Invasive Approaches to Treatment of Venous Thromboembolism

Peter Augustinos, MD; Kenneth Ouriel, MD

Abstract—Deep vein thrombosis (DVT) occurs in one-quarter of a million individuals annually in the United States and results in significant disability from pulmonary embolism and chronic venous insufficiency, especially when the proximal iliofemoral is involved. Treatment has centered on early institution of adequate anticoagulation to prevent thrombus propagation and embolism, but anticoagulation alone does not always restore venous patency and many patients are left with venous outflow obstruction and valvular incompetence—the anatomic underpinnings of the postthrombotic syndrome. Various strategies have been used to restore patency of thrombosed veins, including open surgical thrombectomy, pharmacological thrombolysis, and percutaneous mechanical thrombectomy. Each modality has benefits and shortcomings. Surgical thrombectomy had previously been abandoned secondary to poor long-term results. More recently, with improved techniques and better patient selection, surgical thrombectomy has regained a therapeutic role in treating acute DVT in young patients with short segment occlusions. The advent of percutaneous techniques has allowed thrombolysis, percutaneous mechanical thrombectomy, and stenting to be used in conjunction with each other—allowing for better resolution of venous clot burden than when an individual modality is used alone. Practitioners who treat patients with DVT should be familiar with all the options available to restore venous patency, preserve valvular function, and thereby minimize the risk of late postthrombotic complications. (Circulation. 2004;110[suppl I]: I-27–I-34.)

Key Words: venous thromboembolism ■ postthrombotic syndrome ■ anticoagulation ■ thrombolysis ■ thrombectomy ■ percutaneous intervention

Despite advances in diagnosis and treatment, venous thromboembolism remains a potentially life-threatening disorder affecting hospitalized patients as well as ostensibly healthy individuals.1,2 It has been estimated that the yearly incidence of deep venous thrombosis (DVT) is as high as 250 000 cases in the United States alone3–5 and as many as 100 000 patients die annually from pulmonary embolism (PE).6 In addition to early risk of PE, late morbidity may develop from recurrent thrombosis and the postthrombotic syndrome.7–11 The management of DVT has evolved in recent years to encompass the outpatient use of low-molecular-weight heparin (LMWH), as well as pharmacological thrombolysis and mechanical thrombectomy.12 This article reviews current management of DVT, focusing on the use of open surgical and catheter-directed modalities for treatment of patients with iliofemoral DVT, involving the large proximal veins of the thigh and pelvis. Patients with proximal DVT are most likely to have early and late morbidity and thus stand to benefit most from surgical or percutaneous interventions.13

Goals of Therapy
There are 4 major goals of therapy for DVT, each of which is directed at the clinical sequelae of the disease (Table 1). Therapy is undertaken to:

1. Diminish the severity and duration of lower extremity symptoms
2. Prevent PE
3. Minimize the risk of recurrent venous thrombosis
4. Prevent the postthrombotic syndrome

Symptomatic improvement
During the acute phase, proximal DVT is associated with morbidity in the form of leg edema, pain, and difficulty ambulating that arises from venous hypertension caused by outflow obstruction. Although these symptoms usually subside over days to weeks as collateral venous channels develop, many patients experience some degree of venous outflow obstruction indefinitely. When obstructive symptoms persist, they are especially severe during exercise, when lower extremity blood flow can increase 5-fold.14 Therefore, one of the primary goals of therapy is relief of outflow obstruction. This is not accomplished entirely through anticoagulation alone, because thrombus regression occurs in only 50% of patients15,16 and venous recanalization develops in only a minority of patients treated with anticoagulants alone.17

Prevention of PE
The most dreaded complication of DVT is PE. In almost 50% of patients, embolism has already occurred by the time DVT...
diagnosis is established with proximal DVT, but only one-third of these cases are associated with symptoms.18

Ample data confirm the benefit of anticoagulation for prevention of PE, and immediate anticoagulation with heparin or LMWH is the standard of care for all patients with significant DVT in the absence of absolute contraindications. It is unclear whether other therapies can substitute for heparin in the setting of extensive DVT, but systemic thrombolysis can prevent recurrent PE when given with or without concomitant heparin.19–21 Given the paucity of data on the adequacy of thrombolytic therapy without concomitant heparin, however, it seems prudent to give heparin concurrently while administering thrombolytic drugs for this indication.20,21

Prevention/Minimization of Recurrent Thrombosis
Recurrent venous thrombosis can cause recurrent symptoms in the limbs as well as PE. It can also further compromise venous outflow and valvular function. Even with adequate anticoagulant regimens, recurrent thrombosis develops in 2% to 10% of patients followed-up for up to 3 years.22,23 Several studies have demonstrated the benefit of long-term oral anticoagulant therapy to prevent recurrent DVT; these are discussed in other sections of this monograph series.22,24,25

Prevention/Minimization of Late Postthrombotic Sequelae
The postthrombotic syndrome is the consequence of the venous valvular incompetence, venous hypertension, and stasis that occur in a limb after an episode of DVT.8 Postthrombotic symptoms can include chronic leg heaviness, leg aching and venous claudication, edema, varicosities, hyperpigmentation, and nonhealing ulcers. The syndrome develops in 20% to 50% of patients with DVT.7 Some studies suggest that the majority of patients with DVT followed-up for >5 years have postthrombotic symptoms.10 The combination of venous obstruction and valvular reflux is associated with more severe symptoms, and persistent venous outflow obstruction portends the greatest risk for late development of postthrombotic symptoms.26 The syndrome appears to occur more frequently with extensive multilevel DVT, in patients with recurrent DVT, and when the oral anticoagulant regimen was inadequate.10,27,28 These findings raise the possibility that early removal of a thrombus, by, eg, pharmacological thrombolysis, might protect against distal valvular incompetence and the postthrombotic syndrome.29

Specific Treatment Modalities for DVT
Historically, intravenously administered unfractionated heparin followed by warfarin was the treatment of choice for DVT. Other treatment options have evolved over time, including LMWH and novel anticoagulants. In the past decade, randomized clinical trials have elucidated effective anticoagulant regimens for DVT.16,30–33 Based on their results, subcutaneous LMWH has become one of the standards of care for patients with DVT.32

Although anticoagulants prevent thrombus propagation, PE, and recurrent venous thrombosis, they do not dissolve the occluding thrombus or reduce venous outflow obstruction. Furthermore, the inflammatory process also may be unaffected by anticoagulants.34 These observations have prompted the use of therapies to remove occlusive thrombus and thereby preserve valvular competence and reduce venous outflow obstruction (Table 2). Techniques include open surgical thrombectomy, thrombolytic therapy, and percutaneous mechanical thrombectomy (Figure).

Open Surgical Thrombectomy
Historically, iliofemoral venous thrombectomy combined with ligation of the femoral vein was the treatment of choice for DVT.35,36 Thrombectomy was performed to improve venous outflow from the leg, whereas femoral vein ligation was intended to prevent subsequent PE. Although the useful-

### TABLE 1. Complications Associated with Proximal (Iliofemoral) Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>Immediate in some cases, but greatest risk is early (days)</td>
<td>50%</td>
</tr>
<tr>
<td>Venous valvular incompetence</td>
<td>Late (months to years)</td>
<td>Up to 100%</td>
</tr>
<tr>
<td>Recurrent thrombosis</td>
<td>Most common early, but risk continues long term</td>
<td>Up to 10%</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>Months to many years</td>
<td>50%, but greater with follow-up exceeding 5 years</td>
</tr>
<tr>
<td>Paradoxical embolus</td>
<td>Immediate</td>
<td>Low</td>
</tr>
</tbody>
</table>

### TABLE 2. Treatments for Deep Venous Thrombosis (DVT)

<table>
<thead>
<tr>
<th>Modality</th>
<th>Appropriate Patients</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants</td>
<td>All</td>
<td>Begin immediately</td>
</tr>
<tr>
<td>Pharmacologic thrombolysis</td>
<td>Acute iliofemoral DVT</td>
<td>Early is best, but can be effective up to months after the acute event</td>
</tr>
<tr>
<td>Percutaneous mechanical thrombectomy</td>
<td>Acute iliofemoral DVT</td>
<td>Early is best</td>
</tr>
<tr>
<td>Venous angioplasty and stenting</td>
<td>Chronic iliac vein stenosis (May–Thurner syndrome)</td>
<td>Early treatment after successful restoration of venous patency</td>
</tr>
<tr>
<td>Open surgical thrombectomy</td>
<td>Acute iliofemoral DVT in patients with contraindications to pharmacologic thrombolysis, or in those with poor results with thrombolysis or mechanical thrombectomy</td>
<td>Early (days)</td>
</tr>
</tbody>
</table>
Management of patients with DVT. Anticoagulation is indicated for all DVT with the exception of certain localized calf vein thrombi, particularly those associated with the postoperative state. More aggressive intervention (eg, pharmacological thrombolysis) is reasonable for popliteal and femoral vein DVT if the patient is very symptomatic. Intervention is almost always reasonable for proximal (iliofemoral) DVT. Appropriate therapy for proximal DVT can induce pharmacological thrombolysis, mechanical thrombectomy, or both. Surgical thrombectomy is now used only in patients with contraindications to pharmacological thrombolysis. In all cases, a causative lesion should be sought out and corrected, usually with percutaneous angioplasty and stenting.

The advent of plasminogen activators to promote lysis of intravascular thrombi provided a less invasive strategy to restore venous patency in patients with acute DVT. At first, agents such as streptokinase were administered systemically, but results were unsatisfactory. When thrombolytic agents are given systemically, complete (50% to 100%) thrombus dissolution occurs in ~50% of venous segments with nonobstructive thrombi but in only 10% of fully obstructed segments. Experimental and clinical evidence suggests that systemic administration of thrombolytic agents, which is effective in small arteries such as the coronaries, is ineffective for treatment of DVT, likely because of inefficient diffusion of these agents into the matrix of large venous thrombi under conditions of low flow. Furthermore, systemic thrombolysis for DVT is associated with a greater risk of bleeding compared with that observed with anticoagulation alone. These observations prompted studies of catheter-directed, local infusion of thrombolytic agents to minimize bleeding and enhance clot dissolution. The largest published experience with catheter-based therapy has come from the National Venous Thrombolysis Registry, which included 287 patients treated with urokinase and followed-up for 1 year. Overall, 71% of the patients were treated for iliofemoral DVT. Complete dissolution of thrombus was achieved in 31% of cases, and partial (50% to 99%) thrombus dissolution was reported in an additional 52%. Primary patency at 1 year was 60%. Patency was higher in iliofemoral segments than in femoropopliteal segments and in patients in whom complete dissolution of thrombus occurred during the initial hospitalization. Preservation of valvular competence was demonstrated in 72% of patients with complete thrombolysis. In a subsequent study involving a subset of Registry patients, Comerota et al demonstrated better functioning and quality of life in patients with iliofemoral DVT treated by catheter-directed thrombolysis than in those treated with anticoagulants alone.

In a randomized trial comparing thrombolysis plus anticoagulation with anticoagulation alone in patients with iliofemoro-
oral DVT, thrombolysis was associated with improved patency rates (72% versus 12%; \( P<0.001 \)) and venous valvular competence (89% versus 59%; \( P=0.04 \)) at 6 months.\(^{29} \)

Although most studies of venous thrombolysis used urokinase, recent studies suggest that recombinant tissue-type plasminogen activator (0.5 to 1.0 mg/h)\(^{58} \) or reteplase (0.5 to 1.0 U/h)\(^{59} \) can also be successful.

There are numerous contraindications to thrombolytic therapy, most of which involve factors that increase the risk of bleeding complications, such as recent surgery, stroke, or gastrointestinal bleeding. Overall, only 1 of 5 patients with DVT is an appropriate candidate for thrombolytic therapy.\(^{60} \)

In the National Venous Thrombolysis Registry, bleeding severe enough to require transfusion was reported in 11% of patients. The rate of intracranial bleeding rate was 0.2%, whereas 16% of patients experienced minor bleeding complications. Other than hemorrhage, potential complications of catheter-directed thrombolysis for DVT include PE, which occurs in \( \approx 1\% \) of cases. Most emboli occur before diagnosis of DVT, however, and the incidence of PE is sufficiently low that prophylactic placement of an inferior vena cava (IVC) filter before catheter-directed thrombolysis is not usually recommended. The recent introduction of retrievable caval filters may change this practice, but more information is needed.

Multiple studies in Europe have demonstrated the usefulness of retrievable IVC filters. Indications for placement generally fall within the same spectrum as indications for permanent filter placement. The use of these devices during thrombolysis has been questioned because of the low incidence of complications that occur when lysis is performed without filter protection. An obvious advantage of retrievable filters is the option of removal to avoid possible complications of the filters. Their use is ideal in patients who require optimal protection during a critical time period when risk of PE is high and anticoagulation is contraindicated. Lastly, these filters need not be removed if the risk of PE is still present and they work as well as permanent filters. The Gunther Tulip (Cook Inc), the OptEase (Cordis Endovascular), and the Recovery nitinol (Brad Peripheral Vascular) are the 3 permanent filters approved by the Food and Drug Administration that have the potential for retrieval. The OptEase filter is the only one that can be recovered from a femoral vein approach; the other 2 filters must be removed via a jugular vein. In both the United States and Europe, most experience has been with the Gunther Tulip filter. Optimal timing of removal is unknown. The most common recommendation is within 14 to 21 days. However, the Recovery nitinol filter has been successfully removed 134 days after insertion.\(^{61} \)

To date there are no randomized trials drawing definite conclusions on the usefulness of retrievable IVC filters for treatment of DVT with catheter-directed thrombolysis.

Percutaneous Mechanical Thrombectomy

Percutaneous mechanical retrieval of venous thrombi is a logical extension of open surgical thrombectomy, offering the potential advantage of rapid clearance of thrombus from occluded venous segments.\(^{62,63} \)

In its simplest form, percutaneous venous thrombectomy can be accomplished through large bore sheaths, but this approach is cumbersome and infrequently results in complete thrombus extraction.\(^{64} \)

The introduction of a variety of motorized thrombectomy devices represents an advance over earlier techniques. Mechanistically, these thrombectomy recirculation devices fall within 2 categories—rotational and hydrodynamic.

Rotational thrombectomy devices use a high-speed rotating basket or impeller to fragment the thrombus. In most cases, the resultant small particles travel to the pulmonary circulation.\(^{65–67} \)

Examples of this type are the Amplatz thrombectomy device (Microvena), the Arrow-Trerotola percutaneous thrombolytic device (Arrow), and the Cragg-Castaneda thrombus (Microtherapeutics). Rotational, or "wall-contacting," devices have the potential to damage the endothelial lining of the vein. In an attempt to circumvent this problem, the Bacchus Fino device (Bacchus Vascular) uses a rotating Archimedes screw that is protected from wall contact by a helically oriented nitinol framework. The screw fragments the thrombus, extracting much of it into a sheath through rotational motion. No clinical data with this device are available.

Hydrodynamic, or "rheolytic," recirculation devices are based on the Venturi effect, created by high-speed saline jets directed retrograde. The jets fragment the thrombus and the material is then aspirated into the device. Devices based on this mechanism might possibly produce less valvular or endothelial damage than rotational thrombectomy devices, but this has not yet been evaluated in clinical trials. Examples of hydrodynamic recirculation devices include the AngioJet (Possis), the Hydrolyzer (Cordis), and the Oasis Thrombectomy System (Boston Scientific Corporation). In a study of 37 patients, Kasirajan et al\(^{68} \) reported >50% thrombus extraction in 59% of patients treated with these devices and symptomatic improvement in 82%.

Except in patients with bleeding diatheses, mechanical thrombectomy devices are usually used in conjunction with pharmacological thrombolysis.\(^{67,68} \)

Combining these 2 treatment modalities offers the best opportunity for rapid clearance of thrombus, thereby decreasing the duration and dose of thrombolytic agent. The Bacchus Trellis (Bacchus Vascular) is a relatively recent device, consisting of a catheter with proximal and distal occlusion balloons and a sheath designed to aspirate contents between the balloons. A sinusoidal nitinol wire placed within the catheter is rotated to mix the blood between the balloons. The Trellis device, which combines a high concentration of thrombolytic medication with mechanical disruption of the clot, has been used with some success to rapidly remove thrombus in patients with DVT.\(^{69} \)

The occlusive balloons limit leakage of thrombolytic agent into the systemic circulation, potentially reducing the risk of bleeding complications, whereas the central balloon is intended to reduce embolization of particulate debris to the pulmonary circulation. Although promising, experience with this type of apparatus is limited and there are few published reports documenting its usefulness in patients with acute DVT.

Adjuvant Venous Angioplasty and Stenting

In some patients with DVT there is underlying venous pathology. Left common iliac vein stenosis is frequently
located where the vein crosses beneath the right common iliac artery. This entity, which was originally described in separate reports by May and Thurner, is now known as the May–Thurner syndrome.70 Before the widespread use of postintervention imaging studies, this anomaly usually went undetected, which may account for the high rate of rethrombosis reported in early studies of open surgical venous thrombectomy.38 With the advent of postintervention angiography in patients undergoing percutaneous thrombolytic and thrombectomy procedures, it is now possible to identify a culprit lesion in some patients. Once identified, these lesions can usually be treated with percutaneous venoplasty and stenting.56,71–73 Although objective data are lacking, patency rates for metallic stents placed in the venous circulation appear high but long-term postintervention anticoagulation seems reasonable.

**Inferior Vena Cava Filters**

More than 90% of PEs are secondary to DVT.74 The veins involved in significant PE are proximal to the popliteal trifurcation. Symptoms are clinically present in ≈10% of patients when an embolus is of appropriate size. Emboli larger than 7.5 mm in diameter are commonly fatal.75 IVC filters are often used when anticoagulation therapy is contraindicated, has resulted in complications, or has failed to protect from embolic events.

IVC filters were designed to protect against fatal PE. Currently, 9 such filters have been approved by the Food and Drug Administration, and there are multiple absolute and relative indications for their use. In general, patients with a contraindication to anticoagulation or those who sustained a complication of anticoagulation should be treated with insertion of an IVC filter only. However, there are circumstances in which IVC filter placement and anticoagulation are used simultaneously. Combined therapy is typically used in patients with severe cardiopulmonary disease in which a recurrent embolic event may be fatal. Patients with a large free-floating iliofemoral thrombus are at a greater risk for PE despite anticoagulation treatment. These patients may also benefit from combined therapy.76 In general, when stenosis or poor flow dynamics still exist after lysis, stent placement is warranted, which may account for the high rate of recurrent PE observed during insertion of these devices, although infrequently. Rare complications that can pose significant morbidity and mortality are migration of the filter into the heart, penetration into vascular and gastrointestinal systems, and thrombosis resulting in phlegmasia.

To adequately evaluate the effectiveness of IVC filters, prospective comparison studies are needed. Complication rates and comparison of devices are limited by studies that contain too few patients with poor follow-up. Currently no filter appears to be superior to another. Therefore, it is advisable that clinicians be knowledgeable about several types of IVC filters and tailor the use of a specific filter to the appropriate clinical scenario.

**Therapy for Pulmonary Embolism**

Massive PE is a life-threatening event that requires prompt and aggressive management, and anticoagulation may not always be adequate. The importance of early diagnosis cannot be overemphasized, because mortality follows the initial clinical manifestations of PE in 10% of cases. Among those who survive without prompt diagnosis, the mortality rate approaches 30%. When appropriate therapy is begun in a timely fashion, however, the mortality rate decreases to <10%. These factors may explain why the mortality rate associated with PE has not changed appreciably over the past 3 decades.86,87

Several minimally invasive techniques are available for patients who sustain massive PE, including percutaneous embolectomy, catheter-directed thrombolysis, and clot fragmentation to quickly restore pulmonary circulation. The current indications for use of these interventions in patients with massive PE are88,89:

1. Arterial hypotension (systolic blood pressure <90 mm Hg or a rapid decrease of >40 mm Hg)
2. Systemic hypoperfusion and hypoxemia
3. Need for cardiopulmonary resuscitation
4. Right ventricular failure and/or pulmonary hypertension
5. Arterial–oxygen alveolar gradient >50 torr
6. Contraindication to anticoagulation

Systemic intravenous infusions of thrombolytic agents have been proven superior to anticoagulation for treatment of PE.90,91 Compared with heparin in hemodynamically stable patients with large PEs, systemic thrombolytic therapy reduced mortality (11% versus 4.7%) and recurrent PE (18.7%
versus 7.7%, $P=0.016$) but was associated with higher rates of bleeding complications.

**Catheter-Directed Thrombolysis**
Infusion of lytic agents directly into the pulmonary arteries accelerates clot lysis and results in rapid restoration of the pulmonary circulation in selected patients with massive PE. The technique involves introduction of a catheter through a femoral vein with the tip positioned in or near the pulmonary artery thrombus. A bolus injection of the thrombolytic agent is followed by a continuous infusion for 12 to 24 hours, whereas heparin is administered systemically. In 1 study, rapid clot lysis was achieved in 94% of patients and was pronounced in 66%. Theoretically, delivering a high concentration of thrombolytic agent directly into the affected circuit with catheter-directed thrombolyis should reduce hemorrhagic complications compared with intravenous infusions, but definite evidence of this advantage is lacking.

**Percutaneous Embolectomy**
Percutaneous embolectomy and thrombectomy represent minimally invasive options when thrombolytic therapy either fails or is contraindicated. These devices remove, fragment, macerate, or aspirate the embolic mass, resulting in smaller particles that eventually migrate to the periphery of the pulmonary circulation and thereby improve central hemodynamics. The goal is rapid relief of central obstruction, based on the premise that the cross-sectional area of the distal arterioles is several times that of the proximal pulmonary vessels. Under certain circumstances, thrombectomy devices can be used in conjunction with catheter-directed lysis. Lytic therapy may soften an occlusive thrombus, facilitating fragmentation, whereas fragmentation exposes a larger surface to the lytic agent.

**Surgical Embolectomy**
Surgical embolectomy is the most definitive yet the most invasive treatment for central pulmonary arterial embolus. Historically, surgical intervention was reserved for patients with massive PE and hemodynamic instability and was accompanied by a high mortality rate (30%). In 1994, Gulba et al compared systemic thrombolysis and surgical embolectomy. Lytic therapy was successful in 73% of patients whereas surgical treatment was successful in 85% of patients. Mortality rates were 33% for medical treatment and 23% for surgery, respectively. This study has been criticized for a bias toward treating more severely ill patients with thrombolytics than with surgical embolectomy.

More recently, Aklog et al and Yalamanchili et al have demonstrated that open pulmonary embolectomy can be performed in patients with minimal mortality and morbidity. These studies reported 89% and 92% survival rates, respectively, with early surgical intervention. Both groups attributed high survival rates to patient selection and early diagnosis. They concluded that open pulmonary embolectomy has a role in the treatment of PE and should not be reserved for the hemodynamically unstable patient or after thrombolysis has failed.

**Pulmonary Artery Stenting**
Endovascular stents planted in the proximal main pulmonary artery have been reported to provide prompt relief of cardiopulmonary compromise in patients with profound arterial hypoxemia, right heart failure, and hypotension. The long-term outcomes of stents in the pulmonary circulation are not known, however, and the use of such devices in this vascular bed should be restricted to extraordinary circumstances in which conventional therapy has failed.

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