Acute Pulmonary Embolism

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Abstract: Most large or fatal pulmonary embolisms (PE) at autopsy were unsuspected ante mortem. Newly identified clinical characteristics of PE enhance our ability to identify potential patients. Because of laudable efforts to diagnose PE, about 90% of outpatient computed tomographic (CT) angiograms are negative. Overuse of CT angiography has resulted in huge expenses and exposure of many to radiation. Approximately 30% of patients with suspected acute PE would not need imaging if D-dimer is normal and clinical assessment is not a high probability, but such triage is uncommonly used. Perhaps perfusion imaging should be used more frequently. Radiation and cost with scintigraphy are less than with CT angiography. Single-photon emission computed tomography lung scans appear to be more effective than planar lung scans. Diseases associated with an increased risk of PE are being identified, but recommended prophylaxis usually is not given. Potential benefits and risks of treatment options need to be assessed. (Curr Probl Cardiol 2010;35:314-376.)

Prevalence of Pulmonary Embolism

In 2006, 247,000 adults were hospitalized in short-stay hospitals in the USA with acute pulmonary embolism (PE) (Stein PD, Matta F, unpublished data from the National Hospital Discharge Survey). This was about one third the number hospitalized with acute myocardial infarction (828,000 myocardial infarction patients). PE is the third most common acute cardiovascular disease after myocardial infarction and stroke.[1] Patients with acute PE represented 0.77% of hospitalized patients aged ≥18 years, and 110 patients/100,000 adult population (Stein PD, Matta F, unpublished data from the National Hospital Discharge

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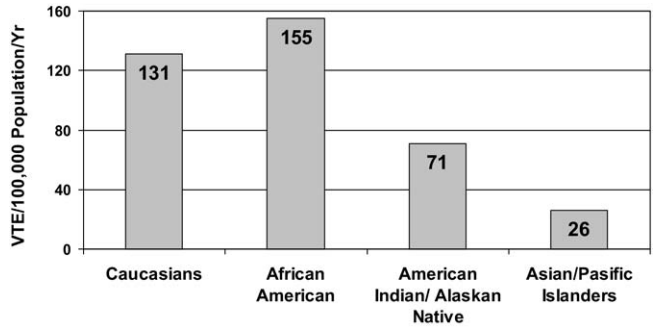

FIG 1. Venous thromboembolism (VTE)/100,000 population/year from 1990 through 1999. (Data from Stein et al.[3-5])

Survey). Based on data from 2006, 467,000 patients were hospitalized with DVT, which represented 1.5% of hospitalized patients and 208/100,000 adult population (Stein PD, Matta F, unpublished data from the National Hospital Discharge Survey).

Gender

The rate of diagnosis of PE, not adjusted for age, was higher in women (60 PE/100,000 women) than in men (42 PE/100,000 men).[2] The age-adjusted rate of diagnosis of PE in men and women, however, was comparable.[2] Regarding DVT, both the unadjusted rate of diagnosis of DVT/100,000 population and the age-adjusted rates of diagnosis of DVT/100,000 population were higher in women.[2]

Race

The incidence of DVT and PE was the same in African Americans and whites.[3] Strikingly, the incidence of PE and of DVT was much lower in Asian Americans/Pacific Islanders than in African Americans and whites[4] (Fig 1). The incidence was also lower in American Indians and Alaska natives than in African Americans and whites.[5] Archeologic studies suggest that Native Americans may be descended from Asians who crossed the Bering Straits thousands of years ago.

Age

The incidence of PE and DVT increases exponentially with age[6] (Figs 2 and 3). There is no cut-off age at which there is no risk of venous thromboembolism (VTE). Even children may suffer a PE or DVT. Age, therefore, does not exclude the diagnosis, but it is uncommon in infants and children[7] (Fig 4).

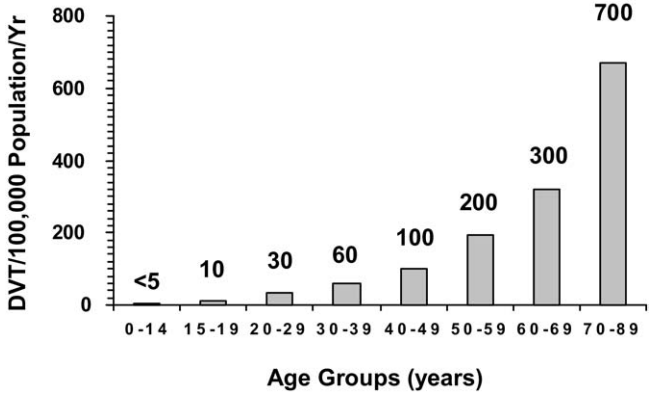

FIG 2. Deep venous thrombosis (DVT)/100,000 population/year shown according to age for the year 1999.[6,7] (Reprinted with permission.[10])

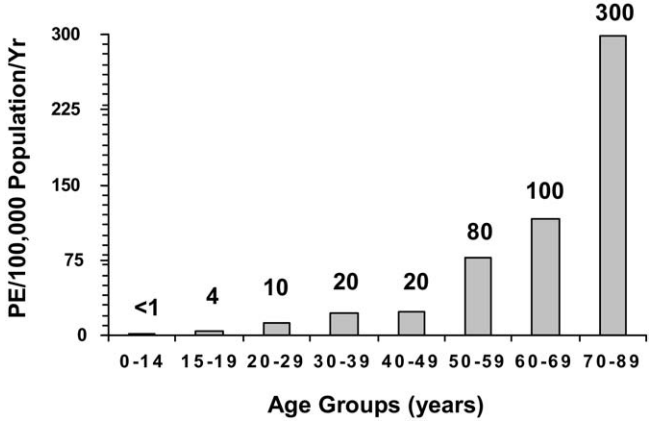

FIG 3. Pulmonary embolism (PE)/100,000 population/year shown according to age for the year 1999. (Data from Stein et al.[5,6]) (Reprinted with permission.[10])

Season and Region

Although it has been stated that there is a seasonal variation in the incidence of PE and DVT, an analysis of data from the National Hospital Discharge survey showed no seasonal difference[8] (Fig 5). Regional differences in the USA, however, were detected.[9] The incidences of PE and of DVT were higher in northeastern states than in western states (Fig 6). Other regional differences were shown as well.

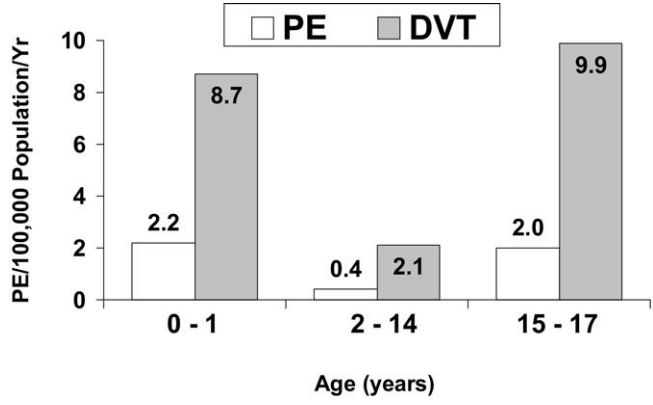

FIG 4. PE and DVT in children. (Data from Stein et al.[7])

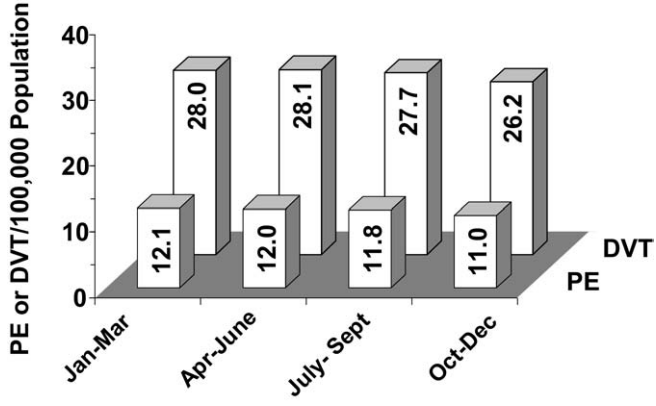

FIG 5. Rates of diagnosis per 100,000 population for PE, DVT, according to quarter of year. Data are averaged from 1979 through 1999. (Reprinted with permission.[8])

Prevalence at Autopsy

Since 1985, pooled data showed PE at autopsy in 932 of 4898 (19%).[10] Large or fatal PE in patients at autopsy since 1985 was observed in 383 of 6181 (6%).[10]

Site of DVT at Autopsy

The most common site of DVT was the calf vein[11,12] (Fig 7). Veins of the foot were affected nearly as frequently as veins of the thigh. Veins of the pelvis were involved less commonly and the inferior vena cava (IVC) was rarely involved.

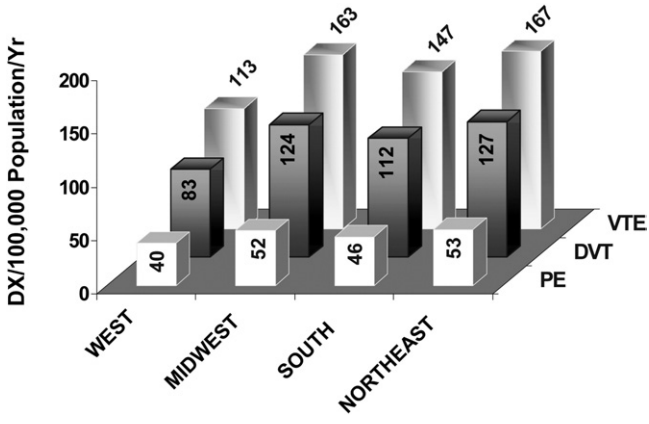

FIG 6. Rates of diagnosis (Dx)/100,000 population/year of PE, DVT, and VTE according to region of the United States from 1979 through 2001. (Reprinted with permission.[9])

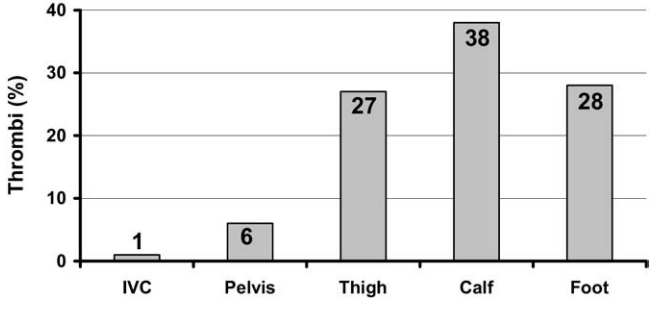

FIG 7. Distribution of DVT among patients at autopsy in whom veins of the foot as well as pelvic, thigh, and calf veins were dissected.[11,12] (Reprinted with permission.[10])

Size of PE

Based on conventional pulmonary angiography, the largest vessel showing PE was a subsegmental vessel in 6% of patients,[13] and based on multidetector computed tomography (CT), the largest vessel showing PE was a subsegmental vessel in 5% of patients.[14] This indicates that clinically diagnosed PE usually involves the main, lobar, or segmental pulmonary arteries. Smaller arteries are frequently involved, however, and with specialized techniques, such as wedge pulmonary angiography, PE in branches 1.5-2.0 mm have been identified[15] (Figs 8 and 9). In fact, small PE occur frequently according to postmortem angiography and

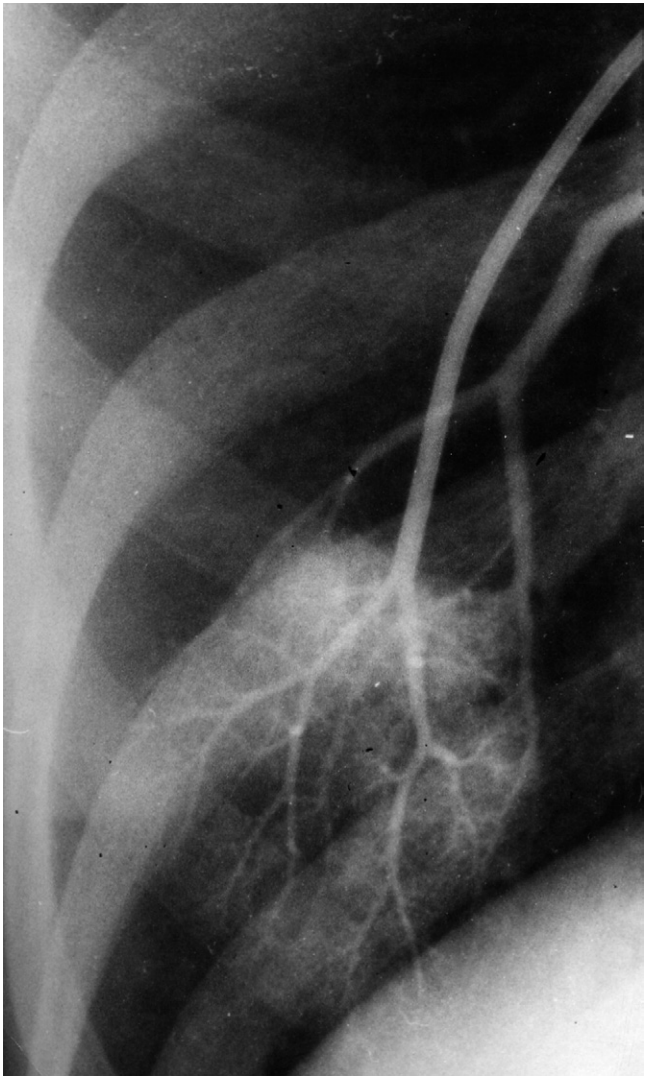

FIG 8. Normal pulmonary wedge arteriogram. Vessels show narrow gradual tapering and numerous fine branches. A background blush of capillary filling and veins draining the segment are shown. Catheter diameter was 2.3 mm. (Reprinted with permission.[15])

careful dissection.[16] An extensive number of small PE in several patients were thought to be fatal.[16] PE limited to muscular pulmonary artery branches (0.1- to 1-mm-diameter) was observed in 26 of 34 patients (76%) who died of PE. The PE in these patients was in elastic pulmonary

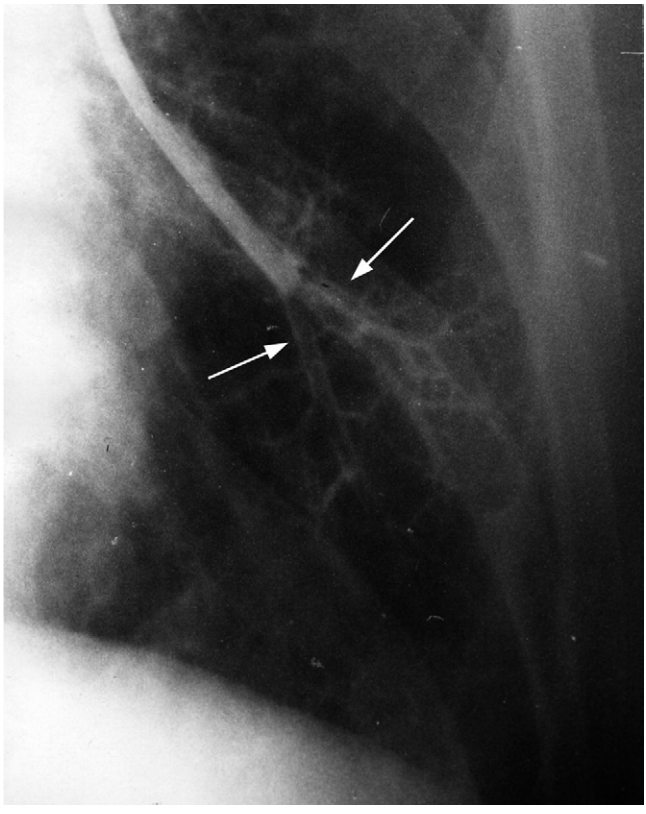

FIG 9. Wedge arteriogram showing intraluminal filling defects in arteries 1.5-2.0 mm in diameter (arrows). (Reprinted with permission.[15])

artery branches (>1-mm-diameter) in 8 of 34 patients (24%).[16] Microscopic examination showed PE in pulmonary arterioles in 13 of 34 (38%) with grossly visible PE.[16]

Fibrous bands, webs, and intimal fibrosis have been interpreted as the final state of organization of PE and these have been reported by some to indicate old PE at autopsy.[17] Meticulous dissection and microscopic examination for minute and barely visible fragments showed traces of fresh or old PE at autopsy in 52% and 64% of patients.[17,18]

Unsuspected PE at Autopsy

PE, based on pooled data, was unsuspected or undiagnosed ante mortem in 3268 of 3876 patients who had PE at autopsy (84%).[10] Remarkably, even in patients with large or fatal PE at autopsy, the majority, 1902 of

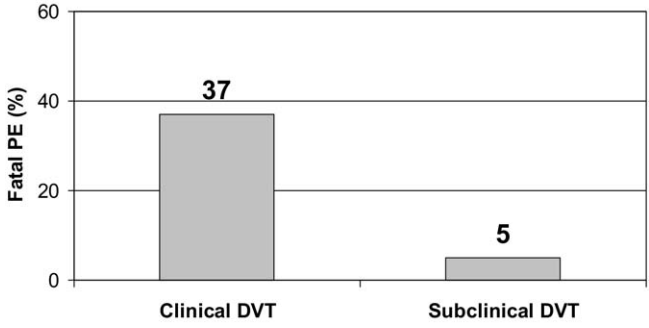

FIG 10. Frequency of fatal PE in untreated patients with clinically apparent DVT, and patients, of whom most had subclinical DVT diagnosed by radioactive fibrinogen scintiscans. (Data are from Byrne[18] and Collins and associates.[21] Reprinted with permission.[10])

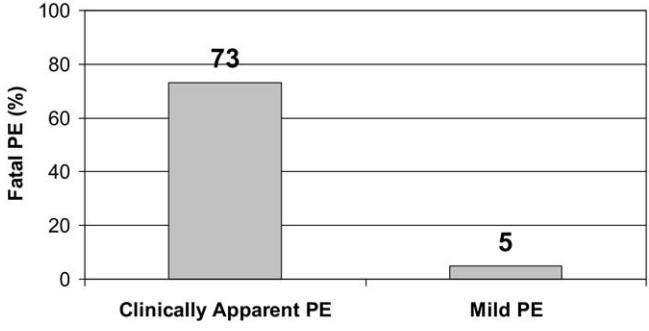

FIG 11. Fatal initial and fatal recurrent PE among untreated patients. Comparison is made between patients in whom the diagnosis was clinically apparent, and presumably PE was severe, and patients in whom PE was mild. (Data are from Hermann and associates[20] and Stein and Henry.[22] Reprinted with permission.[10])

2448 (78%), were unsuspected or undiagnosed ante mortem.[10] Many patients with unsuspected large or fatal PE had advanced associated disease. Whether unsuspected PE at autopsy resulted from an insufficiently high index of suspicion or silent PE is uncertain.

Case Fatality Rate

In untreated patients with clinically apparent DVT, the incidence of fatal PE was 37%[19] (Figs 10 and 11). In patients with clinically apparent PE, 37% died of the initial PE and an additional 36% died of a recurrent PE, with total mortality being 73%.[20] The applicability of these results is questionable in the present era of early diagnosis of mild disease. The

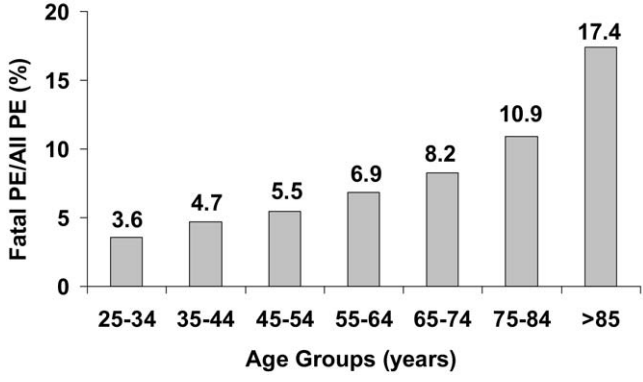

FIG 12. Estimated case fatality rates for PE according to decades of age. (Reprinted with permission.[23])

mortality rate of patients with untreated silent DVT, found by radioactive fibrinogen scintiscans, was 5%.[21] Among patients with mild PE who inadvertently were untreated because the diagnosis was not made from the ventilation-perfusion (V/Q) lung scan, 1 of 20 (5%) died of the initial or recurrent PE.[22]

The case fatality rate of PE (deaths/100 cases of PE) is age-dependent[23] (Fig 12). The estimated case fatality rate, in the modern era of treatment, is about 7.7%.[23] This is higher than reported in diagnostic trials and in pharmaceutical investigations. The case fatality rate in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) was 2.5%.[24] In PIOPED, which was an investigation of the accuracy of V/Q lung scans, patients were excluded if they were too ill to participate. In addition, most deaths from PE occur within the first 2.5 hours after the diagnosis is made,[25] thereby excluding another group of patients. For similar reasons, case fatality rates in trials of treatment with low-molecular-weight heparin (LMWH) were only 0.6%-1.0%.[26,27]

Predisposing Factors

Risk factors in patients with PE identified in PIOPED and PIOPED II are shown in Table 1.[28] Immobilization of only 1 or 2 days may predispose to PE, and 65% were immobilized $\leq$2 weeks.[29]

The risk of PE in patients hospitalized with heart failure is twice that of hospitalized patients who do not have heart failure.[30] The lower the ejection fraction, the greater the risk of VTE.[31] An ejection fraction of $<$20% was associated with a 38-fold increase in the incidence of VTE.[31]

TABLE 1. Predisposing factors in all patients with pulmonary embolism

Risk factors	PIOPED (n = 383) n (%)	PIOPED II (n = 185-192)[a] n (%)
Immobilization	206 (54)[b]	48 (25)[c]
Travel ≥4 h in last month		23 (12)
Surgery (≤3 mo)	160 (42)	41 (21)[d]
Coronary heart disease	76 (20)	
Myocardial infarction	48 (13)	
Heart failure	45 (12)	10 (5)
Collagen vascular disease	15 (4)	
Malignancy[b]	69 (18)	37 (19)
Stroke, paresis, or paralysis	37 (10)	7 (4)
Thrombophlebitis, ever	71 (19)	19 (10)
Prior pulmonary embolism	23 (6)	7 (4)
Trauma (≤3 mo)		
Lower extremities	47 (12)	16 (8)[e]
Other		5 (3)
Asthma	27 (7)	22 (12)
Pneumonia (current)	27 (7)	5 (3)
Chronic obstructive pulmonary disease	37 (10)	10 (5)
Emphysema		7 (4)
Interstitial lung disease	6 (2)	
Lung cancer		5 (3)
Estrogen	22 (6)	
Males, therapeutic		1 (1)
Smoke (ever)		90 (47)
<1 pack/d		43 (22)
1-2 packs/d		37 (19)
≥2 packs/d		1 (1)
Central venous instrumentation (≤3 mo)		22 (12)
Postpartum ≤3 mo	9 (2)	
Sepsis (current)		0 (0)

[a]Nominal value. If value was not reported, it was assumed to be absent.
[b]Actively treated in last 3 mo.
[c]Within last month.
[d]Among 41 patients with surgery as a risk factor, abdominal surgery was in 9, and heart, pelvic, hip/knee-open, hip/knee-replacement, and neurosurgery ranged from 3 to 5.
[e]Includes pelvis.
Data from PIOPED (unpublished) and Stein and associates.[28] Reprinted with permission.[10]

Patients with cancer had twice the incidence of VTE as patients without cancer.[32] The incidence of VTE associated with cancer differs according to the type of cancer.[32] Pancreatic cancer showed the highest risk for VTE and bladder cancer showed the lowest risk (Fig 13).

Stroke is a well-known risk factor for VTE[33] as is chronic obstructive pulmonary disease.[34] Pregnancy is also a well-known risk actor[35] (Fig 14). Obesity in hospitalized patients was shown to be a risk factor for VTE.[36]

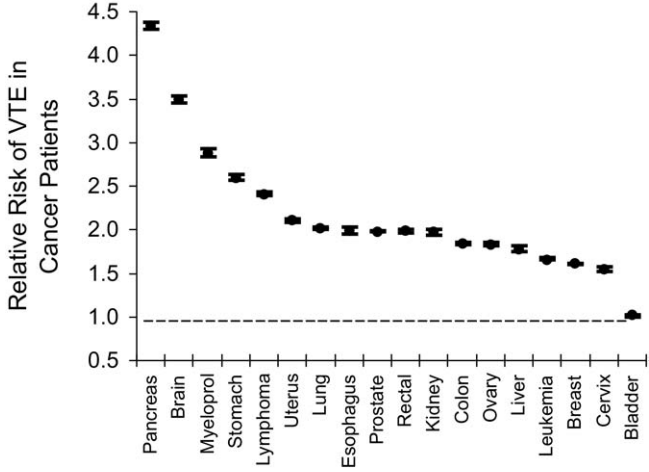

FIG 13. Relative risks of VTE in patients hospitalized with cancer compared with those without cancer. The relative risk of VTE ranged from 1.02 to 4.34. (Reprinted with permission.[32])

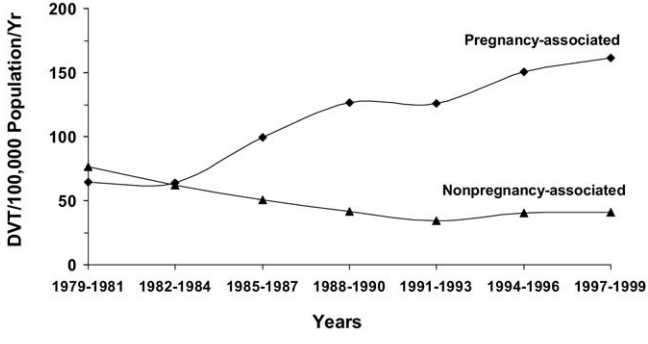

FIG 14. Triennial rates of DVT in women age 15-44 years comparing pregnancy-associated DVT with non-pregnancy-associated DVT. (Reprinted with permission.[35])

Illnesses among hospitalized medical patients who are associated with an increased risk of VTE include sickle cell anemia,[37] nephrotic syndrome,[38] human immunodeficiency virus infection,[39] diabetes mellitus,[40] rheumatoid arthritis,[41] and hypothyroidism.[42]

Oral Contraceptives

Modern-day oral contraceptives contain 20-35 μg of ethinyl estradiol.[43,44] Although the relative risk of VTE is higher among users of oral

estrogen-containing contraceptives than nonusers,[43,45] the absolute risk is low.[46] An absolute risk of VTE <1/10,000 patients/year increased to only 3-4/10,000 patients/year during the time oral contraceptives were used.[46]

Silent PE

Pooled data showed that silent PE was diagnosed in 1665 of 5233 (32%) patients with DVT.[47] Recurrent PE was more frequent among patients treated for DVT who had silent PE (25 of 488 (5.1%)) than was a first PE in patients who had DVT but did not have silent PE (7 of 1093 (0.6%)),[47] although 1 investigator found no difference in the prevalence.

Clinical Diagnosis

None of the clinical manifestations of acute PE are specific, and most are not sensitive. Most data on clinical findings are from patients entered in trials such as the Urokinase Pulmonary Embolism Trial,[48] PIOPED,[49] and PIOPED II.[14] By the very nature of trials, physicians identified patients with a potential diagnosis of PE based on their prior clinical knowledge. The patients were well enough to participate, and those who were too ill, or died suddenly, could not have been included. It is not certain if those who died suddenly, or in whom autopsy showed PE but the diagnosis was not considered ante mortem, had these symptoms and signs.

J. E. Dalen: The "pleuritic pain/hemoptysis syndrome" is usually due to pulmonary infarction and is frequently accompanied by an infiltrate, atelectasis, or small pleural effusion on chest x-ray. Hemoptysis is infrequent. The "circulatory collapse syndrome" occurs in patients with acute cor pulmonale due to massive pulmonary embolism. These patients usually have hypotension and may have distended neck veins. The electrocardiogram may show a S1Q3T3 pattern. The "uncomplicated dyspnea syndrome" occurs in patients with submassive PE who do not develop pulmonary infarction. The presence of hypoxemia helps to make the diagnosis.

Presenting Syndromes

Most patients presented with a typical syndrome of PE, as follows: (1) pleuritic pain/hemoptysis syndrome; (2) circulatory collapse syndrome; and (3) uncomplicated dyspnea syndrome (not complicated by pleuritic pain, hemoptysis, or circulatory collapse). In PIOPED, 65% of patients had the pleuritic pain or hemoptysis syndrome, whereas in PIOPED II only 41% had this syndrome on presentation.[28,29] In the 16 years between the 2 PIOPED investigations, it may be that physicians became more familiar with the fact that patients with PE need not have pleuritic pain or hemoptysis. Results of rigorous studies take many years to be incorpo-

TABLE 2. Symptoms in patients with PE and no preexisting cardiac or pulmonary disease

Symptoms	PIOPED (n = 117) PE n (%)	PIOPED II (n = 127-133) PE n (%)
Dyspnea		
Dyspnea (rest or exertion)	85 (73)	97 (73)
Dyspnea (at rest)	—	73 (55)
Dyspnea (exertion only)	—	21 (16)
Orthopnea (≥2-pillow)	—	37 (28)
Pleuritic pain	77 (66)	58 (44)
Chest pain (not pleuritic)	5 (4)	25 (19)
Cough	43 (37)	45 (34)
Hemoptysis	15 (13)	7 (5)[a]
Purulent	—	7 (5)
Clear	—	7 (5)
Nonproductive	—	26 (20)
Wheezing	10 (9)	27 (21)
Palpitations	12 (10)	—
Calf swelling	—	51 (40)
Thigh swelling	—	10 (8)
Thigh swelling, no calf swelling	—	1 (1)
Calf or thigh pain	30 (26)[b]	56 (44)
Calf pain only	—	30 (23)
Thigh pain only		22 (17)
Thigh pain, no calf pain	—	4 (3)

[a]Hemoptysis, patients with PE: 2 = slightly pinkish, 4 = blood-streaked, 1 = all blood (<1 teaspoonful).
[b]"Leg pain."
Data from Stein and associates[29] and Stein et al.[28] Reprinted with permission.[10]

rated into clinical practice.[50] A few patients did not fit into the traditional syndromes. This proportion increased from 5% in PIOPED to 14% in PIOPED II.[28,29] Again, this may represent learning, in the 16 years between studies, that some patients may present with only an abnormal chest radiograph or may have DVT with no respiratory symptoms.

Symptoms of Acute Pulmonary Embolism

Unexplained dyspnea, tachypnea, or chest pain may suggest a need for diagnostic testing.[51] Among patients with no prior cardiopulmonary disease recognized with the diagnosis of PE and well enough to participate in both PIOPED and PIOPED II, dyspnea was by far the most common symptom, occurring in 73%[28,29] (Table 2). Dyspnea may occur only with exertion.[28] The onset of dyspnea usually occurs over seconds or minutes but may occur over hours or days.[28]

Orthopnea is a symptom of PE.[28] It may occur in those who have dyspnea at rest or only on exertion.[28]

Pleuritic pain is more common than hemoptysis in patients with PE and no prior cardiopulmonary disease.[28,29] Hemoptysis is most often blood-streaked sputum or the sputum is slightly pinkish, but it can be completely bloody. Nonpleuritic chest pain is uncommon.[29] The pain usually does not radiate.[29]

Cough may be a symptom of PE.[28,29] It is usually nonproductive, but it may be productive of clear or purulent as well as bloody sputum.[28]

Calf or thigh pain occurred in 44% of patients with PE and no prior cardiopulmonary disease in PIOPED II, and 23% had calf pain alone, but thigh pain alone was uncommon (3%).[28]

Signs of Acute Pulmonary Embolism

Tachypnea (respiratory rate ≥20/min) occurred in 54% and 70% of patients with PE who did not have prior cardiopulmonary disease.[28,29] Tachycardia (heart rate >100/mint) occurred less frequently (24%-30%)[28,29] (Table 3). Neck vein distension, right ventricular lift, or accentuated pulmonary component of the second sound occurred in only 21% of patients who did not have prior cardiopulmonary disease[28] (Table 3).

J. E. Dalen: The accentuated pulmonary component of the second heart sound is not a specific or sensitive sign of PE. A right ventricular lift, which suggests major PE, may be difficult to appreciate.

Rales (crackles) and decreased breath sounds were the most frequently detected abnormalities on lung examination, occurring in 35% of patients with PE and no prior cardiopulmonary disease.[28] Rales usually occurred in patients who had pulmonary parenchymal abnormalities, atelectasis, or a pleural effusion on the chest radiograph.[29] Wheezes and rhonchi were heard occasionally.[28] A pleural friction rub was rare[28] (Table 3).

Among patients with PE and no other definite or possible cause of fever, the fever was usually low grade.[52] Fever occurred with similar frequency among those with pulmonary hemorrhage/infarction and those with PE who did not have pulmonary hemorrhage/infarction.[52] Patients were defined as having the pulmonary hemorrhage/infarction syndrome it they had hemoptysis, or pleuritic pain or atelectasis/parenchymal abnormality on the chest radiograph. Temperature of 101°F (38.3°C) or higher occurred only in 6% and only 1.6% had a temperature of 102°F (38.9°C) or higher.[52]

Signs of DVT in patients with no prior cardiopulmonary disease were observed in 11% of patients with PE in PIOPED[29] and 47% of patients

TABLE 3. Signs in patients with PE and no preexisting cardiac or pulmonary disease

Signs	PIOPED (n = 117) PE n (%)	PIOPED II (n = 128-132) PE n (%)
General		
Tachypnea (≥20/min)	82 (70)	71 (54)
Tachycardia (>100/min)	35 (30)	32 (24)
Diaphoresis	13 (11)	3 (2)
Cyanosis	1 (1)	0 (0)
Temperature >38.5°C (>101.3°F)	8 (7)	2 (1)
Cardiac examination (any)		28 (21)
Increased P2	27 (23)	15 (15)[a]
Third heart sound	3 (3)	—
Fourth heart sound	28 (24)	—
Right ventricular lift	5 (4)	4 (4)[b]
Jugular venous distension	—	18 (14)
Lung examination (any)		38 (29)
Rales (crackles)	60 (51)	23 (18)
Wheezes	6 (5)	2 (2)
Rhonchi	—	2 (2)
Decreased breath sounds	—	22 (17)
Pleural friction rub	3 (3)	0 (0)
DVT		
Calf or thigh	13 (11)	62 (47)[a]
Calf only	—	43 (32)
Calf and thigh	—	18 (14)
Thigh only	—	2 (2)
Homans' sign	5 (4)	—

[a]Data in 103 patients.
[b]Data in 110 patients.
Abbreviations: *P2*, pulmonary component of second sound; *DVT*, deep venous thrombosis.
Number of patients with PE who *had* 1 or more signs of DVT: edema = 55, erythema = 5, tenderness = 32, palpable cord = 2.
Data from Stein et al.[28,29] Reprinted with permission.[10]

with acute PE in PIOPED II.[28] Among all patients with PE, irrespective of cardiopulmonary disease, signs of DVT occurred in 15% and 47%, respectively.[28,53]

Combinations of Signs and Symptoms

Either dyspnea or tachypnea was shown in over 80% of patients with acute PE and no prior cardiopulmonary disease.[28,29] Among patients who were diagnosed with PE, over 90% had either dyspnea or tachypnea or pleuritic pain (Table 4). One of these findings or signs of DVT was found in 98% of patients with PE.[28] Other combinations of nonspecific findings are shown (Table 4).

TABLE 4. Combinations of clinical characteristics in patients with pulmonary embolism and no prior cardiopulmonary disease

	PIOPED (n = 117) PE n (%)	PIOPED II (n = 131) PE n (%)
Dyspnea or tachypnea (≥20/min)	105 (90)	110 (84)
Dyspnea or tachypnea (≥20/min) or pleuritic pain	113 (97)	120 (92)
Dyspnea or tachypnea (≥20/min) or pleuritic pain or signs of DVT		128 (98)
Dyspnea or tachypnea (≥20/min) or signs of DVT	107 (91)	
Dyspnea or tachypnea (≥20/min) or pleuritic pain or radiographic evidence of atelectasis or a parenchymal abnormality	115 (98)	

Data from Stein et al.[28,29] Reprinted with permission.[10]

Even among patients with circulatory collapse, the most severe presentation of acute PE, both dyspnea and tachypnea may be absent.[28,54] Occasionally, unexplained changes on the chest radiograph or unexplained shock or loss of consciousness may suggest PE.[27,54] The diagnosis requires a high level of suspicion.

Partial Pressure of Oxygen in Arterial Blood and Alveolar-Arterial Oxygen Difference

Patients with acute PE and no prior cardiopulmonary disease may have a normal partial pressure of oxygen in arterial blood (P_aO_2).[28,29,55] Among patients with acute PE and no prior cardiopulmonary disease who had measurements of the P_aO_2 while breathing room air, 38% had a P_aO_2 of 80 mm Hg or higher.[28] When low in patients with suspected acute PE, the P_aO_2 is a helpful adjunct in the diagnostic assessment.[55] A normal alveolar-arterial oxygen difference (alveolar-arterial oxygen gradient) also does not exclude acute PE.[28,56] It was normal in 14%-35% of patients with PE and no prior cardiopulmonary disease.[28,56]

Electrocardiogram

A normal electrocardiogram (ECG) was shown in 30% of patients with PE and no prior cardiopulmonary disease.[29] Abnormalities of the ST segment and T wave are by far the most frequent ECG findings with PE.[29,57] The ECG may contribute to the clinical picture by showing nonspecific ST segment and T-wave changes[29,57] (Table 5). Findings suggestive of acute cor pulmonale ($S_1Q_3T_3$, complete right bundle branch block, P pulmonale, or right-axis deviation) occurred in 26% of patients with PE in the Urokinase Pulmonary Embolism Trial who did not have associated cardiac or pulmonary disease[57] and in <6% of such patients in PIOPED.[29]

TABLE 5. Electrocardiographic manifestations: patients without prior cardiac or pulmonary disease

Electrocardiogram	Pulmonary embolism (%)	
	Mild to massive (n = 89)	Submassive to massive (n = 90)
Normal electrocardiogram	30	13
Rhythm disturbances		
Atrial flutter	1	0
Atrial fibrillation	4	0
Atrial premature contractions	4	2
Ventricular premature contractions	4	3
P wave		
P pulmonale	2	6
QRS abnormalities		
Right-axis deviation	2	7
Left-axis deviation	13	7
Clockwise rotation (V5)	—	7
$S_1S_2S_3$	—	7
$S_1Q_3T_3$	—	12
Incomplete right bundle branch block	4	6
Complete right bundle branch block	6	9
Right ventricular hypertrophy	2	6
Pseudoinfarction	3	11
Low voltage (frontal plane)	3	6
ST segment and T wave		
Nonspecific T wave	—	42
ST segment depression	—	26
ST segment elevation	—	16
Nonspecific ST segment or T wave	49	—

Data from Stein et al.[29,57] Reprinted with permission.[10]
Some patients had more than 1 abnormality.

Sharp T-wave inversions may simulate an ischemic event. A pseudoinfarction pattern was seen in 11% of patients with PE who had no prior cardiopulmonary disease.[57] The ECG may simulate an inferior, anteroseptal, anterior, or infarction.[57] The cause of ischemic T-wave changes in acute PE is unclear. Autopsy has shown myocardial necrosis in patients with acute PE who had normal coronary arteries.[58,59] Experimentally, induced PE in pigs and dogs caused blood flow to increase in the left circumflex and right coronary arteries.[60,61]

Leftward shifts of the frontal plane axis in PE occur more frequently than a rightward shift.[62] PE cannot be excluded on the basis of a leftward shift. Low-voltage frontal plane QRS complexes may be a sign of acute PE,[57] although it is uncommon.

TABLE 6. Plain chest radiograph in patients with acute pulmonary embolism and no prior cardiopulmonary disease

	Mild to massive PE (%) (n = 117)	Submassive to massive PE (%) (n = 169)
Atelectasis or pulmonary parenchymal abnormality	68	—
Atelectasis	—	28
Consolidation	39	—
Pleural effusion	48[a]	30
Pleural-based opacity	35	—
Elevated hemidiaphragm	24	46
Decreased pulmonary vascularity	21	22
Prominent central pulmonary artery	15	21
Cardiomegaly	12	—
Westermark's sign[b]	7	—
Pulmonary edema	4	—
Pulmonary venous hypertension pattern	—	4
Pulmonary arterial hypertension pattern	—	2

Data are from Stein et al.[29,63] Reprinted with permission.[10]
[a]Among patients with a pleural effusion, 86% had only blunting of the costophrenic angle. None had a pleural effusion that occupied more than one third of a hemithorax.
[b]Prominent central pulmonary artery and decreased pulmonary vascularity.

Chest Radiograph

The plain chest radiograph may hint at PE by showing atelectasis or consolidation or an elevated hemidiaphragm[29,63] (Table 6). The chest radiograph is well validated as having clinical usefulness to exclude conditions that mimic acute PE. Nonspecific radiographic abnormalities combined with symptoms and ECG abnormalities may suggest the presence of PE.

A normal chest radiograph was observed in 16% and 24% of patients with PE.[29,63] An elevated hemidiaphragm, consolidation, pleural effusion, or atelectasis occurred in about two thirds with acute PE.[63] Among those with a pleural effusion, only blunting of the costophrenic angle occurred in most.[29] No patients with PE and no prior cardiopulmonary disease had a pleural effusion that occupied more than one third of a hemithorax.[29] A dilated pulmonary artery with decreased pulmonary vascularity is rare (Table 6). The sensitivity and proportion of false positives of various radiographic abnormalities are shown in Fig 15.

Echocardiogram

Echocardiography has a low sensitivity for visualization of emboli within the right atrium, right ventricle, or pulmonary artery. Pooled data showed emboli within the right ventricle or right atrium in only 19 of 195

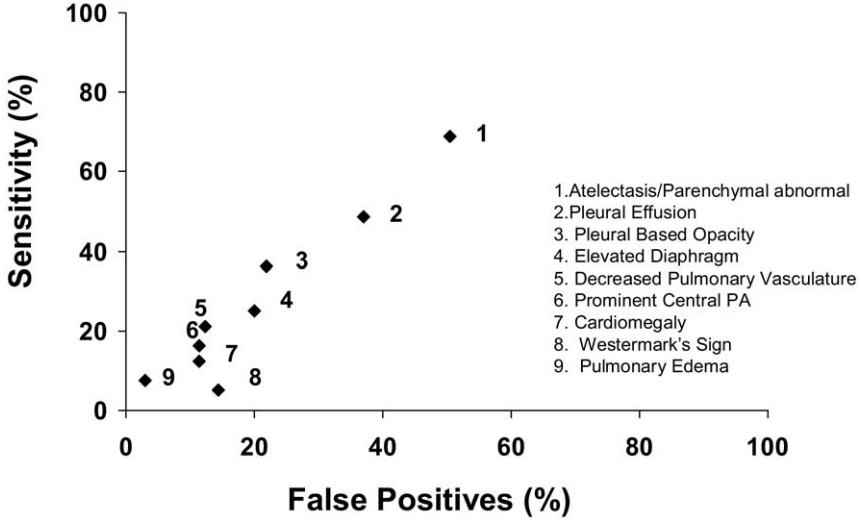

FIG 15. Sensitivity and frequency of false positive values of various abnormalities on the plain chest radiograph. Data are from Stein et al[29] in 364 patients with suspected acute PE and no prior cardiopulmonary disease. The numbers refer to the individual radiographic abnormalities, which are listed in the insert. (Reprinted with permission.[10])

(10%) with PE.[64-66] Thrombi in the right side of the heart or pulmonary artery were shown by echocardiography in 24 of 165 (15%).[64,65] Among patients with massive PE or unstable patients, the sensitivity of echocardiography for thrombi in the right atrium or ventricle ranged from 7% to 18%.[67-69]

Objective Clinical Assessment

Estimates of the clinical probability of PE, based on intuitive assessment by experienced physicians, have a reasonably good predictive value[70,71] (Fig 16). There is no evidence that the predictive value of such probability assessments can be achieved by less experienced clinicians.

Because of the vagaries of clinical diagnosis, objective scoring systems have been developed[71-74] (Tables 7-9). They apply mostly to outpatients. Objective scoring systems give probability assessments similar to physicians experienced with the diagnosis of PE, but are more or less objective and do not require experience (Fig 16).

Differences in the Wells simplified model[73] and the Wells extended model[72] relate to whether leg swelling is measured (extended model) or appears swollen (simplified model), and whether PE is as likely or more likely than an alternative diagnosis (extended model) or just more likely

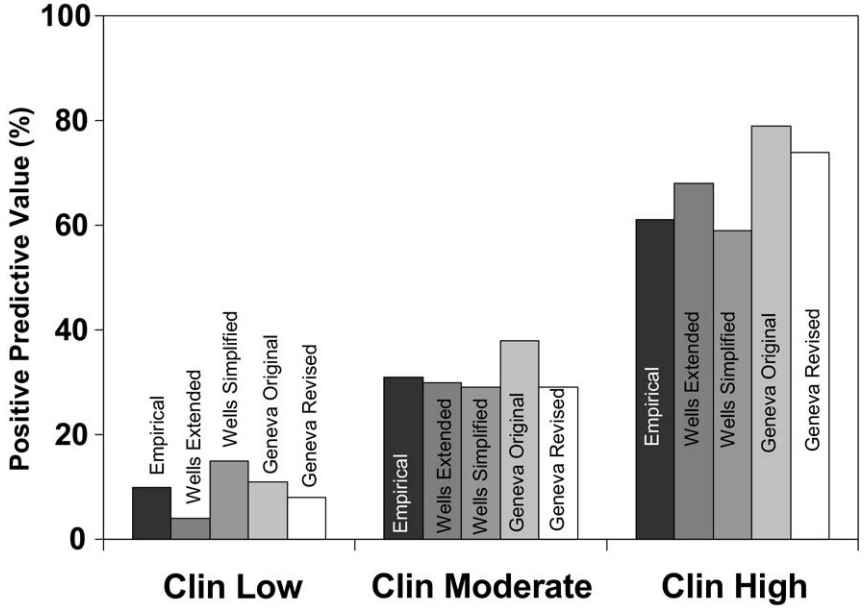

FIG 16. Positive predictive value for PE of low, moderate, and high probability clinical assessments using empiric judgment, Wells extended model, Wells simplified model, original Geneva model, and revised Geneva model. (Reprinted with permission.[10])

(simplified model) (Table 7). A Wells score of <2 points indicates a low probability of PE, 2-6 points indicates a moderate probability, and >6 points indicates high probability of PE.[72,73] A Wells score of ≤ 4 points also has been used to indicate that PE is "unlikely" and >4 points indicates that PE is likely.[73,75] The Wells extended and simplified models are not strictly objective. Judgment is required to evaluate "if PE is as likely or more likely than an alternative diagnosis." To make this judgment, physicians may use the history, physical examination, chest radiograph, ECG, and whatever blood tests are considered necessary to diagnose PE.[72]

J. E. Dalen: Although DVT is present in most patients with acute PE, it is usually silent. New unilateral leg swelling is the most specific finding in DVT, but it is infrequent.

The original Geneva scoring system, although objective, requires analysis of arterial blood gases[71] (Table 8). A revised Geneva score has

TABLE 7. Clinical scoring system for suspected PE (Wells)

Clinical feature[a]	Wells extended model[a]	Wells simplified model[b]	Score
Signs/symptoms of DVT	*Measured* leg swelling plus pain with palpation in deep vein region	Leg swelling plus pain with palpation in deep vein region	3.0
Heart rate >100/min	Yes	Yes	1.5
Immobilization: bedrest (± bathroom privileges) ≥3 consecutive days or surgery in last 4 wk	Yes	Yes	1.5
Prior PE or DVT	Yes	Yes	1.5
Hemoptysis	Yes	Yes	1.0
Malignancy: Treated within 6 mo or on palliative care	Yes	Yes	1.0
Alternative diagnosis	PE as likely or more likely	PE more likely	3.0

Low probability of PE: score <2.
Moderate probability: score 2-6.
High probability of PE: score >6.
Unlikely probability: score ≤4.[b]
Likely probability: score >4.
[a]Wells et al.[72]
[b]Wells et al.[73]
Reprinted with permission.[10]

TABLE 8. Original Geneva Scoring System for suspected PE

Feature	Score
Age (yr)	
60-79	1
≥80	2
Previous PE or DVT	2
Recent surgery	3
Heart rate >100/min	1
P_aCO_2	
<4.8 kPa (<36 mm Hg)	2
4.8-5.19 kPa (36-39 mm Hg)	1
P_aO_2	
<6.5 kPa (<49 mm Hg)	4
6.5-7.99 kPa (49-60 mm Hg)	3
8-9.49 kPa (61-71 mm Hg)	2
9.5-10.99 kPa (71-82 mm Hg)	1
Chest radiograph	
Platelike atelectasis	1
Elevation of hemidiaphragm	1

Low probability of PE: score 0-4.
Moderate probability: score 5-8.
High probability of PE: score ≥9.
Data from Wicki et al.[71] Reprinted with permission.[10]

TABLE 9. Revised Geneva Scoring System for suspected PE

Feature	Score
Age >65 yr	1
Previous PE or DVT	3
Surgery (under general anesthesia) or fracture of lower limbs (≤1 mo)	2
Solid or hematologic malignant condition, currently active or considered cured <1 yr	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate	
75-94 beats/min	3
≥95 beats/min	5
Pain on lower limb deep venous palpation and unilateral edema	4

Low probability of PE: score 0-3.
Intermediate probability: score 4-10.
High probability of PE: score ≥11.
Reprinted with permission.[74]

been developed based entirely on clinical variables and independent from physicians' implicit judgment[74] (Table 9). The simplified Wells prediction rule and the original Geneva prediction rule performed poorly in patients referred from surgical wards.[76] A "Pisa" clinical model showed excellent results, but is more difficult to apply.[77]

The positive predictive value of a low probability clinical assessment, whether empiric or by any of the prediction rules (Wells extended, Wells simplified, Geneva original, Geneva revised, Pisa), on average, was 4%-15% (Fig 16). The positive predictive value of a moderate or intermediate probability clinical assessment was 22%-38%. A high probability clinical assessment showed PE in 59%-98%.

A set of "pulmonary embolism rule-out criteria (PERC)" was also established that requires the physician to answer "no" to the following 8 questions:[78]

1. Is the patient older than 49 years of age?
2. Is the pulse above 99 beats/min?
3. Is the pulse oximetry reading <95% while the patient breathes room air?
4. Is there a present history of hemoptysis?
5. Is the patient taking exogenous estrogen?
6. Does the patient have a prior diagnosis of VTE?
7. Has the patient had recent surgery or trauma (requiring endotracheal intubation or hospitalization in the previous 4 weeks)?
8. Does the patient have unilateral leg swelling (visual observation of asymmetry of the calves)?

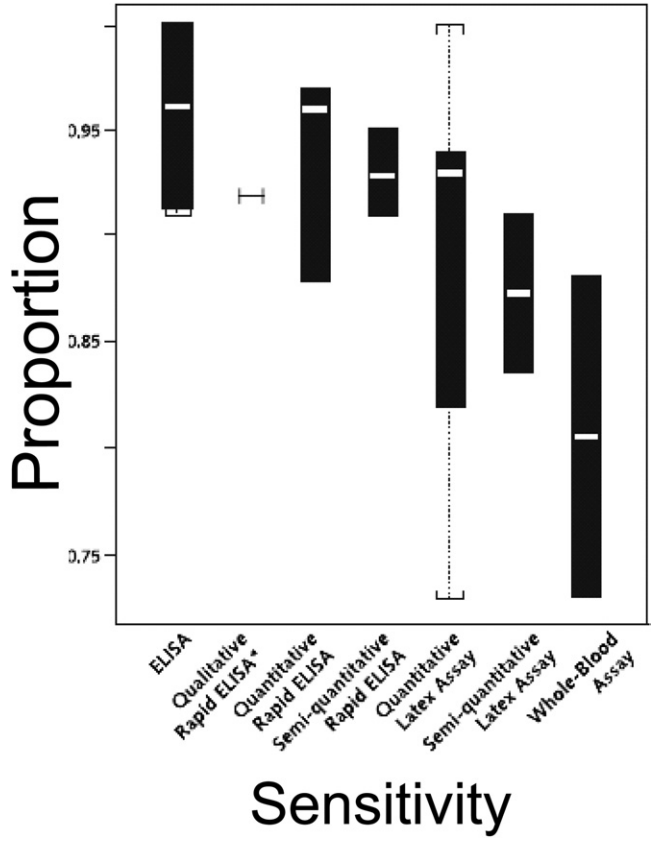

FIG 17. Sensitivity of D-dimer assays for patients with suspected PE. (Reprinted with permission.[79])

A combination of <15% probability of PE based on intuitive assessment plus a "no" answer to all the "PERC" questions indicated a "very low risk" of PE. Among patients with suspected PE in emergency departments, 20% were excluded from further testing by this combination. The false negative rate within 45 days was 1%.[78]

D-Dimer

The enzyme-linked immunosorbent assay (ELISA) and quantitative rapid ELISA assays were significantly superior to semiquantitative latex and whole blood agglutination assays[79] (Fig 17). The quantitative rapid ELISA assay is more convenient than the conventional ELISA and provides a high level of certainty for a negative diagnosis of PE as well as DVT.[79]

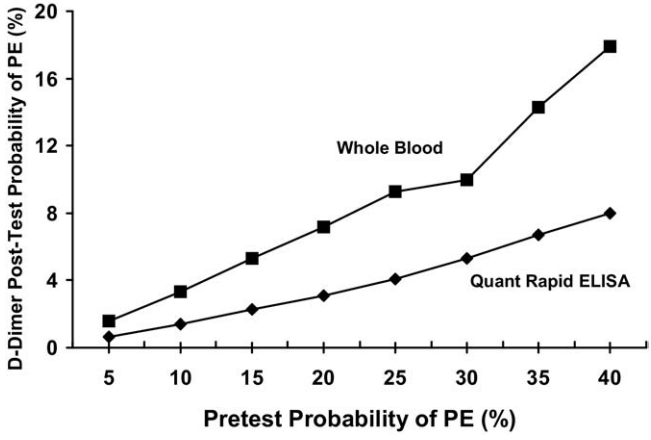

FIG 18. Relation of posttest probability to pretest probability. Data from Stein et al.[79] (Reprinted with permission.[10])

A negative D-dimer, irrespective of the method of measurement, excludes PE if the clinical assessment is low probability.[79] An intermediate clinical probability would also exclude PE with reasonable certainty if D-dimer were measured by ELISA[79,80] or, in the opinion of some, a quantitative latex agglutination test[80] (Fig 18). The 3-month risk of PE in untreated patients with a negative D-dimer measurement and an unlikely or low or intermediate clinical probability was only 0%-0.4%.[75,81] However, a negative D-dimer would not reliably exclude PE if the clinical probability was high.[82]

The sensitivity of D-dimer testing for PE increases with the extent of the PE.[83,84] D-dimer concentrations are highest in patients with PE in the pulmonary trunk[83] and with perfusion scan defects involving >50% of the lung.[84]

J. E. Dalen: Concern for radiation exposure has led some clinicians to use perfusion scans rather than CT angiography in young women and in patients with normal or near-normal chest radiographs.

The clinical utility of D-dimer assays is limited by the nonspecificity of a positive result due to factors such as inflammation, trauma, and surgery, to name a few. The clinical utility differs among patient populations. In pregnancy D-dimer levels increase with the gestational period.[85] During the early weeks of pregnancy (<20 weeks), however, D-dimer remains a

useful test.[85] Normal D-dimer levels are uncommon in patients over 80 years of age.[86,87] D-dimer levels may be elevated in patients with cancer.[88]

The proportion of hospitalized patients in whom PE can be excluded by a normal D-dimer is lower than in outpatients because hospitalized patients more often have unrelated disorders that cause a positive D-dimer test.[89] Also, the proportion of normal D-dimer tests in patients with a history of prior DVT or PE is lower than in patients without previous venous thromboembolic disease.[90]

Serial Noninvasive Leg Tests to Exclude PE

Among patients with suspected PE who had a nondiagnostic V/Q scan, normal cardiorespiratory reserve, and negative serial noninvasive leg tests, PE at 3 months follow-up occurred in only 4 of 627 (0.6%).[91] In those with suspected PE who had a low probability clinical assessment with a nondiagnostic V/Q scan and negative serial noninvasive leg tests, PE at 3 months follow-up occurred in only 2 of 443 (0.5%).[92] In such patients with an intermediate probability clinical assessment, PE occurred in 1 of 248 (0.4%).[92] Serial noninvasive leg tests, therefore, in patients with suspected PE who have nondiagnostic V/Q scans can be used to safely exclude PE.

Ventilation-Perfusion (V/Q) Lung Scan

The V/Q lung scan fell into disfavor after PIOPED.[49] A diagnosis on the basis of a high probability interpretation was present in only 13% of patients and an exclusion on the basis of a nearly normal or normal V/Q scan was made in only 14%.[49] Most patients had either an intermediate probability assessment (39%) or a low probability assessment (34%), both of which are indeterminate for PE. Now nearly 2 decades since PIOPED was published, important advances have been made in imaging equipment, improved methods of interpretation, and new radiopharmaceuticals. With advances in technology and imaging criteria for interpretation, and with the risk of radiation with CT angiography, radionuclear imaging is receiving renewed interest. Improved diagnostic criteria include the revised PIOPED criteria,[93,94] Prospective Investigative Study of Pulmonary Embolism Diagnosis (PISAPED) criteria,[95] very low probability interpretation,[96] mismatched vascular defects,[97] stratification according to prior cardiopulmonary disease,[98] stratification of the number of mismatches required for diagnosis according to clinical assessment,[99] and perfusion scintigraphy combined with the chest radiograph.[100]

TABLE 10. Modified PIOPED criteria for interpretation of perfusion lung scan

PE present	High probability (≥2 segments of perfusion scan—chest radiograph mismatch[a])
PE absent	Normal perfusion
	Near normal
	Contour defect caused by enlarged heart, mediastinum, or diaphragm
	Perfusion defect, not wedge-shaped
Not diagnostic	Cannot classify as PE-positive or PE-negative

[a]May be ≥2 large segmental mismatches, or 1 large and 2 moderate mismatches, or 4 moderate segmental mismatches.
Modified with permission.[100]

TABLE 11. PISAPED criteria for interpretation of perfusion lung scan

PE present	One or more wedge-shaped perfusion defects
PE absent	Normal perfusion
	Very low probability
	Nonsegmental lesion, eg, prominent hilum, cardiomegaly, elevated diaphragm, linear atelectasis, costophrenic angle effusion with no other perfusion defect in either lung
	Perfusion defect smaller than radiographic lesion
	1-3 small segmental defects
	A solitary CXR-Q matched defect in the mid or upper lung zone confined to a single segment
	The stripe sign present around the perfusion defect (best tangential view)
	Pleural effusion ≥ one third of the pleural cavity with no other perfusion defect in either lung
Not diagnostic	All other findings

Modified with permission.[100]

J. E. Dalen: The probability of a false negative chest CT is minimal in patients with massive PE. However false negative or false positive findings may occur in the small group of patients with PE limited to subsegmental arteries.

In 2008, investigators evaluated the perfusion scans obtained in PIOPED II, using CT angiography as a reference standard.[100] They categorized the perfusion scan as "PE present," "PE absent," or "not diagnostic." Perfusion scans were interpreted with the revised PIOPED criteria (Table 10) and with the PISAPED criteria (Table 11). Only 21% of patients had nondiagnostic results using modified PIOPED criteria.[100] Excluding "nondiagnostic" results, the sensitivity of a "PE present" perfusion lung scan was 85% and the specificity of "PE absent" was 93%.[100] Using PISAPED criteria, none had nondiagnostic perfusion scans.[100] The sensitivity of a "PE present" perfusion scan using PISAPED

criteria was 80% and the specificity of "PE absent" perfusion scan was 97%.[100] Among 72% of patients who had a normal or nearly normal chest radiograph, only 11% had nondiagnostic perfusion scans.[100] In those in whom nondiagnostic perfusion scans were excluded, sensitivity was 86% and specificity was 93%. It may be, therefore, that with updated techniques, perfusion scintigraphy combined with a chest radiograph can provide diagnostic accuracy similar to CT angiography at a lower cost and with a lower radiation dose.[100]

SPECT V/Q Imaging

Single-photon emission computed tomography (SPECT) V/Q imaging may further improve the accuracy of pulmonary scintigraphy.[101] SPECT offers the advantages of tomographic sections over the traditional planar V/Q imaging. The ability to obtain SPECT V/Q imaging was still in its relatively early stages when the PIOPED investigation of planar V/Q scans was published. Dual- and triple-headed gamma cameras with ultra-high-resolution collimators have been developed. New radiopharmaceuticals for ventilatory studies also have been developed, prominent among which is ^{99m}Tc technegas (Cyclomedica, Lucas Heights, Australia), which consists of ultrafine carbon particles that behave physiologically like a gas.[102]

Many investigators found SPECT V/Q imaging to be more advantageous than planar imaging.[103-106] Among the advantages of SPECT is the avoidance of overlapping of small perfusion defects by normal tissue. SPECT, in addition, has a higher contrast resolution than planar V/Q. It can, therefore, detect abnormalities particularly at the subsegmental level and in the lung bases, where the segments are tightly packed.[107] Review showed that sensitivity of SPECT in 4 of 5 investigations was higher than planar V/Q.[101] Specificity of SPECT was generally higher, equal, or only somewhat lower than planar V/Q.[101] Nondiagnostic SPECT V/Q scans were reported in $\leq$3% by most investigators.[101]

Conventional Pulmonary Angiography

Conventional digital subtraction pulmonary angiography has been abandoned in favor of CT angiography. Major complications of conventional pulmonary angiography among 1111 patients were death in 5 (0.5%), respiratory distress requiring cardiopulmonary resuscitation or ventilatory support in 4 (0.4%), renal failure requiring dialysis in 3 (0.3%), and hematoma requiring 2 or more units of blood in 2 (0.1%).[108] In skillful hands, superselective angiography may be useful in detecting

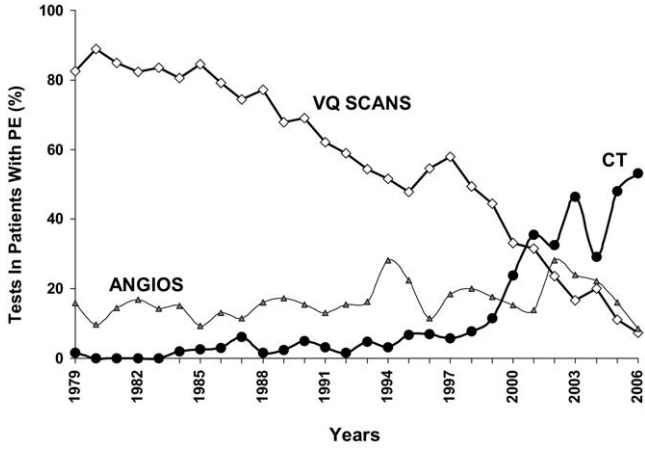

FIG 19. Relative use of diagnostic imaging tests in patients hospitalized with PE from 1979 through 2006. *V/Q*, ventilation/perfusion; *ANGIOS*, pulmonary angiograms. (Reprinted with permission.[10])

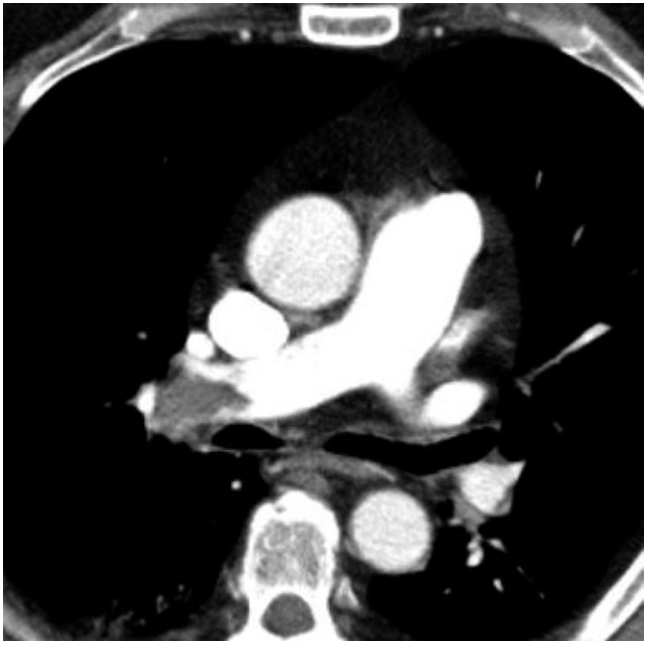

FIG 20. CT pulmonary angiogram showing PE in the right pulmonary artery.

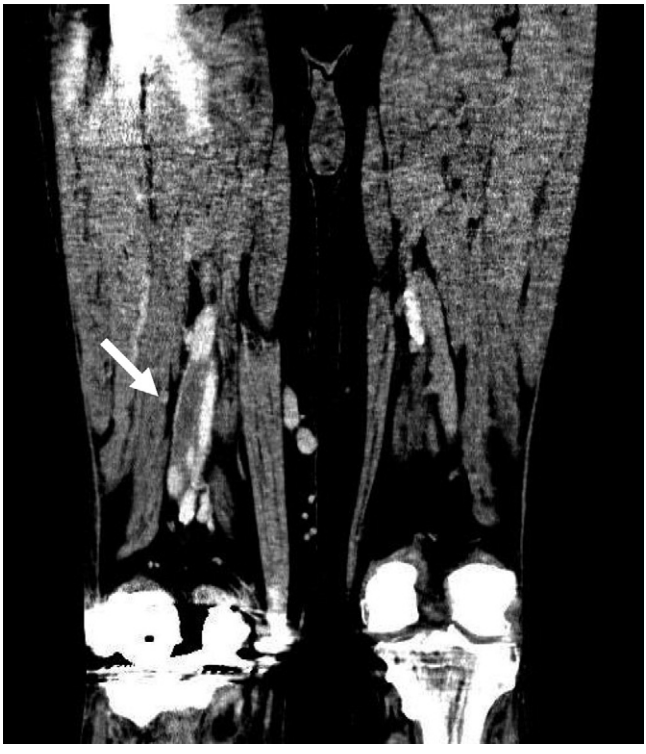

FIG 21. CT venous phase image showing right popliteal vein thrombosis (arrow).

small PE when results of other imaging tests are uncertain. Such techniques include cineangiography,[109] balloon-occlusion cineangiography,[110] and wedge arteriography.[15] These techniques, however, are rarely used.

CT Angiography

By 2001, use of CT angiography for the diagnosis of PE equaled the use of V/Q scans and, by 2006, the vast majority of patients with suspected PE were evaluated by CT angiography (Fig 19). The sensitivity and specificity of CT angiography have been reviewed.[111] The accuracy of multidetector CT angiography was assessed in PIOPED II.[14] With mostly 4-detector equipment, the sensitivity of CT angiography for PE was 83%[14] (Fig 20). In symptomatic patients, DVT was considered a surrogate for the diagnosis of PE, and CT venography in combination with CT angiography increased the sensitivity to 90% (Fig 21). Specificity was 95% with CT angiography and nearly the same (96%) with CT

TABLE 12. Positive predictive values of CTA and CTA/CTV in relation to prior clinical assessment

	High Prob Clin (Wells Score >6) PE +/CT + (%)	Intermediate Prob Clin (Wells Score 2-6) PE +/CT + (%)	Low Prob Clin (Wells Score <2) PE +/CT + (%)
CTA post	22/23 (96)	93/101 (92)	22/38 (58)
CTA or CTV post	27/28 (96)	101/111 (90)	24/42 (57)

Only patients with a reference test diagnosis by V/Q scan or conventional pulmonary DSA were included.
Abbreviations: *CTA*, computed tomographic pulmonary angiography; *CTV*, venous phase venogram.
Reprinted with permission.[14]

TABLE 13. Negative predictive values of CTA and CTA/CTV in relation to prior clinical assessment

	High Prob Clin (Wells Score >6) PE Neg/CT Neg (%)	Intermediate Prob Clin (Wells Score 2-6) PE Neg/CT Neg (%)	Low Prob Clin (Wells Score <2) PE Neg/CT Neg (%)
CTA NEG	9/15 (60)	121/136 (89)	158/164 (96)
CTA and CTV NEG	9/11 (82)	114/124 (92)	146/151 (97)

Only patients with a reference test diagnosis by V/Q scan or conventional pulmonary DSA were included.
Abbreviations: *CTA*, computed tomographic pulmonary angiography; *CTV*, venous phase venogram.
Reprinted with permission.[14]

angiography/CT venography. Positive predictive values were 97% for PE in main or lobar pulmonary arteries, 68% in segmental branches, and, based on sparse data, only 25% in subsegmental branches. A concordant objective clinical assessment strengthened the diagnosis and a discordant objective clinical assessment suggested that further evaluation was needed (Tables 12 and 13). It is speculated that 64-detector units may show PE more accurately in subsegmental branches, but this has not been tested.

Outcome studies following a negative CT angiogram showed PE on follow-up of untreated patients in only 1.3%[75] or 1.7%.[81] This outcome, however, may reflect a low rate of symptomatic recurrent PE in patients with undiagnosed small PE.[112]

Magnetic Resonance Angiography (MRA)

Gadolinium-enhanced MRA is a potentially useful imaging modality for patients with suspected acute PE in whom it is important to avoid exposure to ionizing radiation, or for patients allergic to iodinated

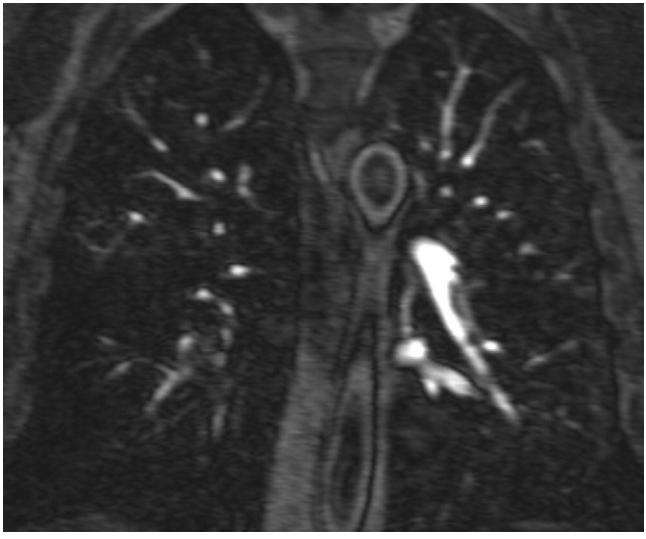

FIG 22. Gadolinium-enhanced magnetic resonance pulmonary angiogram showing PE in the left lower lobe pulmonary artery.

contrast material (Fig 22). Most investigations of MRA had <20 patients with PE.[113-118] Several investigators defined an adequate quality MRA as adequate opacification through segmental vessels,[115,116,119,120] although some evaluated subsegmental branches as well as larger branches.[114,118,121] Adequate visualization of main to segmental pulmonary arteries was reported in 94%-100% of patients.[115-117,119,121]

Sensitivity was higher in larger order vessels. Sensitivities for PE in main or lobar pulmonary arteries was 77%-100%.[114,116,118,121] In segmental branches, sensitivity ranged from 68% to 84%.[114,116,118,121] Most showed 0%-40% sensitivity for detection of PE in subsegmental branches or isolated subsegmental branches,[114,115,117,121] although 1 investigation showed 60% sensitivity.[118] Specificities with blinded readings, irrespective of vessel order, in all but 1 study were ≥92%.[113-118,121]

The sensitivity of magnetic resonance venography (MRV) for the diagnosis of DVT, based on pooled data, was 92% and specificity was 95%.[122] With combined MRA/MRV, 17% more cases of VTE were identified than with MRA alone.[123]

The sensitivity and specificity of MRA combined with MRV were investigated in PIOPED III (please see addendum). The methods were published in detail previously.[124]

There is concern about nephrogenic systemic fibrosis/nephrogenic

fibrosing dermopathy, which occurs rarely in patients with poor renal function who receive gadolinium-containing contrast material.[125,126]

Diagnostic Pathway: Triage With Objective Clinical Assessment and D-Dimer

Based on the results of PIOPED II, a pathway of diagnosis was recommended that combined objective clinical assessment, D-dimer, and CT angiography in combination with CT venography.[82] Preliminary triage was recommended with clinical assessment and D-dimer (see section on D-dimer and clinical assessment). One third of patients with suspected PE were spared further testing by exclusion with an objective clinical assessment in combination with at low D-dimer.[75,81] A high probability clinical assessment, irrespective of the D-dimer result, or a positive D-dimer indicates that imaging is necessary.

If PE was not excluded by D-dimer with objective clinical assessment, contrast-enhanced computed tomographic pulmonary angiography (CT angiography), in combination with venous phase imaging (CT venography), was recommended by most PIOPED II investigators, although CT angiography plus clinical assessment was an option.[82] In pregnant women, V/Q scans were recommended by many as the first imaging test, perhaps with venous ultrasound. In patients with discordant findings of clinical assessment and CT angiograms or CT angiogram/CT venogram, further evaluation was suggested.

CT Venography

Because CT venography was shown to increase the sensitivity of multidetector CT angiography for the detection of PE (where DVT was considered a surrogate for PE),[14] it was recommended that CT venography should be used in combination with CT angiography.[82] Venous ultrasound could be used instead of CT venography to spare the patient exposure to the radiation.[127] Because pelvic vein DVT or thrombi in the IVC occurred in only 3% of patients with DVT in the absence of thigh vein DVT, pelvic vein imaging was considered unnecessary, thereby reducing radiation.[14] Obtaining 5-mm axial images of the veins at 15-mm intervals instead of obtaining continuous axial images would further reduce the radiation.[128] Adopting discontinuous imaging and other dose reduction strategies would reduce pelvic radiation by as much as 75%.[128]

Whether CT angiography should be accompanied by CT venography has been a matter of controversy. Among 1903 patients with suspected PE who were evaluated by 64-detector CT, 206 (10.8%) were shown to have PE by CT angiography and an additional 25 (1.3%) had VTE based on a

TABLE 14. Effective dose of radiations and estimated equivalent number of chest radiographs diagnostic tests as well as background radiation and industrial exposure

Examination	Effective (whole body) dose (mSv)	Equivalent number of PA plus lateral chest radiographs
Chest PA plus lateral	0.07	1
Perfusion lung scan	0.8	11
Ventilation-perfusion lung scan	1.2-2.0	17-28
CT pulmonary angiography	1.6-8.3	23-119
CT venography	5.7	81
Pulmonary DSA	3.2-30.1	46-430
Natural yearly background radiation	2.5	36
Allowable yearly maximal exposure in radiation workers	50	714

Abbreviations: *PA*, pulmonary artery; *CTV*, computed tomographic venous phase imaging; *DSA*, digital subtraction angiography.
Modified from Stein et al.[82]

positive CT venogram with a negative CT angiogram.[129] A 1.3% yield would seem poorly cost-effective. On the other hand, among the 231 patients shown to have VTE, 25 (10.8%) were diagnosed by CT venography alone. From this viewpoint, the proportion diagnosed by CT venography is sufficiently high to merit consideration of its use.

Radiation

Reported values of whole body radiation with imaging studies vary[130-137] (Table 14). Female glandular breast dose may be 10-20 mGy[138,139] and as high as 190 mGy in a full-figured woman.[140] This may be equivalent to 300-1000 chest posterior-anterior plus lateral chest radiographs. The lifetime attributable risk of cancer following a 64-detector CT coronary angiogram in a 20-year-old woman may be 1 in 143.[141] The risk drops sharply with the patient's age and the risk is higher in women than men.[141,142] The risk estimate, however, is based on extrapolated data from Japanese atomic bomb survivors to a USA population with different baseline cancer rates and differences in relative biological effects between x-rays and other types of ionizing radiation.[141]

Because of the risk of radiation with CT angiography, particularly radiation of the breasts, scintigraphy may be the imaging test of choice in women under 50 years of age. Breast irradiation with V/Q scintigraphy is approximately 0.28-0.9 mGy,[143] which is not more than 0.5%-5% of the radiation dose to the breasts resulting from CT angiography. It appears that CT angiography is being used excessively, with CT angiography showing PE in $\leq$10% of patients in some emergency departments.[144] The increasing use of CT angiography may result in an increased incidence of radiation-related cancer in the not too distant future.[142,145]

TABLE 15. Prevention of deep venous thrombosis after total hip replacement surgery (pooled data)[a]

Prophylaxis regimen	Combined enrollment	Total DVT prevalence, %	Proximal DVT prevalence, %[b]
Placebo/control	626	54	27
Elastic stockings	290	42	26
Aspirin	473	40	11
Low-dose heparin	1016	30	19
Warfarin	1828	22	5
IPC	423	20	14
LMWH	6216	16	6

[a]Pooled DVT rates determined by routine contrast venography from randomized trials.
[b]The denominators for proximal DVT may be slightly different from for total DVT, because some studies did not report proximal DVT rates.
Abbreviations: *LMWH*, low molecular weight heparin; *IPC*, intermittent pneumatic compression; *DVT*, deep venous thrombosis.
Reprinted and modified with permission.[146]

Risk of DVT With No Prophylaxis

Among patients who underwent routine testing with venography following general surgery, pooled data showed DVT without prophylaxis in 19%.[146] PE occurred in 1.6% of general surgical patients who did not receive prophylaxis and fatal PE occurred in 0.9%.[146] The prevalence of DVT without prophylaxis following total hip replacement, hip fracture, and knee replacement ranged from 48% to 64% based on routine contrast venography[146] (Tables 15 and 16).

Physician Alerts to Prevent Venous Thromboembolism

Among medical patients in whom DVT prophylaxis was indicated, only 39.5% of hospitalized medical patients received it.[147] A higher proportion of patients on surgical services received DVT prophylaxis when indicated (58.5%).[147] Electronic alerts about appropriate low-dose heparin therapy in hospitalized patients (82.7% of whom were on medical services) increased the proportion who received mechanical prophylaxis from 1.5% to 10.0% and pharmacologic prophylaxis from 13.0% to 23.6%.[148] With alerts and appropriate prophylaxis, the risk of symptomatic DVT or PE at 90 days decreased 41%.[148] A subsequent investigation showed that symptomatic VTE 90 days after discharge was 2.7% with alerts and 3.4% without alerts.[149]

Antithrombotic Prophylaxis

Recommendations for prophylaxis of surgical patients as well as medical patients are given in detail in the American College of Chest

TABLE 16. Prevention of deep venous thrombosis after total knee replacement surgery (pooled data)[a]

Prophylaxis regimen	Combined enrollment	Total DVT prevalence, %	Proximal DVT[b] prevalence, %
Placebo/control	199	64	15
Elastic stockings	145	61	17
Aspirin	443	56	9
Warfarin	1294	47	10
Low-dose heparin	236	43	11
Venous foot pump	172	41	2
LMWH	1740	31	6
IPC	110	28	7

[a]The denominators for proximal DVT may be slightly different from for total DVT, because some studies did not report proximal DVT rates.
[b]Pooled DVT rates determined by routine contrast venography from randomized trials.
Abbreviations: *LMWH*, low molecular weight heparin; *IPC*, intermittent pneumatic compression; *DVT*, deep venous thrombosis.
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Physicians Evidence-Based Clinical Practice Guidelines (8th ed).[150] Some of these recommendations are as follows.

Low-dose unfractionated heparin (UFH), LMWH, or fondaparinux is recommended for patients with a moderate or high risk of VTE (medically ill, congestive heart failure, postoperative thoracic surgery or coronary artery bypass graft, or confined to bed with 1 or more additional risk factors).[150]

Mechanical methods of prophylaxis (properly fitted graded compression stockings and/or intermittent pneumatic compression) are recommended primarily in patients with a high risk of bleeding or as an adjunct to anticoagulant prophylaxis.[150] When the risk of bleeding decreases, it is recommended that pharmacologic prophylaxis should be substituted or added to the mechanical prophylaxis.[150] Aspirin alone is recommended against for VTE prophylaxis.[150]

In patients with impaired renal function, anticoagulants that are primarily excreted by the kidneys such as LMWH and fondiparinux should be avoided for thromboprophylaxis or used at a lower dose, or the drug level or its anticoagulant effect should be monitored.[150] UFH would be preferred over LMWH in such patients.

Doses for Thromboprophylaxis, and Monitoring for Heparin-Induced Thrombocytopenia

Low-dose UFH for thromboprophylaxis is 5000 U every 12 hours and moderate dose is 12,500 U every 12 hours.[151] For patients receiving

TABLE 17. Pooled data based on paired prospective investigations of UFH and LMWH in the treatment of VTE and prophylaxis against VTE

	UFH Heparin-associated thrombocytopenia n/N (%)	LMWH Heparin-associated thrombocytopenia n/N (%)
VTE prophylaxis	57/3463 (1.6)	23/3714 (0.6)
VTE treatment	22/2321 (0.9)	18/3126 (0.6)
All patients—Prophylaxis or treatment	79/5784 (1.4)	41/6840 (0.6)

All included investigations included ≥100 patients in each arm.
Abbreviations: *UFH*, unfractionated heparin; *LMWH*, low-molecular weight heparin; *CI*, confidence interval.
Pooled data modified and reprinted with permission.[153]

thromboprophylaxis with UFH, platelet monitoring at least every 2 or 3 days from day 4 to day 14 is recommended.[152] More frequent monitoring is recommended for patients receiving UFH thromboprophylaxis after surgery.[152]

The dose of LMWH depends on the drug selected and should be used in doses recommended by the manufacturer. When given in prophylactic doses, LMWH has not been shown to increase the risk of bleeding, even in those with renal impairment.[151] However, with a creatinine clearance <30 mL/min, 50% of the usual dose of enoxaparin is recommended.[151] Routine platelet count monitoring for medical patients receiving LMWH thromboprophylaxis is not necessary.[152]

The dose of fondaparinux for thromboprophylaxis is 2.5 mg/d.[151] Some recommend a 50% dose reduction in patients with moderately severe renal insufficiency (creatinine clearance <50 L/min).[151] Fondaparinux is contraindicated in patients with a creatinine clearance <30 mL/min.[151] Routine coagulation monitoring is not recommended.[151] Routine platelet count monitoring is not necessary.[152]

Heparin-Associated Thrombocytopenia

The risk of heparin-associated thrombocytopenia is more duration-related than dose-related, and higher with UFH when used for an extended duration than with LMWH used for an extended duration.[153] Review of prospective investigations of patients who received prophylaxis showed a higher incidence of heparin-associated thrombocytopenia in those receiving UFH than in those receiving LMWH [57 of 3463 (1.6%) vs 23 of 3714 (0.6%)][153] (Table 17). Treatment, however, resulted in a smaller difference in the incidence of heparin-associated thrombocytopenia between UFH and LMWH [22 of 2321 (0.9%) vs 18 of 3126

(0.6%)][153] (Table 17). Treatment and prophylaxis with LMWH resulted in identical incidences of heparin-associated thrombocytopenia [16 of 2753 (0.6%) vs 23 of 3714 (0.6%)] (Table 17). UFH, when used for prophylaxis, was associated with a higher incidence of heparin-associated thrombocytopenia than when used for treatment [57 of 3463 (1.6%) vs 22 of 2321 (0.9%)].[153] It may be that UFH is more likely to cause heparin-associated thrombocytopenia than LMWH, and the difference of risk becomes apparent only after prolonged administration.

Approach to Patients With Suspected of Thrombophilia

Strongly thrombophilic patients are those patients who sustained their first VTE event before aged 50 years, have a history of recurrent thrombosis, or have a first-degree relative with documented VTE events occurring before aged 50 years.[154] If 1 or more of these features are present, a complete evaluation for hereditary thrombophilia is appropriate.[154] Testing should be extended to their first-degree family members as well.[154] Because most of the tests are not reliable during anticoagulation, it is preferable to postpone laboratory testing until after discontinuation of treatment.[154]

J. E. Dalen: Idiopathic, or unprovoked VTE, that is, VTE occurring without risk factors, is an indication for prolonged therapy with vitamin K antagonists in patients with or without thrombophilia.

Genetic causes of thrombophilia are shown in Table 18. The most common acquired cause is antiphospholipid syndrome. Genetic thrombophilic factors increase the relative risk of an initial episode of VTE by a factor of 2 to 10, but the actual risk remains relatively modest.[155] Therefore, thrombophilia screening to identify those who may require antithrombotic prophylaxis to prevent initial episodes of VTE is not indicated, except possibly in women with a family history of idiopathic VTE who are considering oral contraceptive therapy.[155] Some physicians screen for thrombophilia to aid making decisions concerning the duration of anticoagulant therapy. However, several studies demonstrated that, with the exception of antiphospholipid syndrome, thrombophilia does not significantly increase the risk of recurrent VTE.[155] On the other hand, idiopathic VTE significantly increases the risk of recurrence in patients with or without thrombophilia.[155]

TABLE 18. Incidence of various thrombophilic disorders and associated venous thromboembolism

Thrombophilic disorders	Prevalence of disorders in patients with unexplained VTE (%)	Prevalence of disorders in general population (%)	Frequency of VTE with disorder (%)	Relative risk for VTE
Inherited thrombophilic factors				
Antithrombin III deficiency	0.5-8	0.02	90	8-10
Protein C deficiency	1.5-11.5	0.3	88	4-10
Protein S deficiency	1.5-13.2	—	74-100	8-10
Factor V Leiden	20	5[a]	57	2-8
Prothrombin 20210-A mutation	6	2[a]	6	2.8
Elevated factor VIII levels	25	11[a]	—	5-6
Elevated factor XI levels	—	—	—	2.2
Heparin cofactor II deficiency	—	—	36	—
Dysfibrinogenemia	—	—	10	—
Hyperhomocysteinemia	10	5-10	—	2.5
Acquired thrombophilic factors				
Antiphospholipid syndrome	—	—	29-55	11

[a]Prevalence of disorder among whites in general population.
Abbreviations: *DVT*, deep venous thrombosis; *VTE*, venous thromboembolism.
Modified and reprinted from Stein.[10]

Intermittent Pneumatic Compression

Intermittent pneumatic compression is effective in reducing the frequency of DVT (Tables 15 and 16). Following neurosurgery, intermittent pneumatic compression is particularly useful because there is no risk of bleeding with this procedure. The number of patients enrolled in trials of prophylaxis using intermittent pneumatic compression is considerably fewer than in trials of LMWH.[146] Intermittent pneumatic compression and LMWH have not been directly compared in prospective investigations.

Graded Compression Elastic Stockings

Graded compression elastic stockings following general surgery and following elective neurosurgery seemed to reduce the frequency of DVT, although such elastic stockings failed to produce much benefit following hip replacement and total knee replacement (Tables 15, 16, and 19). The data regarding elastic stockings should be interpreted guardedly, however, because high-risk patients were specifically excluded in some studies,[146] and patients with malignant disease have not been evaluated in sufficient numbers. Presumably, the use of graded compression elastic stockings with

TABLE 19. Prevention of deep venous thrombosis after general surgery (pooled data)[a]

Regimen	Number of patients	Number of patients with DVT	Incidence (%)
Untreated controls	4310	1084	25
Aspirin	372	76	20
Elastic stockings	196	28	14
Low-dose heparin	10,339	784	8
LMWH	9364	595	6
IPC	132	4	3

[a]Pooled data from randomized trials using fibrinogen leg scanning as the primary outcome.
Abbreviations: *LMWH*, low molecular weight heparin; *IPC,* intermittent pneumatic compression; *DVT*, deep venous thrombosis.
Reprinted and modified with permission.[146]

appropriate antithrombotic drugs would give better protection against DVT than either approach alone, but combined prophylactic measures have not been studied.[146]

It has become common practice to prescribe graduated compression stockings for patients with DVT, particularly proximal DVT, to prevent postthrombotic syndrome.[156,157] Systematic review confirmed the importance of compression stockings in the prevention of postthrombotic syndrome.[158] Among patients treated with venous compression, mild to moderate postthrombotic syndrome occurred in 64 of 296 (22%) compared with 106 of 284 (37%) in controls.[159-163] Severe postthrombotic syndrome occurred in 14 of 296 (5%) treated with venous compression compared with 33 of 284 (12%) controls.[159-163]

In healthy subjects, in both the supine and the sitting positions, ankle exercise increased popliteal vein blood velocity[164] (Fig 23). Such ankle exercise would transiently eliminate venous stasis in the lower extremities with sitting. This may be particularly useful during prolonged travel in a sitting position, although we have no data to indicate the amount and frequency of ankle exercise that would be necessary to prevent stasis-induced DVT. On the other hand, graduated compression stockings in healthy subjects did not increase time-averaged peak velocity, time-averaged mean velocity, diameter, or mean volumetric flow in the popliteal vein while supine or sitting, at rest, or during ankle exercise[165] (Fig 24). This suggests that repetitive ankle exercise during prolonged travel would be more effective in preventing stasis than compression stockings in healthy travelers.

J. E. Dalen: In patients with a history of VTE, or with risk factors for VTE, who embark on prolonged travel, repetitive ankle flexion may be helpful and graduated compression stockings should be considered.

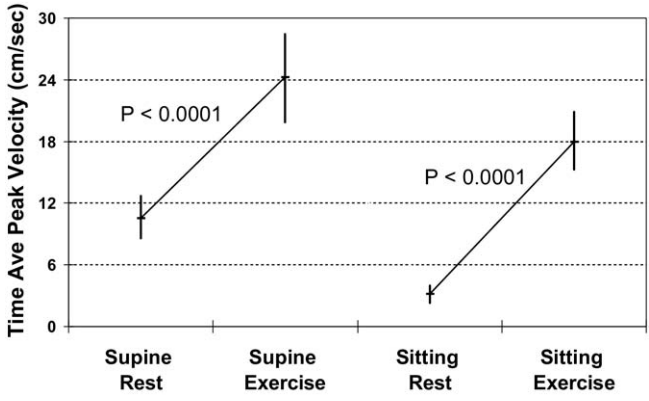

FIG 23. Time-averaged peak blood velocity in the right popliteal vein at rest while supine, during ankle exercise while supine, sitting at rest, and sitting in healthy subjects with ankle exercise. Time-averaged peak velocity increased with exercise while supine ($P < 0.0001$), and while sitting ($P < 0.0001$). Values shown are mean and 95% confidence interval. (Reprinted with permission.[165])

Heparin in the Treatment of Acute Pulmonary Embolism

The rationale for initial treatment with UFH or LMWH is to rapidly prevent the formation of new thrombi in the lower extremities while giving thrombi already present time to adhere to the venous walls, and to give vitamin K antagonists time to reach therapeutic levels. However, data on the effectiveness of heparin and its value in the treatment of acute VTE suggest that the benefits may be related to the reduction of late recurrences and not the prevention of an early catastrophic result.[166] Later recurrences are the norm and may be reduced by early treatment with heparin.

Based on a single investigation of heparin compared with no heparin preceding oral anticoagulants in the treatment of DVT, most recurrences of VTE were after 5 days.[167] Among patients treated with acencoumarol alone, 12 of 60 (20%) suffered a recurrent DVT or PE within 6 months. In those treated with heparin followed by acencoumarol, 4 of 60 (6.7%) suffered a recurrent DVT or PE within 6 months. Of note, 8 of 12 (67%) were after 5 days in the acencoumarol only group and 3 of 4 (75%) were after 5 days in the group that received heparin plus acencoumarol. The dreaded early occurrence of PE (5 days or less) while waiting for the vitamin K antagonist to become antithrombotic did not occur in any who received acencoumarol only, but it occurred in 1 of 60 (1.7%) of those who received heparin plus acencoumarol.[167]

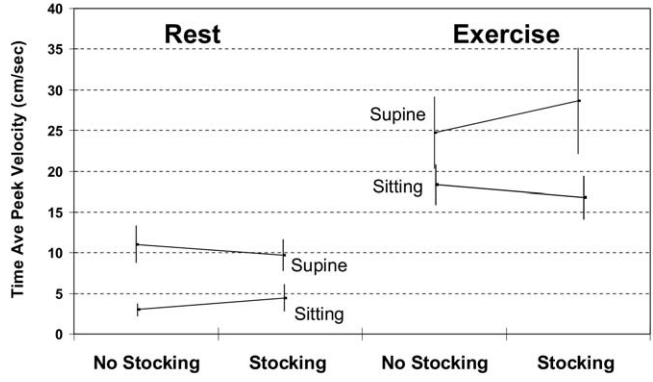

FIG 24. Time-averaged peak blood velocity in the right popliteal vein at rest while supine and sitting with and without a graduated compression stocking (GCS) (left) and during ankle exercise while supine and sitting with and without GCS (right) healthy subjects. Vertical bars indicate 95% confidence intervals. (Reprinted with permission.[166])

Fewer total recurrences resulted if a therapeutic level of heparin was reached within the first 24 hours of treatment of DVT.[168,169] Subtherapeutic doses of UFH during the first 24 hours of therapy for proximal DVT were associated with a 7 of 30 (23.3%) frequency of recurrent VTE compared with 4 of 87 (4.6%) for those whose activated partial thromboplastin time (APTT) was therapeutic within 24 hours and 6 of 104 (5.7%) for those in whom the APTT was supratherapeutic for the first 24 hours.[168] Five of 7 (71%) of the recurrences occurred after 5 days in the subtherapeutic group and 9 of 10 (90%) occurred after 5 days in the therapeutic or supratheraputic groups, with recurrences observed over 3 months.[168] The importance of achieving adequate therapy within 24 hours was confirmed in the Galilei study.[169] The incidence of recurrent VTE was 3 times higher in patients who failed to achieve a therapeutic APTT level within the first 24 hours of therapy with UFH for VTE compared with those who did not.

Fewer total recurrences also resulted if heparin was consistently maintained at therapeutic levels.[170] Among patients with an APTT <50 seconds on 2 consecutive days, the frequency of recurrent VTE was 5 of 72 (6.9%). Among those in whom the APTT did not fall below 50 seconds on 2 consecutive days, the frequency of recurrent VTE while on UFH was 0 of 90 (0%). Among those with inadequate UFH, PE occurred on days 2 or 3, 5, 7, and 11.

Initial Treatment of Acute Pulmonary Embolism

The following recommendations for treatment of acute PE are from the American College of Chest Physicians Evidence-based Clinical Guidelines (8th ed).[157] For patients with objectively confirmed PE, short-term treatment with subcutaneous LMWH or intravenous UFH, fixed-dose subcutaneous UFH, or fondaparinux, is recommended for at least 5 days and until the international normalized ratio (INR) is ≥2 for 24 hours.[157] Patients with acute PE should also be assessed for fibrinolytic therapy.[157]

For patients with a high clinical suspicion of PE, treatment with anticoagulants while awaiting the outcome of diagnostic tests is recommended.[157] Vitamin K antagonists should be initiated together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation. The dose of vitamin K antagonists should be adjusted to an INR of 2.0-3.0.[157]

In patients with acute nonmassive PE, LMWH is recommended over intravenous UFH.[157] In patients with massive acute PE, in patients where there is concern about subcutaneous absorption, and in patients in whom fibrinolytic therapy is being considered or planned, intravenous UFH is recommended over LMWH, fondaparinux, or subcutaneous UFH.[157] In patients with severe renal failure, the use of intravenous UFH over LMWH is suggested.[157]

Early Discharge

Large proportions of patients with a primary diagnosis of PE and of DVT are being discharged before adequate heparin can be administered and before warfarin can become antithrombotic[171] (Fig 25). An increased mortality among patients with PE discharged in ≤4 days in comparison with those hospitalized 5-6 days was reported.[172] If patients are to be discharged before adequate heparin can be administered, outpatient treatment with LMWH for at least 5 days and until the INR is ≥2.0 for 24 hours is recommended or extended outpatient treatment with LMWH may be considered.[171]

Outpatient Treatment of DVT and PE

Outpatient treatment of DVT with LMWH followed by vitamin K antagonists was shown in 1996 to be safe and effective in carefully chosen patients.[173,174] Subsequent investigations supported the outpatient approach to the treatment of DVT. Patients with PE were excluded from most investigations of outpatient treatment of DVT or treatment of DVT after early discharge. PE is a more ominous and potentially fatal form of

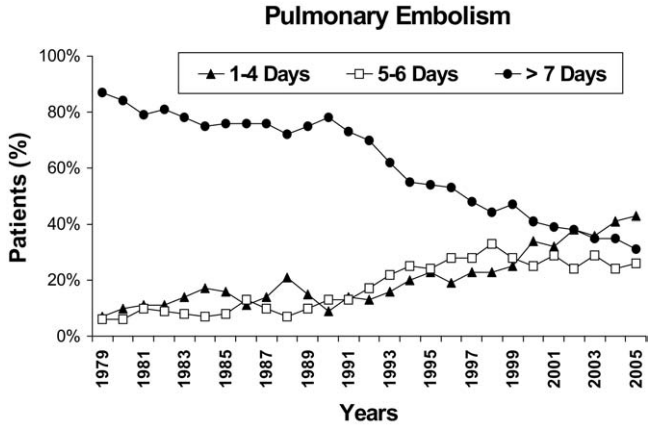

FIG 25. Length of hospital stay for patients with PE according to whether discharged in 1-4 days, 5-6 days, or >7 days. Length of stay >7 days decreased linearly from 1979 to 2005 ($r = -0.9673$, $P < 0.0001$). From 1990 to 2005, proportion of patients discharged in 1-4 days increased linearly ($r = 0.9748$, $P < 0.0001$). (Reprinted with permission.[172])

VTE than DVT. The risk of fatal recurrent PE in patients treated for PE is greater than the risk of fatal PE in patients treated for DVT (1.5% vs 0.4%).[175] By 2002, patients with PE were sometimes included among patients with DVT who were selected to have treatment.[176] By 2008, review showed 7 investigations of patients with PE who were treated entirely as outpatients or after early discharge and received adequate LMWH followed by oral anticoagulants or continuing LMWH.[177] All investigations included only low-risk patients or patients with small- or medium-sized PE. Results suggested that outpatient therapy of acute PE is probably safe in low-risk, carefully selected compliant patients who have access to outpatient care if necessary.[177]

Duration of Treatment With Heparin

Heparin is recommended for at least 5 days for the treatment of acute PE.[157] Heparin not only acts more rapidly than vitamin K antagonists, it also has a better antithrombotic effect.[178] It takes 3 days of treatment with UFH to eliminate detectable microthrombi from flowing cephalad in patients with acute DVT.[179] It takes 4-5 days for experimental venous thrombi to become adherent to the vessel wall.[180] It requires 5 days of treatment with warfarin to provide an antithrombotic effect.[181] The efficacy of warfarin depends particularly on depletion of clotting factor II (prothrombin) as well as depletion of factor X.[181,182] Both have long

half-lives compared with factor VII, which is the principal factor that affects the INR.[183] An INR of 2.0 or higher during the first 2 or 3 days of warfarin therapy may not indicate sufficient anticoagulation to prevent progression of thrombosis.[183]

Recurrent VTE within 6 months in patients with acute DVT was not more frequent after 3 or 4 days of hospitalization (5.4% and 5.1%) than after 5 days of hospitalization (5.4%) during which patients presumably received UFH.[184] Irrespective of its long-term effectiveness, however, the patient risks 1 or 2 days of subtherapeutic warfarin if heparin is discontinued after only 3-4 days.[183]

INR for Long-Term Treatment

Long-term treatment of unprovoked VTE (beyond 3-7 months of conventional treatment) with a vitamin K antagonist at an INR of 2.0-3.0 was shown to have a lower incidence of recurrent VTE (0.7%/year) than had been shown in controls (7.2%/year).[185,186] With a lower INR of 1.9-2.6, the incidence of recurrent VTE was higher (1.9%-2.6%/year). The incidence of major bleeds was not reduced with the lower INR (1.1%/year compared with 0.9%/year).[185,186]

D-Dimer as Guide to Continuation of Treatment

One month after the discontinuation of treatment of unprovoked DVT, D-dimer was measured and patients were followed an average of 1.4 years.[187] The incidence of recurrent VTE was 6.2% if D-dimer was normal and no further treatment with anticoagulants was given.[187] If D-dimer was abnormal and no further anticoagulants were given, the incidence of recurrent VTE was 15.0%. If, however, anticoagulants were given to those with an abnormal D-dimer, the incidence of recurrent VTE was 1.9%.

Patients With High Risk of Bleeding

Withholding treatment of nonmassive acute PE, providing serial non-invasive leg tests are negative and cardiopulmonary reserve is adequate, may be 1 possible strategy of management of patients with a high risk of bleeding or other contraindication to anticoagulants.[188] Such a strategy may be associated with fewer adverse events than anticoagulants or an IVC filter in patients with a high risk of bleeding.

Doses for Treatment, Anticoagulation Reversal, and Monitoring of Heparin

If intravenous UFH is chosen, it should be administered by continuous infusion after an initial bolus with 80 U/kg or 5000 U.[157] Dose adjustment

should be made to achieve and maintain an APTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity.

If monitored subcutaneous UFH is chosen, an initial dose of 17,500 U or a weight-adjusted dose of about 250 U/kg twice daily is recommended with dose adjustments to achieve and maintain an APTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay when measured 6 hours after injection rather than starting with a smaller initial dose.[157]

LMWHs are typically administered in fixed weight-adjusted doses.[150] Coagulation monitoring is generally not necessary, except perhaps in obese patients and patients with renal insufficiency.[150] There is no proven way of neutralizing LMWH.[150] If the anticoagulant effect of LMWH needs to be neutralized, protamine sulfate is recommended.[150]

The dose of fondaparinux for treatment of DVT or PE is 5 mg/d for patients weighing <50 kg, 7.5 mg/d for body weight 50-100 kg, and 10 mg/d for body weight >100 kg.[151] Coagulation monitoring is not recommended routinely. For uncontrolled bleeding, recombinant factor VIIa may be helpful.[150] Heparin-induced thrombocytopenia has not been reported following treatment with fondaparinux.[150]

Duration of Treatment With Vitamin K Antagonists

The recommended duration of treatment of patients with PE who have a reversible risk is 3 months with a vitamin K antagonist.[149] For a first episode of unprovoked PE, treatment for at least 3 months with a vitamin K antagonist is recommended, and longer if the risk of bleeding is low and good anticoagulant monitoring is achievable. For patients with a second episode of unprovoked VTE, "long-term" treatment is recommended. For patients with cancer and VTE, 3-6 months of treatment with LMWH is recommended, followed by treatment indefinitely with LMWH or a vitamin K antagonist, or until the cancer is resolved. In patients unexpectedly found to have asymptomatic PE, the recommended initial and long-term treatment is the same as with symptomatic PE.[149]

Troponin I

In-hospital all-cause mortality among patients with acute PE who had an elevated troponin I ranged from 14% to 36%, and in patients with a normal troponin I, in-hospital all-cause mortality ranged from 2% to 7%.[189-193] Patients with a troponin I level above 1.5 ng/mL had a higher mortality from PE (22% mortality) than those with a modest elevation of 0.07-1.5 ng/mL (10% mortality).[190]

Natriuretic Peptides

Brain natriuiretic peptide (BNP) is produced to a large degree from ventricular myocytes.[194] The principal stimulus for BNP synthesis and secretion is cardiomyocyte stretch.[194] Because it takes several hours for the plasma natruiretic levels to increase significantly after the onset of stretch, a second measurement should be obtained 6-12 hours after an initially negative test in a PE patient with symptom duration <6 hours.[195] Elevations in BNP[195] and N-terminal prohormone of brain natriuretic peptide (NT-pro BNP)[196] are associated with right ventricular dysfunction in acute PE. Elevated levels of BNP in patients with PE usually predicted a higher mortality than when normal. When normal, a benign clinical outcome was predicted.[194] Published cut-off values for NT-pro BNP and for BNP vary.

Right Ventricular Enlargement

Right ventricular dysfunction in a patient with PE and normal systolic blood pressure has been classified as "impending hemodynamic instability."[197] Some have recommended thrombolytic therapy for all patients with PE who have right ventricular dysfunction unless contraindicated.[198] Right ventricular dysfunction was defined as a right ventricular to left ventricular end-diastolic dimension ratio greater than 1 in the apical 4-chamber view, right ventricular end-diastolic dimension greater than 30 mm, or paradoxical septal systolic motion.[199] Right ventricular dysfunction has been used as an indication for surgical embolectomy in normotensive patients with PE.[199] Data from patients in PIOPED II showed that right ventricular enlargement alone in patients with PE did not indicate a poor prognosis or an indication for thrombolytic therapy.[200] Among 76 patients with right ventricular enlargement treated with anticoagulants and/or IVC filters, in-hospital deaths from PE were 0 of 76 (0%) and all-cause mortality was 2 of 76 (2.6%). None required ventilatory support, vasopressor therapy, rescue thrombolytic therapy, or catheter embolectomy. The extent to which findings in addition to right ventricular enlargement, such as right ventricular hypokinesis, affect prognosis is unsettled.

Resolution of PE

Pulmonary emboli resolve because of natural thrombolytic processes.[48] In most patients with PE, therefore, thrombolytic therapy is unnecessary. The rate of resolution of perfusion defects, calculated as a percentage of the pretreatment defect among 70 patients treated with anticoagulants

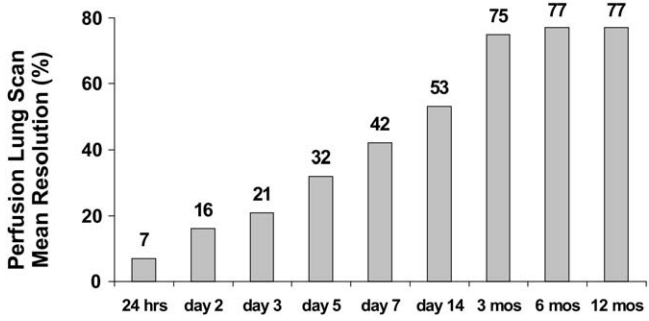

FIG 26. Mean resolution of perfusion defects shown as a percentage (%) of pretreatment defects in relation to time of treatment of PE. *Hrs,* hours; *mos,* months. (Data from The Urokinase Pulmonary Embolism Trial.[48] Reprinted with permission.[10])

in the Urokinase-Pulmonary Embolism Trial,[48] is shown in Fig 26. Complete resolution occurred in 77% of patients.[48] The proportion of patients showing complete resolution of CT pulmonary angiograms was similar.[201] Most patients (81%) showed complete CT angiographic resolution after 28 days.[201] Emboli resolved faster in main or lobar pulmonary arteries than in segmental branches.[201]

Fibrinolytic Therapy

For the majority of patients with acute PE, fibrinolytic therapy is recommended against.[157] Systemic administration of fibrinolytic therapy is suggested for patients with evidence of hemodynamic compromise unless there is a major contraindication due to a risk of bleeding.[157] In patients with hemodynamic compromise, fibrinolytic therapy should not be delayed because irreversible cardiogenic shock may ensue. The decision to use fibrinolytic therapy depends on severity of the PE, prognosis, and risk of bleeding.[157]

If fibrinolytic therapy is used, it is recommended that treatment be administered via a peripheral vein rather than placing a catheter in the pulmonary artery to administer treatment.[157] Short infusion regimes (eg, 2-hour infusion) are recommended over prolonged infusion times (eg, 24-hour infusion) because of the increased risk of bleeding with the long infusion times.[157] There is no evidence that fibrin specific agents such as r-tPA are more effective than non-fibrin-specific agents such as streptokinase or urokinase, and there is no evidence that a bolus injection of r-tPA is any more effective than an infusion.

Interventional Catheterization

For most patients with PE, interventional catheterization is recommended against.[157] In selected highly compromised patients who are unable to receive fibrinolytic therapy because of the risk of bleeding or whose critical status does not allow sufficient time to for fibrinolytic therapy to be effective, the use of interventional catheterization techniques is recommended provided there is appropriate expertise available.[157]

There currently are 3 categories of catheter interventional techniques for removing PE or for decreasing clot burden, as follows: (1) aspiration thrombectomy; (2) fragmentation; and (3) rheolytic thrombectomy.[202] Aspiration thrombectomy uses sustained syringe suction applied to a vacuum suction cup at the tip of the catheter to securely hold the embolus while it is removed via the venotomy.[202] Fragmentation of PE has been done by manually breaking clots with an angiographic (usually pigtail) catheter sometimes used with a guidewire over which the catheter is rotated.[202] A more advanced fragmentation device, the Amplatz catheter (Microvena Corp., White Bear Lake, MN), uses an impeller to homogenize the thrombus.[202] Rheolytic thrombectomy catheters (Angiojet; Possis Medical, Inc., Minneapolis, MN; Hydrolyser; Cordis Corp., Miami, FL; and Oasis; Meditech/Boston Scientific Corp., Natick, MA) use a high-speed jet of saline to create a Venturi effect that fragments adjacent thrombi and entrains the debris into an evacuation lumen.[202]

Pooled data showed that clinical success with the Greenfield catheter (Meditech/Boston Scientific), when used alone, was 81%, and when used in combination with thrombolytic agents, was 100%.[202] Clinical success with fragmentations using standard angiographic catheters was 71% when used in combination with systemic thrombolytic agents and 95% when used with a local infusion of thrombolytic agents.[202] Data with the Amplatz catheter and rheolytic catheters, when used alone, were sparse or absent. Clinical success when used in combination with thrombolytic agents was 87%-100%.[202] Minor bleeding at the insertion site among all patients, with and without thrombolytic agents, occurred in 8% and major bleeding at the insertion site occurred in 3%.

Although originally it was thought that catheter embolectomy or fragmentation could substitute for thrombolytic therapy, it now appears to be an adjunct to thrombolytic therapy. Mechanical embolectomy, when used in combination with thrombolytic agents, allows a larger surface area of the fragmented emboli to be exposed to the thrombolytic

agents.[202] All the devices appear to be useful in the management of acute massive PE. The limited data suggest that ordinary angiographic catheters, when used for fragmentation of PE, are as effective as impellar blade or rheolytic catheters.

To minimize the risk of perforation or dissection of vessels and cardiac chambers, it was recommended that catheter embolectomy be performed only in the main and lobar pulmonary arteries, not in the segmental pulmonary arteries, and the procedure should be terminated as soon as hemodynamic improvement is achieved, regardless of the angiographic result.[157]

Pulmonary Embolectomy

For most patients with PE, pulmonary embolectomy is recommended against.[157] In selected highly compromised patients who are unable to receive fibrinolytic therapy or whose critical status does not allow sufficient time for fibrinolytic therapy to be effective, pulmonary embolectomy may be used if appropriate expertise is available.[157]

The following criteria have been recommended for pulmonary embolectomy: (1) massive PE, angiographically documented if possible; (2) hemodynamic instability (shock), despite heparin therapy and resuscitative efforts; and (3) failure of thrombolytic therapy or a contraindication to its use.[203]

Pooled data from 41 reported case series of patients operated from 1961 to 2005 showed an average mortality of 391 of 1283 (31%).[204] Among patients operated before 1985, the average mortality was 33%, compared with 18% among patients operated from 1985 to 2005. Among patients who suffered a cardiac arrest before pulmonary embolectomy, the operative mortality was 60% vs 29% among patients who did not have a preoperative cardiac arrest. Despite a generally high mortality in patients undergoing pulmonary embolectomy, it may have lifesaving potential in some instances.

Vena Cava Interruption for Pulmonary Embolism

For most patients with PE, an IVC filter in addition to anticoagulant therapy are recommended against.[157] In patients with PE, if anticoagulant therapy is not possible because of a risk of bleeding, placement of an IVC filter is recommended.[157] If the risk of bleeding resolves after an IVC filter is inserted, a conventional course of anticoagulant therapy is recommended.

J. E. Dalen: Many clinicians would prefer to treat acute PE patients with a high risk of bleeding with an IVC filter.

The number of patients who had permanent IVC filters increased from 2000 in 1979 to 49,000 in 1999.[205] In 1999, 45% of IVC filter insertions were in patients with DVT alone, 36% were in patients with PE, and 19% of insertions were in patients who presumably were at high risk, but did not have DVT or PE listed as a discharge code.[205]

Complications of permanent IVC filters include improper anatomic placement (7%), migration (2%-3%), angulation of the filter (2%), caval stenosis (2%), caval occlusion (2%-9%), air embolism (1%), penetration of the caval wall (1%), lower extremity edema (13%-26%), and sequelae of venous stasis (27%).[205] DVT at the puncture site has been reported in 8%-25%,[205] and, in a series of 17 patients, 41% developed DVT at the puncture site.[205] Additional complications include filter deformation, filter fracture, insufficient opening of the filter, and erosion of the caval wall.[205]

Regarding retrievable IVC filters, thrombi trapped in the filter were frequent with most types of filters.[206] Anticoagulants generally were not used routinely. Among patients in whom percutaneous removal of the filter was attempted, the filter was successfully removed in 144 of 159 (91%).[206] Surgery was necessary to remove the filter from 1 patient (1%), and, in 14 patients (9%), filters could not be removed because of large trapped thrombi. Retrievable filters have been successfully removed after 1 year, but typically, successful retrieval was within 1-3 months.

In summary, most large or fatal PE identified at autopsy, 78% on average, was unsuspected ante mortem. This high proportion of patients with unsuspected large or fatal PE has not changed over 3 decades. The prevalence of unsuspected PE is the same at university hospitals and community hospitals. A high level of vigilance has been urged, but obviously there are barriers in making the diagnosis of PE. We are learning clinical characteristics of patients with PE that were not recognized in the past, which enhances our ability to identify patients in whom PE may be in the differential diagnosis. Although we have known for several years that acute PE may be silent, we only recently have come to recognize that about one third of patients with acute DVT have silent PE. PE may involve only muscular branches (0.1-1-mm-diameter). Such small PE cannot be identified by contrast-enhanced multidetector CT or by conventional digital subtraction pulmonary angiography, although perhaps with specialized techniques, such small PE could be visualized.

Because of the laudable desire of emergency service physicians to avoid missing a patient with PE, the vast majority of CT pulmonary angiograms on the emergency service, about 90%, are negative. In efforts to diagnose PE, physicians have overused CT pulmonary angiography, resulting in huge expense and exposure of many patients to potentially harmful ionizing radiation. Many patients with suspected acute PE could be triaged to no imaging if D-dimer is normal and clinical assessment is not high probability. Such triage could reduce the proportion of negative CT angiograms by 30%, but it is uncommonly used. Perhaps we have come full circle to the point where perfusion imaging in patients with a normal chest radiograph may be the imaging procedure of choice. The exposure to radiation is only a fraction of CT angiography and the cost is less. SPECT V/Q scans have been shown to be highly advantageous in Europe and Australia. A problem in testing the accuracy of SPECT V/Q scans is the lack of a definitive reference standard. Does a perfusion scan that shows hypoperfusion in a patient with a normal CT angiogram indicate a false positive perfusion scan or a false negative CT angiogram? Prevention is a problem, as well as diagnosis. Diseases associated with an increased risk of PE are being identified. Recommended prophylaxis, however, usually is not given. Regarding treatment, many options are now available, but all carry risk. It is critical to recognize the potential benefits and risks.

Addendum

Magnetic Resonance Angiography

The PIOPED III Trial of the accuracy of gadolinium-enhanced MR pulmonary angiography showed that most centers had difficulty in obtaining adequate quality MR pulmonary angiograms. This led the PIOPED III investigators to conclude that MRA should only be considered at centers that routinely perform it well, and for patients who have contraindications to standard tests.[207]

The PIOPED III investigators defined an adequate quality MRA as adequate opacification through subsegmental vessels.[207] Averaged across participating centers, MR pulmonary angiograms were technically inadequate in 25%, but at one center, only 11% were inadequate.[207] Among 371 patients, adequate quality images were obtained in 91% in main or lobar pulmonary arteries, 87% in segmental pulmonary arteries and in 73% in subsegmental branches.[207] Including patients with technically inadequate images, MRA identified 57% with PE.[207] Technically adequate MRA had a sensitivity of 78% and specificity of 99%.[207] Sensitivity

of MRA for detecting PE in a main or lobar pulmonary artery was 79%.[207] Pulmonary embolism was rarely identified by MRA when the largest PE was in a segmental or subsegmental branch.[207] Specificity was 98% to 100%, irrespective of the order of the vessel. The combination of a technically adequate MRA with magnetic resonance venography (MRA/MRV) had a higher sensitivity than MRA alone, 92%, while maintaining a high specificity of 96%.[207] However, 52% of patients had technically inadequate tests.[207]

J. E. Dalen: This comprehensive review by Stein and Matta is by far the most informative review of venous thromboembolism that I have ever encountered. If someone wants to read just 1 article on VTE, this is the 1 to read! Dr. Stein, who has published more than 200 articles on pulmonary embolism over a 40-year career, is clearly the ultimate authority on venous thromboembolism.

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