

# Natural History of Venous Thromboembolism

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**Abstract**—Most deep vein thromboses (DVTs) start in the calf, and most probably resolve spontaneously. Thrombi that remain confined to the calf rarely cause leg symptoms or symptomatic pulmonary embolism (PE). The probability that calf DVT will extend to involve the proximal veins and subsequently cause PE increases with the severity of the initiating prothrombotic stimulus. Although acute venous thromboembolism (VTE) usually presents with either leg or pulmonary symptoms, most patients have thrombosis at both sites at the time of diagnosis. Proximal DVTs resolve slowly during treatment with anticoagulants, and thrombi remain detectable in half of the patients after a year. Resolution of DVT is less likely in patients with a large initial thrombus or cancer. About 10% of patients with symptomatic DVTs develop severe post-thrombotic syndrome within 5 years, and recurrent ipsilateral DVT increases this risk. About 10% of PEs are rapidly fatal, and an additional 5% cause death later, despite diagnosis and treatment. About 50% of diagnosed PEs are associated with right ventricular dysfunction, which is associated with a  $\approx$ 5-fold greater in-hospital mortality. There is  $\approx$ 50% resolution of PE after 1 month of treatment, and perfusion eventually returns to normal in two thirds of patients. About 5% of treated patients with PE develop pulmonary hypertension as a result of poor resolution. After a course of treatment, the risk of recurrent thrombosis is higher (ie,  $\approx$ 10% per patient-year) in patients without reversible risk factors, in those with cancer, and in those with prothrombotic biochemical abnormalities such as antiphospholipid antibodies and homozygous factor V Leiden. (*Circulation*. 2003;107:1-22-1-30.)

**Key Words:** embolism ■ epidemiology ■ risk factors ■ thrombosis ■ veins

DVT usually starts in the calf veins, from where it may extend to the proximal veins, and subsequently break free to cause PE.<sup>1-4</sup> Each of these stages of VTE (eg, calf DVT, proximal DVT, PE) may or may not be associated with symptoms. The development of symptoms depends on the extent of thrombosis, the adequacy of collateral vessels, and the severity of associated vascular occlusion and inflammation. An additional factor that influences the development of symptoms is the capacity of the patient to tolerate thrombosis; for example, a PE of moderate size might cause no symptoms in an otherwise healthy subject but severe symptoms or death in the presence of advanced cardiopulmonary disease.<sup>5-7</sup>

This review will describe: (1) the average frequency with which VTE progresses to a more advanced stage (eg, calf DVT to proximal DVT to PE to fatal PE); (2) the factors influencing the probability of progression at each stage; (3) the frequency and extent of thrombus resolution at each stage of VTE; (4) long-term sequelae of DVT and PE; and (5) the effect of anticoagulant and thrombolytic therapy on the natural history of VTE. Throughout this discussion, a distinction is made between asymptomatic VTE, which is detected by screening tests in high-risk surgical patients (eg, fibrinogen leg scanning, venography, lung scanning), and symptomatic VTE. It is also important to emphasize that VTE is a dynamic process; progression and resolution may proceed

simultaneously at different sites of thrombosis, and the balance between these two processes may change, resulting in clinical exacerbations or remissions.

## Natural History of Untreated VTE

### Postoperative DVT Detected by Screening

Thrombosis that occurs in association with surgery usually starts in the deep veins of the calf, often originating in the valve cusps (Table 1).<sup>1,2</sup> Leg scanning and venographic studies have shown that such thrombi often begin intraoperatively.<sup>2,8,9</sup> About half of such calf DVTs resolve spontaneously within 72 hours, and only about one sixth extend to involve the proximal veins.<sup>2,8</sup> Extension to the proximal veins greatly increases the risk of PE; in one early study, 4 of 9 patients who developed proximal DVT detected by leg scans had a subsequent PE diagnosed clinically, whereas this occurred in 0 of 31 patients in whom DVT resolved or remained confined to the calf.<sup>2</sup>

### Delayed Onset of Postoperative DVT

Although venous thrombi often begin during the intraoperative period, some start days, weeks, or even months after surgery. Of DVTs diagnosed by screening tests in hospital, 34% (general surgery) and 20% (knee replacement) occurred in legs initially free of thrombosis postoperatively.<sup>8,9</sup> Simi-

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*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000078464.82671.78

larly, of 211 DVT diagnosed by leg scanning within 2 weeks of surgery in the absence of antithrombotic prophylaxis in the International Multicenter Trial, 61% started on or after day 3, and 9% started after the first week.<sup>10</sup> After exclusion of DVT by a normal venogram before discharge from hospital in patients undergoing hip or knee replacement, ≈15% develop new thrombi within the next 3 weeks.<sup>11–13</sup>

The timing of postoperative thrombosis may differ with the type of surgery. Compared with hip replacement, knee replacement is associated with (1) twice the frequency of asymptomatic, venographically detected DVT at discharge from hospital; (2) at least as high a risk of symptomatic VTE while in hospital; (3) about half the risk of symptomatic VTE after leaving hospital; and (4) a median of 7 rather than 17 days to the occurrence of postoperative symptomatic VTE.<sup>14,15</sup>

#### **Location of Postoperative DVT**

About two thirds of asymptomatic postoperative DVT that are detected by routine bilateral venography before discharge from hospital are confined to the calf veins.<sup>16–18</sup> Most postoperative proximal DVT also start in the calf, although thrombi may arise within the proximal veins, particularly if the proximal veins are injured during surgery. Hence, about three quarters of proximal DVTs that occur after major orthopedic surgery are in the operated leg,<sup>16,19</sup> and pelvic surgery is expected to be associated with a higher frequency of isolated pelvic vein thrombosis.

#### **Symptomatic Calf DVT and Risk of Extension**

The majority of symptomatic episodes of DVT also start in the calf veins; however, symptoms are uncommon until there is involvement of the proximal veins.<sup>3,20,21</sup> Hence, in a consecutive series of 189 outpatients with a first episode of venographically diagnosed symptomatic DVT, 89% had proximal thrombi. Ninety-nine percent of patients with proximal DVT also had associated calf vein thrombosis, and there was continuous involvement between the proximal and distal veins in >90% of these, suggesting that most thrombi originated in the calf.<sup>3</sup>

There is also evidence that, in the absence of treatment, about one quarter to one third of episodes of symptomatic, isolated distal DVT extend to involve the proximal veins. Lagerstedt and associates found that 29% (8 of 28) of patients with symptomatic, isolated calf DVT treated with 5 days of heparin without subsequent oral anticoagulant therapy had recurrence or extension during 3 months of follow-up.<sup>22</sup> In a study evaluating serial compression ultrasound of the proximal veins in consecutive symptomatic patients with suspected DVT, the prevalence of proximal DVT on the day of presentation was 18%.<sup>23</sup> This implies a prevalence of undetected DVT of ≈5% at initial presentation, most of which occur in distal veins (assuming 20% of symptomatic DVT are distal<sup>3</sup>), and to a lesser extent, small thrombi in proximal veins. Of those patients with initially normal compression ultrasound findings in the proximal veins, the test became abnormal in 1.8% of patients during 1 week of serial testing, consistent with extension during this period of 36% of initially untreated distal DVT to involve the proximal veins.<sup>23</sup>

#### **Symptomatic Proximal DVT and Risk of PE**

Forty to 50% of patients with symptomatic proximal DVT without symptoms of PE have ventilation–perfusion lung scan findings associated with a high probability of embolism.<sup>24–28</sup> As a high-probability lung scan has a sensitivity for PE of only ≈50%,<sup>29,30</sup> it is evident that PE occurs with most episodes of symptomatic proximal DVT.

It is more difficult to estimate the proportion of patients with symptomatic proximal DVT who would progress to symptomatic PE if left untreated. In one study of patients with proximal DVT who were treated with 10 days of intravenous heparin (adequate initial therapy) followed by 3 months of low-dose subcutaneous heparin (inadequate therapy), 47% (9 of 19) developed recurrent VTE during this period.<sup>31</sup> Of these 9 cases, 6 were symptomatic, and 1 was PE. In contrast, Nielsen and colleagues repeated venography after 30 days in 30 fully ambulant patients with symptomatic DVT (three quarters proximal) treated with phenylbutazone alone.<sup>32</sup> Progressive thrombosis in the proximal veins was found in 27% of patients, with additional patients having progression in the calf veins. Ventilation–perfusion lung scanning showed progression in 8% (3 of 39) after 10 days and 3% (1 of 30) at 60 days. During 3 months of follow-up, 1 patient had a confirmed episode of PE, and 8 patients were suspected of having recurrent DVT (no objective testing performed).<sup>32</sup> These 2 studies, together with the high frequency of asymptomatic PE in patients with proximal DVT<sup>24–28</sup> and the high prevalence of recurrent PE in untreated PE patients,<sup>33</sup> suggest that ≈50% of patients with untreated proximal DVT will develop symptomatic PE within 3 months. This risk appears highest at the time of acute DVT, with a subsequent rapid decline over a 3-month period.<sup>31,34</sup>

It is now evident that when anticoagulant therapy is stopped, the risk of recurrence is much lower (≤3% per year) when VTE is associated with a risk factor that has resolved than in patients with idiopathic thrombosis or a persistent risk factor (≈10% per year, or more).<sup>35–40</sup> Similarly, the risk of recurrent or progressive VTE in untreated patients is also expected to be greater in those with idiopathic thrombosis than in those with continuing risk factors such as cancer, compared with those in whom the initiating risk factor rapidly resolves.

#### **Postoperative PE Detected by Screening**

Postoperative thromboembolic complications usually occur in the first 10 to 20 days after general surgery; prophylaxis is typically given until hospital discharge, normally ranging from 5 to 14 days.<sup>41</sup> Pulmonary embolism was less likely to occur in association with DVT when patients had received prophylaxis with an antithrombotic agent (8% versus 42%).<sup>42</sup> Most studies have shown that PE occurs less commonly with isolated distal DVT than it does with proximal thrombosis.<sup>2,4,26,43</sup>

#### **Symptomatic PE**

It is estimated that ≈10% of symptomatic PE cause death within 1 hour of onset.<sup>44,45</sup> Those patients with PE who do not die acutely often have nonspecific symptoms, and for this reason, the diagnosis of PE is often delayed or missed

**TABLE 1. Natural History of VTE**


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Most DVT start in the calf.<sup>1–3</sup>

A large proportion (perhaps one half) of DVT associated with surgery start intraoperatively; many resolve spontaneously (about half within 72 hours).<sup>2,8,9</sup>

The risk of progression of postoperative VTE is greater when there are continuing risk factors for thrombosis (eg, immobilization) and when the initial thrombosis is large.<sup>2,9,128</sup>

The risk of VTE differs with type of surgery: major orthopedic surgery is associated with about twice the risk of VTE associated with major general surgery.<sup>15,129,130</sup>

75% of DVT after orthopedic surgery occur in the operated leg.<sup>16,19</sup>

The risk of symptomatic VTE is highest within 2 weeks of surgery and remains elevated for ≈2 to 3 months.<sup>10–12,15,131</sup>

Timing of postoperative VTE depends on the type of surgery; for example, risk of VTE is higher initially but drops more rapidly after knee replacement than after hip replacement.<sup>14,15</sup>

Antithrombotic prophylaxis facilitates spontaneous lysis of perioperative DVT and prevents new thrombi from forming.<sup>10</sup> Consequently, the longer the duration of prophylaxis, the lower the prevalence of asymptomatic DVT after prophylaxis is stopped (ie, at hospital discharge).<sup>132</sup>

Isolated calf DVT rarely cause leg symptoms (80% of symptomatic DVT involve the proximal veins)<sup>3,20</sup> and rarely cause clinically important PE.<sup>2,4,20</sup>

About 25% of untreated symptomatic calf DVT extend to the proximal veins, mostly within 1 week of presentation.<sup>20,22,23,133</sup>

The majority of patients with symptomatic proximal DVT and without chest symptoms have evidence of PE on lung scans; in 40% to 50% of such patients the lung scan shows “high-probability” perfusion defects.<sup>24–28</sup>

Asymptomatic PE are common in postoperative patients with asymptomatic DVT not given prophylaxis.<sup>42</sup>

About 70% of patients with symptomatic PE have DVT; these involve the proximal veins in about two thirds of cases.<sup>134–136</sup>

≤25% of patients with symptomatic PE have clinical evidence of DVT.<sup>20,137</sup>

Without treatment, ≈50% of patients with symptomatic proximal DVT or PE have recurrent thrombosis within 3 months.<sup>31,33</sup>

Following symptomatic DVT, the cumulative incidence of severe post-thrombotic syndrome is ≈10% after 5 years; most episodes occur within 2 years and may subsequently resolve.<sup>35,76,77</sup>

The highest risk period for fatal postoperative PE occurs 3 to 7 days following surgery.<sup>10,46,48,49</sup>

≈10% of symptomatic PE are fatal within 1 hour of first symptoms.<sup>44,45</sup>

Clinical diagnosis of PE is established in a minority of patients dying from PE.<sup>44,46,47</sup>

5% to 10% of patients with PE present with shock.<sup>82,83</sup>

50% of patients with diagnosed PE have right ventricular dysfunction on echocardiography, which is associated with high short-term mortality.<sup>82,83,88,89</sup>

The risk of recurrent VTE is higher in patients with “idiopathic” VTE or with continuing risk factors for thrombosis such as cancer, than in patients with transient risk factors such as recent surgery (eg, 10% versus 3% per year, after stopping anticoagulation).<sup>35–40,138</sup>

Isolated calf DVT is associated with about half the risk of recurrence as proximal DVT or PE.<sup>38,111,113</sup>

Risk of recurrence is similar following proximal DVT and PE.<sup>38,51,96,109</sup>

Recurrent VTE are usually PE after initial PE (≈60% of episodes) and DVT after initial DVT (≈80% of episodes);<sup>51,95,96</sup> this makes mortality from recurrent VTE 2- to 3-fold greater after PE than DVT.<sup>125</sup>

Antiphospholipid antibodies; hyperhomocysteinemia; homozygous factor V Leiden; very high levels of factor VIII; and probably, deficiencies of antithrombin, protein C, and protein S are risk factors for recurrent VTE.<sup>35,39,113–115,139,140</sup>

The risk of recurrence remains elevated after a first episode of VTE.<sup>35,109,141</sup>

Recurrent DVT in the same leg predisposes to post-thrombotic syndrome.<sup>35</sup>

≈50% resolution of perfusion defects occurs after 2 to 4 weeks of treatment for PE.<sup>86,88,100–102</sup> Eventually, complete resolution of PE occurs in about two thirds of patients.<sup>104–106</sup>

Chronic thromboembolic pulmonary hypertension occurs in ≈5% of patients with treated PE.<sup>93</sup>

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entirely. Consequently, most fatal episodes of PE that occur in the hospital<sup>44,46</sup> or the community<sup>47</sup> are not identified without an autopsy. The highest risk period for postoperative fatal PE appears to be 3 to 7 days after surgery.<sup>10,46,48,49</sup>

In the classic trial of Barritt and Jordan, 26% (5 of 19) of untreated patients with clinically diagnosed PE (severe end of the spectrum) died of PE during a follow-up period of ≈2 weeks, and another 26% of patients experienced nonfatal recurrences.<sup>33</sup> In the Prospective Investigation of PE Diagnosis (PIOPED) study, 10% (2 of 20) of patients with PE in whom the diagnosis was missed (less severe end of the spectrum) and, consequently, who were not treated with

anticoagulants, were judged to have had a recurrence during 3 months of follow-up.<sup>50</sup>

## Natural History of Treated VTE

### Resolution of DVT With Anticoagulation

Anticoagulation is the mainstay of treatment of symptomatic VTE. Anticoagulation prevents further thrombus deposition, allows established thrombus to undergo stabilization and/or endogenous lysis, and reduces the risk of interval recurrent thrombosis. After 3 months of therapeutic anticoagulation, the frequency of extension of symptomatic, isolated calf DVT was shown to be reduced from 29% to 0%.<sup>22</sup> During these 3 months, ≈4% of patients with proximal DVT have a recur-

## Natural History of VTE: Implications for Patient Management

### Primary Prophylaxis

Because most patients who die from PE do not have preceding symptoms of DVT, primary prophylaxis is a high priority.

Patient-related and surgical risk factors identify candidates for primary prophylaxis.

A minimum duration of prophylaxis may be required after high-risk procedures to facilitate spontaneous lysis of thrombi that form during or shortly after surgery (eg, 7 to 10 days after major orthopedic surgery).

Extended prophylaxis (eg, 3 weeks after hospital discharge) may be indicated after surgical procedures associated with a prolonged risk of VTE (eg, hip replacement).

### Diagnosis

Most calf DVT that extend to the proximal veins can be detected by ultrasound 1 week after an initial normal examination.

Detection of asymptomatic DVT can be used to diagnose PE in patients with a nondiagnostic lung scan or helical CT.

Incomplete resolution of previous DVT or PE may reduce the specificity of diagnostic testing for recurrent VTE.

rent episode of VTE.<sup>51,52</sup> Still, asymptomatic extension is not uncommon during the initial phase of therapy; repeat venography after 7 to 10 days reveals interval extension in  $\approx 6\%$  of patients treated with low-molecular-weight heparin and  $\approx 10\%$  of those treated with unfractionated heparin.<sup>52</sup> Cancer is associated with a  $\approx 3$ -fold increase in the frequency of recurrent VTE during treatment.<sup>53–55</sup>

Resolution of DVT in anticoagulated patients is slow. Repeat venography 6 months after diagnosis and treatment of DVT originally confined to the femoral or more distal veins showed complete lysis in 38%, partial lysis in 54%, and extensions in 7% of patients.<sup>56</sup> In other studies,  $\approx 50\%$  of patients have an incompletely compressible (ie, abnormal) venous ultrasound 1 year after diagnosis and treatment of proximal DVT.<sup>57–60</sup> Residual thrombosis is more likely in patients with large DVT or cancer.<sup>59</sup> Recanalization of the deep veins and development of collateral venous drainage occurs more rapidly than normalization on ultrasound, such that 90% of patients with treated proximal DVT have normal findings on impedance plethysmography after 1 year.<sup>61,62</sup>

### Resolution of DVT With Thrombolytic Therapy

Thrombolytic therapy accelerates the rate of lysis of DVT. In an overview of 8 randomized trials, Hirsh and Lensing calculated that, as assessed by early repeat venography, moderate or marked thrombolysis occurred 3 times more often in patients who received thrombolytic therapy than in those treated by anticoagulation alone ( $\approx 63\%$  versus  $22\%$ ).<sup>63</sup> Two of the studies included in this review suggested that thrombolytic therapy could also reduce the frequency of the post-thrombotic syndrome (see below).<sup>64,65</sup> These findings are supported by a subsequent trial of 250 younger patients with proximal DVT randomized to treatment with 1 of 4 thrombolytic regimens or with anticoagulant therapy alone.<sup>66</sup> At repeat venography after 7 days, the 2 systemic thrombolytic therapy regimens achieved opening of 80% of “closed venous segments” compared with only 17% in

controls. These differences were less marked after 1 year (58% versus 37%). This study also found that systemic thrombolytic therapy was associated with improved venous hemodynamics and reduced symptoms of the post-thrombotic syndrome, although it may have increased the frequency of PE within the first week of treatment.<sup>66</sup>

### Post-thrombotic Syndrome After DVT

Thrombosis damages the deep venous valves, which promote venous return during contraction of leg muscles. Destruction of the venous valves results in venous reflux and venous hypertension in the lower limbs. Valvular incompetence may also occur in venous segments not involved in the initial DVT.<sup>67</sup> This type of reflux has a distinctive anatomic distribution and is more likely to be temporary. However, venous reflux associated with thrombosis and residual venous obstruction are largely responsible for the development of post-thrombotic syndrome, which is characterized by pain, heaviness, and swelling of the leg aggravated by standing or walking. In its more severe form, the post-thrombotic syndrome results in skin and subcutaneous tissue changes that include varicose eczema, subcutaneous atrophy (“lipodermatosclerosis”), hyperpigmentation, and chronic skin ulceration. Although this pathophysiological sequence is generally accepted, there is a poor correlation between the severity of the post-thrombotic syndrome and either the extent of previous DVT<sup>35,68–70</sup> or associated hemodynamic changes.<sup>66,68,69,71–75</sup>

### Frequency of Post-thrombotic Syndrome After Symptomatic DVT

In a prospective study of 355 consecutive patients with symptomatic DVT, all of whom were instructed to wear graduated compression stockings for 2 years, Prandoni and associates observed a cumulative incidence of classic post-thrombotic syndrome of 17% after 1 year, 23% after 2 years, 28% after 5 years, and 29% after 8 years of follow-up. The cumulative incidence of severe post-thrombotic syndrome was 3% after 1 year and 9% after 5 years.<sup>35</sup> Recurrent ipsilateral DVT during follow-up was associated with a 6-fold increase in the risk of developing post-thrombotic syndrome.<sup>35</sup> During long-term follow-up, symptoms of post-thrombotic syndrome resolved in over half the affected patients, regardless of the severity of initial symptoms.<sup>76</sup>

In a randomized, controlled trial evaluating 2 years of graduated compression stockings, Brandjes and colleagues observed a similar cumulative incidence of mild-to-moderate and severe post-thrombotic syndrome in the group using stockings, and twice this frequency in the no-stocking control group.<sup>77</sup> There was no apparent relationship between recurrent DVT and development of post-thrombotic syndrome. In both studies, most patients who developed the post-thrombotic syndrome did so within 2 years of their acute episode of DVT.

A separate syndrome of venous claudication, in which patients with previous extensive iliofemoral thrombosis develop a “bursting” leg pain during exercise, has also been described but is uncommon.<sup>78,79</sup> This is thought to occur secondary to venous hypertension caused by residual iliofem-

oral venous obstruction.<sup>80,81</sup> Outcome is generally dependent on the rate and adequacy of collateral development.

#### ***Frequency of the Post-thrombotic Syndrome After Asymptomatic DVT***

In a cross-sectional study of 255 patients, Ginsberg and associates examined the association between asymptomatic DVT after hip or knee arthroplasty treated for 6 to 12 weeks, and the subsequent risk of the post-thrombotic syndrome.<sup>70</sup> After an average of 5 years, the prevalence of the post-thrombotic syndrome (moderate or severe symptoms with venous reflux) was low and the same ( $\approx 5\%$ ) in patients that had isolated calf DVT (n=66), proximal DVT (n=25), or no DVT (n=164).<sup>70</sup>

#### **Treated PE: Prognosis in Relation to Initial Severity and Comorbid Illness**

##### ***Shock at Presentation***

As previously noted,  $\approx 10\%$  of symptomatic PE are rapidly fatal.<sup>44,45</sup> The International Cooperative Pulmonary Embolism Registry, established to ascertain PE mortality, reported 2% of patients were first diagnosed with PE at autopsy.<sup>82</sup> Of patients diagnosed with PE before death, 5% to 10% have shock at presentation,<sup>82,83</sup> which is associated with a mortality of  $\approx 25\%$  to 50%.<sup>82–85</sup> Thrombolytic therapy can be life-saving in these patients.<sup>84,86</sup>

Consistent with the poor prognosis associated with echocardiographic evidence of right ventricular dysfunction, an increase in cardiac troponin with acute PE is a powerful independent marker for early death (odds ratio of 15).<sup>87</sup>

##### ***Right Ventricular Dysfunction Without Shock***

About 50% of patients with PE who are hemodynamically stable at presentation have echocardiographic evidence of right ventricular dysfunction,<sup>82,83,88,89</sup> a finding that is associated with a high in-hospital mortality.<sup>82,83,89</sup> In 126 consecutive patients with PE, Ribeiro and colleagues found that echocardiographic evidence of right ventricular dysfunction was associated with a relative risk of in-hospital death of 6.0 (mortality of 14% versus 0%), and of death at 1 year of 2.4.<sup>89</sup> In an analysis of >700 patients from the International Cooperative Pulmonary Embolism Registry, right ventricular dysfunction was associated with a hazard ratio (HR) of 2.2 for death at 3 months (mortality of  $\approx 20\%$ ).<sup>82</sup> Age >70 years (HR 1.6), cancer (HR 2.3), congestive heart failure (HR 2.4), chronic obstructive lung disease (HR 1.8), systolic hypotension (HR 2.9), and tachypnea (HR 2.0) were additional independent risk factors for 3-month mortality.<sup>82</sup> Similarly, Grifoni and colleagues found that 10% (6 of 65) of normotensive patients with PE who had echocardiographic right ventricular dysfunction subsequently developed shock (3 died) compared with 0 of 97 patients without right ventricular dysfunction.<sup>83</sup> The etiology of right ventricular dysfunction in patients with acute PE is multifactorial, as there is a limited correlation between this finding and the extent of perfusion defects, even in patients without prior cardiopulmonary disease.<sup>90</sup>

##### ***Long-Term Mortality***

Mortality rates after an episode of PE are high; approximately one quarter of patients die within 1 year.<sup>47,82,89,91–94</sup> However, whereas a majority of the deaths that occur within 1 month of diagnosis are because of PE, only  $\approx 20\%$  of deaths within 1 year (5% of patients) are caused by PE (usually a recurrence). Most late deaths are because of malignancy or, less commonly, cardiopulmonary disease.<sup>6,82,83,89,91,92,94</sup> Consistently with these observations, patients with PE have a much higher in-hospital mortality than patients with DVT, but roughly the same mortality after the first month of treatment.<sup>47,51,95,96</sup>

##### **Resolution of Pulmonary Arterial Obstruction**

Angiographic studies suggest that, in the absence of prior cardiopulmonary disease,  $\approx 25\%$  of pulmonary arteries become occluded before there is any increase in pulmonary arterial pressure.<sup>97</sup> Elevated pulmonary artery pressures occur in about half of patients with acute PE.<sup>93</sup> This pressure drops progressively during treatment, with most patients achieving a normal and stable pressure within 1 month.<sup>93,98</sup> This drop in pressure appears to be due to reversal of pulmonary arterial vasoconstriction and to spontaneous thrombolysis. The latter process appears to occur more rapidly in the lungs than in the leg veins, presumably because of a higher blood flow in pulmonary arteries that exposes thrombi to plasminogen, and possibly, a greater thrombolytic capacity of pulmonary arteries than peripheral veins.<sup>99</sup> In patients with PE treated with anticoagulation alone, serial pulmonary angiograms and perfusion lung scans suggest that resolution of PE is negligible after 2 hours,  $\approx 10\%$  after 24 hours, 40% after 7 days, and 50% after 2 to 4 weeks.<sup>86,88,100–103</sup> Thrombolytic therapy accelerates the rate of resolution (to  $\approx 10\%$  at 2 hours, 30% at 24 hours, 45% at 7 days, and 50% at 2 to 4 weeks) but does not alter the extent of residual thrombosis. Eventually, complete resolution of PE occurs in about two thirds of patients, with partial resolution in the remainder.<sup>104–106</sup> However, pulmonary artery pressure of over 50 mm Hg at presentation and age >70 years are associated with persistent pulmonary hypertension.<sup>93</sup> A recent prospective study suggests that chronic thromboembolic pulmonary hypertension occurs in  $\approx 5\%$  of patients after PE.<sup>93</sup> Surgical thromboendarterectomy can be highly effective in such patients.<sup>107</sup>

##### **Risk of Recurrent VTE**

The risk of recurrent VTE after stopping anticoagulant therapy differs markedly depending on whether or not the initial thrombosis was associated with a transient VTE risk factor (eg, recent surgery).<sup>35–38,40,108</sup> In patients with a first episode of VTE associated with a major transient risk factor, the risk of recurrence after anticoagulants are stopped is  $\approx 3\%$  per year.<sup>35–38,108</sup> In those with a continuing risk factor such as an underlying malignancy,<sup>35,37,55,96,109</sup> or those with idiopathic thrombosis,<sup>35,37–39,108</sup> this risk is at least 10% per year, and the risk is greatest shortly after stopping therapy.

Certain biochemical abnormalities are also associated with an increased risk of recurrence. The most convincing association is the presence of an antiphospholipid antibody (lupus anticoagulant or anticardiolipin antibody), which is associated with a  $\approx 2$ -fold increase in risk of recurrent VTE.<sup>39,110,111</sup>

Deficiencies of antithrombin, protein C, and protein S;<sup>35,112</sup> homozygous factor V Leiden;<sup>113</sup> and elevated levels of homocysteine<sup>114</sup> and coagulation factor VIII (>234 IU/L)<sup>115</sup> have also been associated with higher recurrence rates. Heterozygous forms of factor V Leiden and the G20210A prothrombin gene mutation confer relatively little increased risk of recurrent VTE.<sup>39,113,116–121</sup>

Compared with proximal DVT or PE, isolated distal (calf) DVTs are associated with a lower risk of recurrent VTE.<sup>38,108,113</sup> A history of more than 1 episode of VTE is a weak risk factor for recurrence,<sup>96,109</sup> and installation of a vena caval filter appears to represent a risk factor for DVT but not for PE.<sup>122,123</sup> Within 6 months of starting a short course of therapy (eg, 6 weeks of anticoagulation<sup>124</sup>), recurrent DVT more often develops in the same leg, probably because of reactivation of the initial thrombus.<sup>124</sup> After >6 months of treatment, recurrent DVT is at least as likely to affect the opposite leg, suggesting that late recurrences reflect a systemic rather than a local predisposition to thrombosis.<sup>60,124</sup> Although not predictive of the location of thrombosis, the risk of recurrence is greater when anticoagulants are stopped while there is still evidence of residual DVT on ultrasound imaging.<sup>59,60</sup> It is uncertain whether an abnormal ultrasound should be considered a risk factor for recurrence as it takes time (median ≈1 year) for ultrasound findings to return to normal after an episode of DVT, and the risk of recurrence decreases during this interval.<sup>109,125</sup>

The risk of recurrent VTE is the same for patients with proximal DVT or PE, but the risk of fatal PE is 2- to 3-fold higher after an episode of PE than of DVT.<sup>47,51,96</sup> This is because recurrent episodes of VTE tend to duplicate the initial mode of presentation; after initial PE, ≈60% of recurrences are PE, whereas after initial DVT only 20% of recurrences are PE.<sup>51,95,96</sup> It is not known whether the relatively weak association between factor V Leiden and isolated PE translates into a lower risk of recurrent PE in patients with VTE who have factor V Leiden than in those with VTE without this genetic abnormality.<sup>126,127</sup>

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