*). Sonography is highly dependent on operator skill and experience, is technically difficult in patients who are obese or who have swollen limbs, and is not useful in patients fitted with orthopedic casts (*17*).

Both contrast venography and sonography detect changes in venous anatomy caused by the presence of an intraluminal thrombus that is formed sufficiently to either reduce vascular filling with contrast medium or resist compression. An alternative approach to the diagnosis of acute DVT is detection of a molecular marker of acute DVT that is not present in old, organized (sometimes referred to as chronic) DVT. Recently, ^{99m}Tc-apcitide (formerly known as ^{99m}Tc-P280), a synthetic glycoprotein (GP) IIb/IIIa receptor–binding peptide, has been investigated in humans for detecting acute DVT (*22*). ^{99m}Tc-apcitide binds with high affinity and specificity to the GPIIb/IIIa receptors expressed on the activated platelets that are involved in acute thrombi (*23*). The purpose of the phase 3 clinical trials was to compare ^{99m}Tc-apcitide scintigraphy with contrast venography as the gold standard for imaging acute DVT.

MATERIALS AND METHODS

Study Design and Patient Population

Two well-controlled clinical trials, referred to as trial A and trial B, were conducted under identical protocols. Each study was a prospective, multicenter, single-dose, within-patient comparison of ^{99m}Tc-apcitide scintigraphy and contrast venography as the "truth" for detecting and localizing acute DVT in the lower extremities. These studies were also designed to evaluate the safety and tolerance of a single intravenous administration of ^{99m}Tc-apcitide in patients.

Patients were to be within 10 d of onset of signs and symptoms of acute DVT or within 10 d after a surgical procedure associated with high risk for development of acute DVT. Patients were required to provide written informed consent in accordance with 21CFR50, the Declaration of Helsinki, and the institution's investigational review board and be at least 18 y old. Patients were excluded if they were pregnant or breast-feeding or were of childbearing potential, unless pregnancy was ruled out by a negative β–human chorionic gonadotropin test or medical history (older than 60 y, postmenopausal for at least 1 y, or surgically sterilized). Patients were also excluded if they had received another investigational drug within 30 d before enrollment in this study. ^{99m}Tc-apcitide scintigraphy and contrast venography were to be performed within 36 h of each other.

Radiopharmaceutical Preparation

^{99m}Tc-apcitide was prepared from single-dose, sterile, nonpyrogenic lyophilized kits (AcuTect; Diatide, Inc., Londonderry, NH). Each kit was formulated to contain 100 μg of the peptide bibapcitide (formerly referred to as P280). Each kit was reconstituted with 1 mL sterile, nonpyrogenic, oxidant-free sodium ^{99m}Tc-pertechnetate in normal saline containing approximately 1.1 GBq (30 mCi) ^{99m}Tc. ^{99}Mo–^{99m}Tc generators from DuPont (Billerica, MA), Mallinckrodt Medical Inc. (St. Louis, MO), Mallinckrodt Diagnostica, Medi-Physics (Arlington Heights, IL), Amersham International plc (Buckinghamshire, UK), and CIS International were used in this trial. The reconstituted kit was heated in a boiling water bath for 15 min and then allowed to cool to provide a solution containing ^{99m}Tc-apcitide. The radiochemical purity of the ^{99m}Tc-apcitide solution was determined using instant thin-layer chromatography (3 chromatography strips: 1 developed in water, 1 developed in methyl ethyl ketone, and 1 developed in saturated saline solution). The radiochemical purity of the ^{99m}Tc-apcitide was required to be at least 90%, and the preparation had to be used within 6 h.

Scintigraphic Imaging Protocol

^{99m}Tc-apcitide scintigraphy was performed using γ cameras with a large field of view and fitted with low-energy, high-resolution parallel-hole collimators. The cameras had a photopeak of 140 keV with a 10%–20% window, and digital images were acquired in a 128 × 128 (occasionally 256 × 256) matrix. Patients were asked to void immediately before imaging and to maintain hydration and void frequently during the study.

Each patient received approximately 740 MBq (20 mCi) ^{99m}Tc-apcitide (70–100 μg peptide) by intravenous injection. Patients were positioned supine on the camera table, a lead shield was placed over the urinary bladder in some cases, and anterior and posterior planar images of the pelvis, thighs, knees, and calves were collected at 10, 60, and 120–180 min after injection of ^{99m}Tc-apcitide. Images were acquired for a minimum of 750,000 counts over the pelvis and 300,000 counts over the lower regions.

Contrast Venography Protocol

Contrast venography was performed according to each institution's standard protocol.

^{99m}Tc-Apcitide Image Masked-Reading Protocol

The ^{99m}Tc-apcitide images, identified only by code number, were read by 3 experienced individuals, each board certified in nuclear medicine, with masking of all other patient information including the contrast venography results. Each reader independently interpreted images from only 1 of the 2 trials, and none was a participant in any other capacity in either trial.

The images were read from a large computer screen. Beforehand, the readers were trained using images either from the trial not being read with masking or from earlier clinical trials. The readers were encouraged to optimize image contrast and to use color if necessary. Complete sets of 10-, 60-, and 120- to 180-min images were read for each patient.

The criteria for acute DVT were asymmetric uptake of ^{99m}Tc-apcitide in a deep vein relative to the corresponding contralateral deep vein segment or to contiguous segments of the ipsilateral vein, with the asymmetry persisting or increasing over time. In addition, the asymmetry was to be present in both anterior and posterior projections (if appropriate to the anatomic location of the vein).

For each patient, the following 9 anatomic regions were evaluated: the inferior vena cava, the right and left iliac veins, and the deep veins of the right and left thighs, knees, and calves. Each region was scored as positive or negative for acute DVT or as indeterminate. The final ^{99m}Tc-apcitide result was that found by the majority of the 3 readers. Cases without a majority result were defined as indeterminate. The results were compiled by anatomic region and by patient. ^{99m}Tc-apcitide images were also read by personnel in the institutions in which the images were acquired (referred to as institutional reading of ^{99m}Tc-apcitide scintigraphy). These institutional readers had access to the patients' general clinical information but were not aware of the venography results.

Venography Masked-Reading Protocol

The contrast venograms, identified only by code number, were read by 3 experienced radiologists, with masking of all other patient information including the ^{99m}Tc-apcitide results. Because each reader was an experienced radiologist, no special training in reading venograms was provided. Each reader independently read venograms from only 1 of the 2 trials, and none was a participant in any other capacity in either trial.

Each reader interpreted the contrast venograms according to that reader's own criteria. For each patient, the following 9 anatomic regions were evaluated: the inferior vena cava, the right and left iliac veins, and the deep veins of the right and left thighs, knees, and calves. Each region was scored as positive or negative for DVT or as indeterminate. The final contrast venography result was that found by the majority of the 3 readers. Cases without a majority result were defined as indeterminate. The results were compiled by anatomic region and by patient. The contrast venograms were read also by personnel in the institutions in which the images were acquired (referred to as institutional reading of venography).

Hamilton Contrast Venography Masked-Reading Protocol

The contrast venograms, identified only by code number, were read by 2 experienced radiologists, with masking of all other patient information including the ^{99m}Tc-apcitide results. For this masked reading, the final result was reached through consensus. When the 2 radiologists could not reach a consensus, a third radiologist read the venograms and the final result was the consensus of all 3.

This masked reading used the following standard criteria. For each patient, the iliac, common femoral, superficial femoral, popliteal, peroneal, posterior, and anterior tibial veins were evaluated for intraluminal filling defects. An intraluminal filling defect was defined as an area of reduced or absent filling, at least partially surrounded by contrast medium and seen in at least 2 views, or a vein that lacked filling except for the area proximal to a cutoff configured like a thrombus. A study showing an intraluminal filling defect was defined as positive for DVT. A study showing all the deep veins and no intraluminal filling defect was defined as negative for DVT. Venography was considered inadequate if a region of the deep veins lacked filling and showed no intraluminal filling defect.

Efficacy Data Analysis

The primary efficacy endpoint was the patient-based agreement of the masked ^{99m}Tc-apcitide scintigraphy reading and the masked venography reading. A ^{99m}Tc-apcitide result was considered to be true-positive if the ^{99m}Tc-apcitide and venography findings were positive in the same anatomic region or in a contiguous region. A ^{99m}Tc-apcitide result was considered to be true-negative if both tests showed negative findings in all regions. A ^{99m}Tc-apcitide result was considered to be false-positive if it was positive or indeterminate and the venography result was negative. A ^{99m}Tc-apcitide result was considered to be false-negative if it was negative or indeterminate and the venography result was positive. The target primary efficacy endpoint was 75% agreement between ^{99m}Tc-apcitide scintigraphy and contrast venography within the 1-sided 95% confidence interval. Secondary efficacy endpoints were the anatomic region–based agreement between the masked ^{99m}Tc-apcitide scintigraphy reading and the masked contrast venography reading, patient and region-based agreement between ^{99m}Tc-apcitide scintigraphy and institutional reading of venography, and the sensitivity and specificity of ^{99m}Tc-apcitide scintigraphy when either masked reading or institutional reading of venography was used as the truth.

Binomial distribution was used to test hypotheses about efficacy agreement rates and to establish 95% confidence intervals for estimates of agreement rate, sensitivity, and specificity. Subgroups determined by anticoagulant drug use were compared for primary efficacy data using 2×2 frequency tables and χ^2 statistics. SAS software (Cary, NC) was used to perform all analyses.

Safety Data and Analysis

Vital signs, including blood pressure, pulse rate, respiration rate, and temperature, were measured before and at 10, 30, 60, 90, and 180 min after injection of ^{99m}Tc-apcitide and of contrast medium. The McNemar test was used to compare the incidence of adverse events for ^{99m}Tc-apcitide and contrast venography. The signed rank test was used to test for vital sign changes before and after the tests within each treatment group and to test for differences between vital sign changes with ^{99m}Tc-apcitide and with venography.

RESULTS

The 2 trials included 280 enrolled patients from 34 participating institutions. Table 1 shows treatment-related adverse events observed after administration of ^{99m}Tc-apcitide and contrast medium. Significantly fewer ($P < 0.001$) adverse events occurred after administration of ^{99m}Tc-apcitide than after administration of contrast medium.

Thirty-seven patients were ineligible for efficacy evaluation, resulting in 243 evaluable patients (118 in trial A and 125 in trial B). In trial A, 80.1% of the studies were conducted in North America and 19.5% in Europe; in trial B, 62.4% of the studies were conducted in North America and 37.6% in Europe. The demographics of the evaluable patient populations were similar for trial A (60 men, 58 women; age range, 22–83 y; mean age ± SD, 59.8 ± 15.8 y; weight

TABLE 1
Treatment-Related Adverse Events

Adverse event	^{99m}Tc-apcitide scintigraphy (n = 278)	Contrast venography (n = 272)
Body		
Pain	0	3
Asthenia	0	1
Injection site edema	0	1
Injection site reaction	0	1
Cardiovascular system		
Hypotension	1	0
Syncope	0	1
Digestive system		
Nausea	0	2
Vomiting	0	1
Nervous system		
Hypoesthesia	0	1
Skin		
Rash	0	1
Total	1	12*

*$P < 0.001$.

range, 40–142 kg; mean weight ± SD, 81.1 ± 18.0 kg), trial B (63 men, 62 women; age range, 19–87 y; mean age, 59.4 ± 15.6 y; weight range, 40–155 kg; mean weight, 76.1 ± 19.2 kg), and both trials combined (123 men [50.6%], 120 women [49.4%]; age range, 19–87 y; mean age, 59.6 ± 15.7 y; weight range, 40–155 kg; mean weight, 78.5 ± 18.7 kg). Presenting signs and symptoms and period between onset of signs and symptoms and the first diagnostic test, shown in Table 2, also were similar for the 2 trials. However, the prevalence of a history of DVT or PE (58 patients, 24% in both trials combined) was higher in trial B (35 patients, 28%) than in trial A (23 patients, 20%).

Table 2 shows anticoagulant medication use from the onset of signs and symptoms through completion of both diagnostic procedures. Seventy percent of evaluable patients were receiving some form of anticoagulant or antiplatelet medication, and 61.7% were being treated with heparin. Again, consistency was observed between the 2 trials.

The mean injected dose of ^{99m}Tc-apcitide was 746 ± 100 MBq (20.2 ± 2.7 mCi) (range, 468 MBq to 1.09 GBq [12.6–29.4 mCi]), and the mean dose of peptide was 88.9 ± 9.4 μg (range, 70.0–100 μg) in a mean volume of 1.05 ± 0.49 mL (range, 0.7–5.0 mL).

More than 90% of patients (91.8%, 223/243) underwent ^{99m}Tc-apcitide scintigraphy and contrast venography within 36 h of each other. Of the other 20 patients, 17 underwent contrast venography before ^{99m}Tc-apcitide scintigraphy. Contrast venography was performed before ^{99m}Tc-apcitide scintigraphy in 178 patients (73.3%) (55 patients within 12 h and 123 patients within 12–36 h) and after ^{99m}Tc-apcitide scintigraphy in 45 patients (18.5%) (19 patients within 12 h and 26 patients within 12–36 h).

For the efficacy analyses, some patients had incomplete datasets, resulting in inclusion of fewer than 243 patients. The actual number of patient datasets analyzed is noted in the tables of results. Table 3 shows the primary and secondary efficacy endpoints for both trials. The primary efficacy endpoint for trial A and the secondary efficacy endpoints for both trials met the prospectively defined target. Also, the secondary efficacy endpoints for both trials were in general agreement. However, the primary efficacy endpoint for trial B was surprisingly low.

A review of the results revealed that masked reading of ^{99m}Tc-apcitide images agreed better with institutional reading of venography than did masked reading of venography (69% versus 63%), as shown in Tables 3 and 4. The low agreement between masked venography reading and institu-

TABLE 2
Evaluable Patient Demographics

Demographic parameter	Trial A (n = 118)		Trial B (n = 125)		Combined trials (n = 243)	
	n	%	n	%	n	%
Signs and symptoms						
Pain, tenderness, Homans' sign	106	89.8	104	83.2	210	86.4
Swelling	100	84.7	102	81.6	202	83.1
Increased warmth	49	41.5	51	40.8	100	41.2
Erythema	40	33.9	52	41.6	92	37.9
Palpable cord	9	7.6	11	8.8	20	8.2
Time from onset of signs and symptoms or surgery to first test* (d)						
<1	4	3.4	11	8.8	15	6.2
1	18	15.3	10	8.0	28	11.5
2	13	11.0	13	10.4	26	10.7
3	16	13.6	19	15.2	35	14.4
4	15	12.7	12	9.6	27	11.1
5	13	11.0	13	10.4	26	10.7
6	10	8.5	15	12.0	25	10.3
7	10	8.5	14	11.2	24	9.9
8	10	8.5	9	7.2	19	7.8
9	8	6.8	6	4.8	14	5.8
10	1	0.8	3	2.4	4	1.6
Concomitant anticoagulant medication						
At least 1 antiplatelet or anticoagulant	80	67.8	91	72.8	171	70.4
Medication class†						
Heparin group	69	58.5	81	64.8	150	61.7
Vitamin K antagonists	36	30.5	38	30.4	74	30.5
Antiplatelet aggregation	16	13.6	14	11.2	30	12.3
No medications	38	32.2	34	27.2	72	29.6

*Nine patients (1 in trial A, 8 in trial B) were asymptomatic but had undergone high-risk surgery.

†World Health Organization level 4 (includes heparin group; vitamin K antagonists, including warfarin; and platelet aggregation inhibitors, including aspirin and enzyme-acting drugs).

TABLE 3
Primary and Secondary Efficacy Endpoints

Efficacy endpoint	Trial A	Trial B	Combined trials
Primary			
Masked ^{99m}Tc-apcitide scintigraphy versus masked venography			
Agreement (%)	73.5*	59.3	66.1*
Lower 1-sided 95% confidence boundary (%)	65.7	51.5	60.7
n	113	123	236
Masked ^{99m}Tc-apcitide scintigraphy versus Hamilton-read venography			
Agreement (%)	68.2*	70.0*	69.1*
Lower 1-sided 95% confidence boundary (%)	60.0	62.3	63.7
n	110	120	230
Secondary			
Masked ^{99m}Tc-apcitide scintigraphy versus institutionally read venography			
Agreement (%)	69.6*	69.1*	69.3*
Lower 1-sided 95% confidence boundary (%)	61.7	61.5	64.0
n	113	123	238
Institutionally read ^{99m}Tc-apcitide scintigraphy versus institutionally read venography			
Agreement (%)	79.8*	68.6*	74.0*
95% confidence interval (%)	71.1–86.3	59.4–76.4	67.9–79.4
n	114	121	235

*Statistically significantly ≥ 75% (lower 1-sided 95% confidence boundary ≥ 60%); $P < 0.05$.

tional venography reading suggested a problem with the masked venography reading.

Further inspection of the masked venography results revealed that the 3 readers of the trial A venograms read with a positivity rate for DVT of 42%, 56%, and 37% (majority, 45%), compared with a 38% positivity rate for the institutional venography reading. Thus, all 3 readers were consistent with one another and with the institutional readers, and the positivity rate for most of the readers was approximately 40%, which is consistent with the 20%–50% known prevalence rate of DVT (*11,12*).

On the contrary, in trial B, although the institutional venography reading had a positivity rate of 54%, only 1 masked venography reader came close (59%) to that value. The other 2 masked venography readers had positivity rates of 83% and 94%. Considering that the 2 trials had patient populations with similar demographics and similar signs and symptoms, one would have expected a similar prevalence of DVT in both groups. The inordinately high venography positivity rates from 2 of the masked readers indicated a considerable degree of over-reading by those 2 readers. In fact, the agreement rate between the reader who read with the highest positivity and the reader who read with lowest positivity was so low (63%, with a 55% lower boundary for 1-sided 95% confidence) that these 2 assessments of venography would not have achieved the prospectively defined agreement rate for the new test. Clearly, the gold standard was flawed in trial B. Interobserver variability for readers of contrast venograms can be high (*24*). Nevertheless, the interobserver variability seen in the masked venography reading of trial B was extraordinary and, consequently, did not allow an accurate comparison of the new test, ^{99m}Tc-apcitide, with the truth, represented by contrast venography.

In 73% of the studies in both trials, contrast venography

TABLE 4
Contrast Venography Results

Type of reading	Trial A	Trial B	Combined trials
Masked venography versus institutionally read venography			
Agreement (%)	66.1	60.2	63.0
95% confidence interval (%)	56.6–74.3	50.9–68.6	56.5–69.1
n	115	123	238
Hamilton-read venography versus institutionally read venography			
Agreement (%)	79.6	74.8	77.1
95% confidence interval (%)	70.8–86.2	66.0–81.8	71.1–82.1
n	113	123	236
Masked venography versus Hamilton-read venography			
Agreement (%)	63.6	49.2	56.1
95% confidence interval (%)	53.9–72.3	40.0–58.3	49.4–62.5
n	110	120	230

was performed and read before ^{99m}Tc-apcitide scintigraphy was performed, so the probability of bias toward ^{99m}Tc-apcitide scintigraphy in the institutional reading of the venograms was low. Therefore, agreement between ^{99m}Tc-apcitide scintigraphy and institutionally read venography, which was a secondary efficacy endpoint in these trials, was considered to more closely represent true agreement between these 2 tests. This secondary efficacy endpoint met the prospectively defined efficacy target in both trials.

Because of the problems encountered with masked reading of venography, we sought a validated core facility whose staff would read the contrast venograms with masking using well-defined criteria. The Hamilton Civic Hospital Thrombosis Research Center in Ontario, Canada, is a Vascular Medicine Center of Excellence in which venography is the institutional standard of practice. Furthermore, this institution has well-defined criteria and procedures—validated in treatment outcome studies (*25*)—for the interpretation of venograms. Therefore, Hamilton was asked to conduct a new masked reading of the contrast venograms of both trial A and trial B using the validated procedures. The results are shown in Tables 3 and 4. Hamilton's masked venography reading agreed much better with the institutional venography reading (Table 4) than did the original masked venography reading, consistent with the more rigorous procedures of Hamilton. Using a validated reference test, the agreement rates between ^{99m}Tc-apcitide scintigraphy and Hamilton's masked venography reading met the prospectively defined target for the primary efficacy endpoint and were consistent (within 2%) in the 2 trials, as would be expected considering the similar demographics and presenting signs and symptoms of the 2 trial populations.

Table 5 shows the sensitivity and specificity of ^{99m}Tc-apcitide. The data from the masked contrast venography reading are included because they represent a prospectively defined endpoint. However, the results are of questionable value because of the inadequacy of the truth test. Using Hamilton-read venography as the truth, the masked reading of ^{99m}Tc-apcitide scintigraphy in all evaluable patients in both trials combined had a sensitivity, specificity, and agreement of 73.4%, 67.5%, and 69.1%, respectively. Using institutionally read venography as the truth, the corresponding values were 75.5%, 72.8%, and 74.0%.

Table 6 shows the results based on the calf, knee, and thigh regions. In no patient was a vena cava thrombus detected by venography, and only 6 patients had positive venography findings for the iliac region, none of which were positive by ^{99m}Tc-apcitide scintigraphy. The anatomic distribution of disease in the study, based on Hamilton-read contrast venography, was 38% in the calf, 31% in the knee, 26% in the thigh, and 4% in the pelvis.

The complete patient populations included patients with a history of DVT or PE (24%) and patients who presented as long as 10 d from the onset of signs and symptoms. Differentiation of acute from nonacute DVT by contrast venography is known to be difficult (*15*); therefore, in the complete trial populations, contrast venography results may have been read as positive because of an old, nonacute thrombus, whereas ^{99m}Tc-apcitide results would be expected to be negative in the absence of acute DVT. Alternatively, in patients who did not have a history of DVT or PE and who presented within 3 d of the onset of signs and symptoms of acute DVT, contrast venography would be expected to be positive because of acute DVT and not old DVT. The sensitivity, specificity, and agreement of ^{99m}Tc-apcitide, compared with institutionally read venography (63 patients) and Hamilton-read venography (60 patients), are shown in Table 7. In these patients, the sensitivity of institutionally read (i.e., normal practice) ^{99m}Tc-apcitide, compared with institutionally read or Hamilton-read venography (as the best available measures of truth), was 90.6% and 100%, respectively. Thus, in a patient population in which positive contrast venography findings were likely to represent only

TABLE 5
Efficacy Summary

Type of reading	Sensitivity (%)	Specificity (%)	Agreement (%)	True-positive	True-negative	False-positive	False-negative
Masked ^{99m}Tc-apcitide scintigraphy versus masked venography (n = 236)	59.9 (52.9–66.4)	77.4 (68.4–84.2)	66.1 (60.7)	91	65	19	61
Masked ^{99m}Tc-apcitide scintigraphy versus Hamilton-read venography (n = 230)	73.4 (60.7–82.9)	67.5 (59.7–74.3)	69.1 (63.7)	47	112	54	17
Institutionally read ^{99m}Tc-apcitide scintigraphy versus institutionally read venography (n = 235)	75.5 (66.2–82.7)	72.8 (64.0–80.0)	74.0 (67.9–79.4)	83	91	34	27
Institutionally read ^{99m}Tc-apcitide scintigraphy versus Hamilton-read venography (n = 227)	81.3	65.0	69.6	52	106	57	12

Values in parentheses are 95% confidence interval or lower 1-sided 95% confidence boundary.

TABLE 6
Efficacy by Anatomic Region

Type of reading*	Sensitivity (%)	Specificity (%)	Agreement (%)	True-positive	True-negative	False-positive	False-negative
Masked ^{99m}Tc-apcitide scintigraphy							
Calf	72.9	77.8	76.6	43	140	40	16
Knee	58.3	81.1	76.7	28	163	38	20
Thigh	62.5	86.4	82.4	25	172	27	15
Institutionally read ^{99m}Tc-apcitide scintigraphy							
Calf	83.1	76.8	78.4	49	136	41	10
Knee	68.8	82.7	80.0	33	163	34	15
Thigh	62.5	87.7	83.4	25	171	24	15

*Versus Hamilton-read venography.

acute disease, ^{99m}Tc-apcitide was shown to be highly sensitive for the detection of acute DVT.

The predictive value of a test depends on the prevalence of the disease (*26*). Over a disease prevalence range of 20%–50% (*11,12*), using the results from the patient population most likely to have only acute thrombosis, the negative predictive value of institutionally read ^{99m}Tc-apcitide scintigraphy ranged from 90% to 97%.

A comparison of ^{99m}Tc-apcitide scintigraphy in patients who were receiving anticoagulant medication (agreement rate with Hamilton-read venography, 70% for patients receiving anticoagulant or antiplatelet medication and 69% for patients receiving heparin) and those who were not (agreement rate, 68%) showed no discernable difference between the 2 groups. Acute DVT is readily visualized with ^{99m}Tc-apcitide scintigraphy, as is shown in images of 2 patients from the phase 3 trial (Figs. 1 and 2).

DISCUSSION

Deep venous thrombi originate in regions of low flow in the deep venous system of the lower extremities, frequently in a venous valve cusp or in a large venous sinus in the calf (*27*). Hypercoagulability and vascular endothelial irritation are believed to be comorbid factors (*1,8*). The initial process in thrombosis is platelet deposition, followed by proximal propagation of the initial thrombus, with incorporation of fibrin, red blood cells, and platelets. As platelets are incorporated into a thrombus, they become activated (*28*). One of the consequences is that the GPIIb/IIIa receptors on the surface of the activated platelets become competent to bind fibrinogen, which cross-links the platelets, resulting in platelet aggregation (*29*). The thrombus may lyse or may eventually become organized. Until it has lysed or become organized, the thrombus is susceptible to continued propagation, sometimes extending along the entire course of the deep venous system of the lower extremity (*30*), and to detachment from the vessel wall and embolization. This condition is acute venous thrombosis, and it is this type of venous thrombus that is most likely to result in PE (*8,31*).

Once a thrombus has become organized, it stabilizes and is difficult to dislodge (*31*). This condition is sometimes referred to as chronic DVT, but we use the term "nonacute DVT" to avoid confusion with chronic recurrent acute DVT. During thrombus organization, which may start within 48 h, platelets and platelet residue are phagocytosed, and by the second week, the process has progressed to a fibrotic mass covered by smooth muscle cells, which are eventually covered by new endothelium (*31*). In the process, venous valves may be rendered incompetent, leading to inadequate return of venous blood from the legs and postphlebitic syndrome. Also, in approximately 25% of patients, old nonacute DVT develops subsequent to recurrent acute DVT (*7*).

Anatomic tests, such as contrast venography and sonogra-

TABLE 7
Efficacy in Patients with No History of DVT or PE

Type of reading	Sensitivity (%)	Specificity (%)	Agreement (%)	True-positive	True-negative	False-positive	False-negative
Masked ^{99m}Tc-apcitide scintigraphy versus Hamilton-read venography (n = 60)	83.3	73.8	76.7	15	31	11	3
Institutionally read ^{99m}Tc-apcitide scintigraphy versus institutionally read venography (n = 63)	90.6	83.9	87.3	29	26	5	3
Institutionally read ^{99m}Tc-apcitide scintigraphy versus Hamilton-read venography (n = 60)	100	69.0	78.3	18	29	13	0

Data are for patients who presented within 3 d of onset of signs and symptoms.

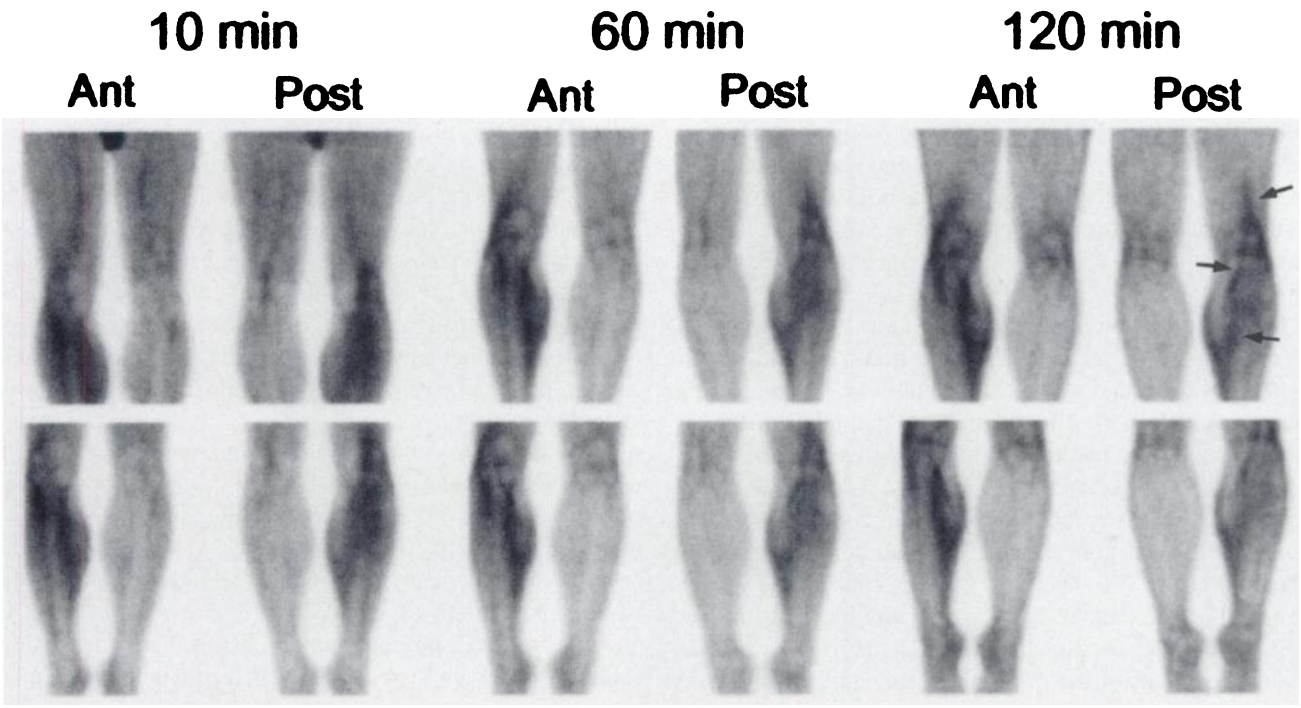

FIGURE 1. A 39-y-old man with no history of DVT who presented with pain, tenderness, and swelling of right calf of 2-d duration. Contrast venography showed thrombus in deep veins of right calf extending into popliteal vein. Ten-, 60-, and 120-min ^{99m}Tc-apcitide scintigraphic images (anterior [Ant], left; posterior [Post], right) show acute DVT in right calf extending through knee to distal thigh.

phy, cannot readily differentiate acute from old, nonacute DVT. Therefore, a diagnostic method is needed that exploits a functional or biochemical difference between acute and nonacute thrombi. Because platelets are involved in acute but not nonacute thrombi, radiolabeled platelets have been investigated for imaging thrombi (*32*). However, this method was found to be of limited use in heparinized patients and also required a long delay between injection and imaging (*33*). Platelets express surface receptors of the integrin family known as GPIIb/IIIa (or $\alpha_{IIb}\beta_3$) receptors, which become competent to bind fibrinogen when the platelet is activated (*29*). Because activated platelets are present in acute thrombi but not in old, organized, nonacute thrombi, the GPIIb/IIIa receptor is a molecular marker of acute

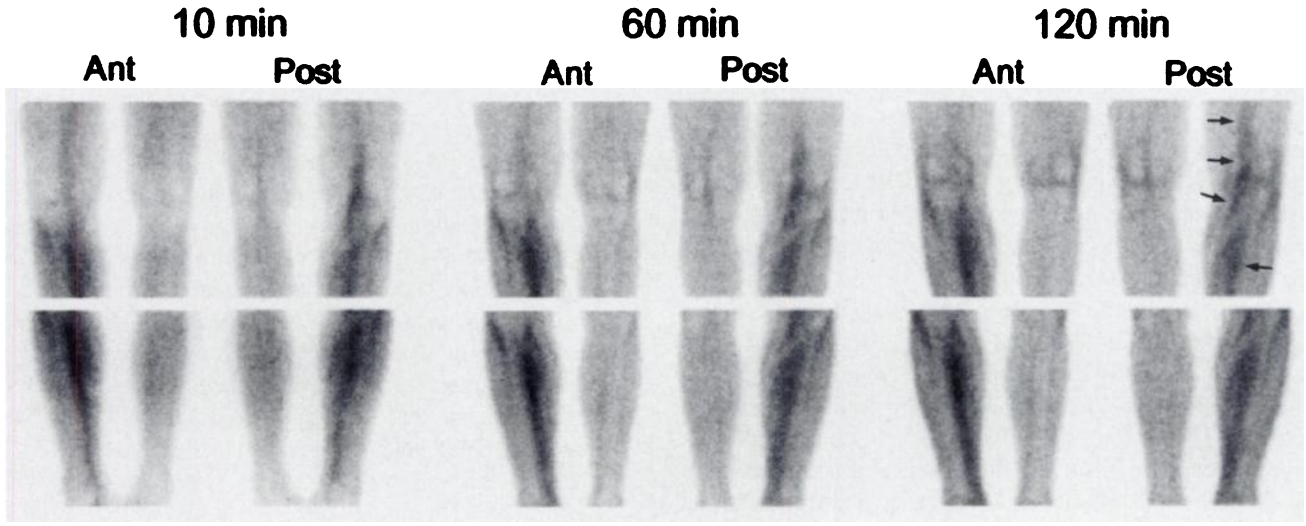

FIGURE 2. A 66-y-old man with history of DVT, and receiving heparin and warfarin, who presented with pain, tenderness, and swelling of left leg of 5-d duration. Contrast venography showed no filling of veins of left calf but showed thrombus in left popliteal vein. Ten-, 60-, and 120-min ^{99m}Tc-apcitide scintigraphic images (anterior [Ant], left; posterior [Post], right) show acute DVT in deep veins of left calf extending through knee into distal thigh.

thrombi (*34*). ^{99m}Tc-apcitide is a small, synthetic peptide containing a region for binding to the GPIIb/IIIa receptor and a complex of the radionuclide ^{99m}Tc. In vitro studies have shown that ^{99m}Tc-apcitide binds with high affinity to GPIIb/IIIa receptors (*23*), does not bind appreciably to the vitronectin receptor ($\alpha_V\beta_3$) found on endothelial cells (*23*), and binds to activated human platelets 3 times more than to resting platelets. In vivo studies in animals have shown that ^{99m}Tc-apcitide localizes in experimental acute venous thrombi (*23*).

In designing a clinical trial to show the efficacy of ^{99m}Tc-apcitide, the challenge was to find a way to definitively measure the truth. Sonography is the diagnostic method used most often to diagnose DVT, but this method is not amenable to a masked reading, has several limitations, and is not accepted as the gold standard. Although contrast venography assesses venous anatomy and not function, it is accepted as the gold standard for thrombus detection. Therefore, the ^{99m}Tc-apcitide phase 3 clinical trials were designed to compare ^{99m}Tc-apcitide scintigraphy with contrast venography as the truth for the detection of acute venous thrombosis. The primary efficacy endpoint, masked reading of ^{99m}Tc-apcitide scintigraphy compared with masked reading of contrast venography, was chosen to remove any bias from the image evaluation. However, this choice also created an artificial condition, because in normal practice, images are evaluated with knowledge of all patient clinical information. In recognition of this factor and the known interobserver variability in masked reading of venograms (*24*), the target endpoint was defined as an agreement rate of 75%.

The results showed that contrast venography read with masking and without well-defined image reading criteria was not a good gold standard. This conclusion was evident from the poor agreement rate between masked reading of venography and institutional reading of venography and from the large interobserver variability. Therefore, the Hamilton Thrombosis Research Center was selected as a validated (*25*) center for masked reading of contrast venograms. As the data show, the results of Hamilton-read venography were consistent across the 2 clinical trials and agreed well with institutionally read venography results. Using Hamilton-read venography as truth, ^{99m}Tc-apcitide scintigraphy met the prospectively defined efficacy endpoint (75% agreement rate).

Nonetheless, there remained the fundamental problem that the functional test, ^{99m}Tc-apcitide scintigraphy, was being compared with the anatomic test, contrast venography. Thus, the anatomic findings could be positive because of nonacute DVT, whereas ^{99m}Tc-apcitide findings would not be expected to be positive in the absence of acute thrombosis. To address this issue, data were analyzed from a subset of patients who had no history of DVT or PE and who presented soon after (within 3 d) the onset of signs and symptoms of acute DVT. In these patients, one would expect that positive contrast venography findings would be caused only by acute thrombus. The analysis showed that, in these patients, ^{99m}Tc-apcitide scintigraphy was highly sensitive (90.6%) for the detection of acute DVT. On the basis of these results, the negative predictive value of ^{99m}Tc-apcitide scintigraphy was high (90%–97%), indicating that negative ^{99m}Tc-apcitide findings should be of value in excluding acute DVT. Although the positive predictive value was not as high as the negative predictive value, the true accuracy of contrast venography is unknown. The apparent false-positive findings from ^{99m}Tc-apcitide scintigraphy may have resulted from a greater sensitivity of ^{99m}Tc-apcitide scintigraphy than of contrast venography in detecting acute thrombi, which do not produce a visible intraluminal filling defect on venography.

From the shortcomings of contrast venography and sonography and the results of the ^{99m}Tc-apcitide clinical trials, one can reason that ^{99m}Tc-apcitide scintigraphy will be of particular use in patients with suspected acute DVT but negative or equivocal sonography findings; patients with suspected recurrent acute DVT, a history of DVT, and a possible residual nonacute thrombus; patients in whom contrast venography is contraindicated or would be technically difficult; patients with a calf-vein thrombus; obese patients; patients with duplicate veins; noncompliant patients; patients who have sustained trauma; and patients with orthopedic casts in place.

Figures 1 and 2 show the ability of ^{99m}Tc-apcitide scintigraphy to image acute DVT. Figure 1 clearly shows asymmetric (compared with the contralateral leg) uptake along the course of the deep veins of the right calf, extending through the left popliteal vein and into the distal femoral vein. Superficial venous uptake is also seen in the knee. Figure 2 shows how ^{99m}Tc-apcitide scintigraphy can be useful in patients with a history of DVT and indeterminate venography findings. Although the popliteal thrombus was seen by venography, the calf veins were not filled, and the calf therefore could not be evaluated by venography. ^{99m}Tc-apcitide scintigraphy shows the acute DVT along the course of the deep veins of the calf, knee, and distal thigh.

CONCLUSION

Masked reading of ^{99m}Tc-apcitide scintigraphy, compared with masked reading of contrast venography by a validated institution, met the prospectively defined agreement rate for imaging acute DVT. In patients for whom the reference standard, contrast venography, was expected to show positive findings only when acute DVT was present, ^{99m}Tc-apcitide scintigraphy was shown to have high sensitivity. The results indicate that ^{99m}Tc-apcitide is safe and effective for the scintigraphic imaging of acute DVT.

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