INTRODUCTION

Despite advances in the efficacy, safety, and frequency of pharmacologic and mechanical prophylaxis against it, the incidence of venous thromboembolism (comprising deep venous thrombosis and pulmonary embolism), frequently encountered in the emergency department (ED), has not decreased during the past 3 decades. In fact, owing to the aging of the US population, ever more successful long-term management of chronic diseases associated with increased risk of venous thromboembolism, and the obesity epidemic, venous thromboembolism incidence may now be increasing.\(^1\)\(^-\)\(^3\) It is estimated that 2 million cases of venous thromboembolism occur annually in the United States, with 350,000 to 600,000 new cases diagnosed (two thirds deep venous thrombosis, one third pulmonary embolism)\(^2\)\(^-\)\(^6\); the population of individuals with previous deep venous thrombosis, who through the remainder of their lives will remain at increased risk of developing postthrombotic syndrome (or chronic, painful venous insufficiency of the lower extremities) and also experiencing recurrent deep venous thrombosis, may number 20 million or more. Venous thromboembolism, which may result in 100,000 deaths yearly,\(^4\) is now the third most common life-threatening cardiovascular disease in the United States (behind only myocardial infarction and stroke)\(^5\) and is considered the leading preventable cause of inhospital death.\(^2\) The incidence of venous thromboembolism increases markedly with age for both men and women but is somewhat higher in women during childbearing years and generally higher in men after age 45.\(^1\)\(^,\)\(^2\)

In recent years, new and high-profile attention has been directed to the health issue of venous thromboembolism. On September 15, 2008, acting Surgeon General Stephen K. Galson announced a national call to action (only the seventh such action from that office for the preceding 11 years) on deep venous thrombosis and pulmonary embolism,
specifying a need for research on causes, prevention, and treatment, including evaluation of new clot removal therapies as a critical research priority.\textsuperscript{4,8} Two years earlier, in May 2006, the Surgeon General’s Workshop on deep venous thrombosis was cosponsored by the National Heart, Lung, and Blood Institute, which has also been working to expand venous thromboembolism research through targeted requests for proposals.\textsuperscript{9} Also in 2006, a consensus statement requiring protocols for deep venous thrombosis prophylaxis and treatment was published by the National Quality Forum under leadership of The Joint Commission, which then in 2008 announced new requirements for reducing risks associated with anticoagulant therapy.\textsuperscript{10,11} Meanwhile, recent guideline updates from specialty organizations including the ACCP,\textsuperscript{12} the American Academy of Family Physicians/American College of Physicians,\textsuperscript{13,14} and the Society of Interventional Radiology\textsuperscript{15,16} hold that health care providers should practice a more calculated and aggressive preventive and treatment approach for deep venous thrombosis. Of particular note for emergency physicians is the 2008 ACCP article, which contains the latest guidelines on the optimal use of anticoagulation (grade 1A and 1C levels of evidence) and specifically recommends thrombolyis for selected patients with extensive acute proximal (above the popliteal vein) deep venous thrombosis, “if appropriate expertise and resources are available,” to “reduce acute symptoms and post-thrombotic morbidity” (grade 2B level of evidence) (Table 1).\textsuperscript{12} Although thrombolysis for deep venous thrombosis without pulmonary embolism is not a treatment ordinarily pursued in the ED, these guidelines expand the post-ED therapeutic armamentarium for deep venous thrombosis beyond simple anticoagulation. According to the guidelines, early thrombolytic treatment is potentially appropriate for selected patients with extensive iliofemoral deep venous thrombosis, symptoms for fewer than 14 days, good functional status, and life expectancy of greater than or equal to 1 year.\textsuperscript{12} For such patients, the ACCP guidelines recommend pharmacomechanical thrombolysis (lysis plus thrombus fragmentation with or without aspiration) in preference to catheter-directed thrombolysis alone (grade 2C level of evidence), again “if appropriate expertise and resources are available,” to shorten treatment time. When these endovascular procedures are not possible, for patients who have a low risk of bleeding, systemic thrombolytic therapy and operative venous thrombectomy are recommended by the guidelines as additional options for realizing the same treatment goals. With respect to ED decisionmaking, the ACCP guidelines recommend that patients who do undergo thrombolytic therapy also receive “the same intensity and duration” of anticoagulation therapy that would be received by comparable patients (without contraindications) who do not undergo thrombolysis.\textsuperscript{12}

### Setting, Interventions, and Outcomes

Treatment of acute deep venous thrombosis in the ED is considered essential to reduce the risk of pulmonary embolism, a potentially mortal complication. According to the ACCP guidelines,\textsuperscript{12} the evidence for anticoagulation as the first line of treatment for deep venous thrombosis derives from studies performed more than 40 years ago, and the only trial ever to compare anticoagulation (1.5 days of heparin plus 14 days of vitamin K antagonist) with no anticoagulation was published in 1960.\textsuperscript{17} The now long-standing standard of care for initial treatment of deep venous thrombosis within the ED—confirmed in the ACCP guidelines at a grade 1A level of evidence for objectively confirmed deep venous thrombosis, at a grade 1C level of evidence for high clinical suspicion of deep

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### Table 1. Selected 2008 recommendations of the ACCP for management of acute iliofemoral deep venous thrombosis.\textsuperscript{12}

<table>
<thead>
<tr>
<th>Number</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.3</td>
<td>1C</td>
<td>Initial treatment with LMWH, UFH, or fondaparinux for at least 5 days and until the INR is ≥2.0 for 24 h.</td>
</tr>
<tr>
<td>1.1.4</td>
<td>1A</td>
<td>Initiation of VKA together with LMWH, UFH, or fondaparinux on the first treatment day rather than delayed initiation of VKA.</td>
</tr>
<tr>
<td>1.4.1</td>
<td>1C/1A</td>
<td>Initial treatment with SC LMWH once or twice daily, as an outpatient if possible (grade 1C) or as inpatient if necessary (grade 1A), rather than treatment with IV UFH.</td>
</tr>
<tr>
<td>1.9.1</td>
<td>2B</td>
<td>In selected patients with extensive acute proximal DVT (eg, iliofemoral DVT, symptoms for &lt;14 days, good functional status, life expectancy ≥1 y) who have a low risk of bleeding, CDT may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available.</td>
</tr>
<tr>
<td>1.9.2</td>
<td>2C</td>
<td>After successful CDT, correction of underlying venous lesions with balloon angioplasty and stents.</td>
</tr>
<tr>
<td>1.9.3</td>
<td>2C</td>
<td>Pharmacomechanical thrombolysis (eg, with inclusion of thrombus fragmentation or aspiration) in preference to CDT alone to shorten treatment time if appropriate expertise and resources are available.</td>
</tr>
<tr>
<td>1.9.4</td>
<td>1C</td>
<td>After successful CDT, the same intensity and duration of anticoagulant therapy as for comparable patients who do not undergo CDT.</td>
</tr>
<tr>
<td>1.10.1</td>
<td>2C</td>
<td>In selected patients with extensive proximal DVT (eg, symptoms for &lt;14 days, good functional status, life expectancy ≥1 y) who have a low risk of bleeding, systemic thrombolytic therapy may be used to reduce acute symptoms and postthrombotic morbidity if CDT is not available.</td>
</tr>
<tr>
<td>1.11.1</td>
<td>2C</td>
<td>Patients with acute DVT should not be treated with percutaneous mechanical thrombectomy alone.</td>
</tr>
<tr>
<td>1.12.1</td>
<td>2B</td>
<td>In selected patients with acute iliofemoral DVT (eg, symptoms for &lt;7 days, good functional status, and life expectancy ≥1 y), operative venous thrombectomy may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available.</td>
</tr>
</tbody>
</table>

LMWH, Low-molecular-weight heparin; UFH, unfractionated heparin; INR, international normalized ratio; VKA, vitamin K agonist; SC, subcutaneous; IV, intravenous; DVT, deep venous thrombosis; CDT, catheter-directed thrombolysis.
venous thrombosis—is initiation of a short-term course of subcutaneous low-molecular-weight heparin, subcutaneous pentasaccharide, or intravenous unfractionated heparin, which is continued until the international normalized ratio from treatment with warfarin (initiated at the same time) is greater than or equal to 2.0 on 2 consecutive days (Table 1). The necessity of using an initial “bridging” course of a non-vitamin-K-dependent anticoagulant (typically, a heparin) in addition to the vitamin K antagonist, versus beginning treatment with a vitamin K antagonist alone was confirmed in a randomized controlled trial published in 1992: there was a threefold greater rate of recurrent deep venous thrombosis for patients who received the vitamin K antagonist alone. The so-called “bridging” approach may be pursued partially or fully on an outpatient basis, with close follow-up, in selected patients.

The ultimate duration of warfarin therapy depends on whether the acute deep venous thrombosis has been effectively treated and on the risk of new or recurrent episodes, as suggested by the nature of the acute deep venous thrombosis—whether it is secondary to a transient reversible risk factor or unprovoked, whether it is recurrent, whether it is proximal versus distal, or whether it is occurring in a cancer patient or a patient with an irresolvable high-risk condition such as paraplegia.

Insertion of inferior vena cava filters is not recommended routinely in addition to anticoagulants but may be appropriate for the prevention of clot embolization in patients with acute proximal deep venous thrombosis when anticoagulant therapy is not possible because of the risk of bleeding.

An often overlooked, additional reason for the aggressive management of deep venous thrombosis diagnosed in the ED is reduction in the risk of the subsequent development of postthrombotic syndrome, a goal that is highlighted alongside pulmonary embolism risk mitigation by the current professional society guidelines. Postthrombotic syndrome is a potentially debilitating cluster of lower-extremity symptoms and signs that is the most common complication of venous thromboembolism, ultimately occurring in 20% to 50% of deep venous thrombosis patients even after treatment with simple anticoagulation.

In most cases, postthrombotic syndrome develops within 1 to 2 years after deep venous thrombosis, but an increase in the cumulative incidence of postthrombotic syndrome has been found as late as 8 years after an initial episode of acute symptomatic deep venous thrombosis.

Postthrombotic syndrome causes major long-term quality-of-life impairment, including detriments in physical function and general health and health perceptions, severe activity limitations, and impaired social function. The direct and indirect economic effect has not been precisely quantified but is surely significant because the disease not only requires high-intensity ongoing medical care but may also significantly hamper employability and other aspects of quality of life.

Symptoms of postthrombotic syndrome, the severity of which can vary over time, include leg pain, aching, heaviness, swelling, itching, and cramping, particularly when the patient is walking or standing, whereas the clinical signs include leg edema, pain when the calf is compressed, varicose veins or telangiectasias, and hyperpigmentation of the leg.

The risk of subsequent postthrombotic syndrome is thought to be higher when deep venous thrombosis is not managed aggressively; this concern has contributed to the greater emphasis on early thrombolytic management in extensive proximal deep venous thrombosis. Recurrence of deep venous thrombosis in the same leg (the most important predictor for postthrombotic syndrome) and occurrence of the other symptoms of postthrombotic syndrome are directly correlated with residual thrombus burden after the initial treatment. It has been established through the work of Kahn et al that the strongest predictor of postthrombotic syndrome within 2 years’ follow-up is the presence of deep venous thrombosis symptoms and clinical signs at 1 month after initial treatment. Other postthrombotic syndrome risk factors that would be apparent at the initial diagnosis of deep venous thrombosis include higher body mass index, older age, thrombophilia (linked also with recurrence of deep venous thrombosis), and the extent of the initial deep venous thrombosis (patients with iliofemoral deep venous thrombosis having generally the largest thrombus burden) (Figure 1). In fact, up to 75% of patients with iliofemoral clot experience chronic painful edema, and 40% develop venous claudication after treatment with anticoagulation alone.

Pulmonary embolism does not in itself appear to predispose to postthrombotic syndrome. Pulmonary embolism risk mitigation by the current professional society guidelines.

The continued presence of thrombus within the deep venous system during the initial weeks after deep venous thrombosis presentation can lead to postthrombotic syndrome through the mechanical limitation of blood flow and the stimulation of inflammation that directly damages the venous valves, causing valvular incompetence and reflux. In association with the...
obstruction and reflux, ambulatory venous hypertension can then develop, followed by edema, tissue hypoxia and injury, calf pump dysfunction, subcutaneous fibrosis, and skin ulceration.\textsuperscript{28} Thrombus removal during initial deep venous thrombosis treatment can directly relieve venous obstruction and restore function in immobilized valves while indirectly preventing late development of venous valvular incompetence as a result of venous dilatation in distal venous segments that were never involved with thrombosis.\textsuperscript{12} Thrombus removal and relief of venous obstruction may also reduce the risk of recurrent venous thromboembolism.\textsuperscript{12} The potential value of prompt thrombolysis is reinforced by the fact that plasminogen content is highest in acute clot, whereas over time, as the plasminogen is depleted, the composition and morphology become more resistant to treatment.\textsuperscript{3}

Theoretical Model of the Problem

In contemporary practice, thrombolysis for venous thromboembolism in the ED is limited to the treatment of acute pulmonary embolism with hemodynamic compromise. However, in light of the recommendations in the 2008 ACCP guidelines and the evidence reviewed here, ED management of certain patients with acute extensive iliofemoral deep venous thrombosis might appropriately include referral to vascular surgery or interventional radiology for consultation about the possible long-term benefit of early endovascular thrombolysis.

The proof of concept for the “open vein” hypothesis—that a strategy of early thrombus removal can reduce the incidence of postthrombotic syndrome long term—comes incrementally from experimental observations, natural history studies of acute deep venous thrombosis (for example, in cases of spontaneous clot lysis in patients receiving anticoagulation alone), venous thrombectomy data, and studies of systemic thrombolysis and of catheter-directed thrombolysis.\textsuperscript{28,40,41} In a controlled randomized study of the value of elastic stockings for preventing postthrombotic syndrome in a consecutive series of 180 patients with first-episode proximal deep venous thrombosis, postthrombotic syndrome developed in 67 patients (37.2%), and irrespective of the use of the stockings, the researchers found that the relative risk of postthrombotic syndrome was 1.56 (1.01 to 2.45) in patients with residual vein thrombosis.\textsuperscript{42} Multivariate analysis in another study of 244 deep venous thrombosis patients followed for a median 4.9 years found that those who spent more than 50% of their time while receiving warfarin with international normalized ratio less than 2.0 were at higher risk for subsequent postthrombotic syndrome (OR 2.71; 95% CI 1.44 to 5.10).\textsuperscript{34} A meta-analysis of 11 randomized trials of anticoagulant therapy for venous thromboembolism reported between 1990 and 2003 found by meta-regression analysis that quantitative change in thrombus burden during treatment was a strong predictor of subsequent recurrent venous thromboembolism (coefficient of correlation 0.81; \(P = .005\)).\textsuperscript{41}

Surgical venous thrombectomy receives a grade of 2B in the ACCP guidelines (Table 1), although the guidelines also stipulate that catheter-directed thrombolysis is “usually preferable” if patients do not have a high risk of bleeding (grade 2C level of evidence).\textsuperscript{12} Although this invasive procedure requiring general anesthesia is only infrequently performed, in deference to catheter-directed thrombolysis, it is noted that with development of contemporary operative techniques and more effective anticoagulant regimens, outcomes have improved over time.\textsuperscript{12,40} The ACCP guidelines make note of a randomized trial of 63 patients receiving iliofemoral venous thrombectomy with a temporary arteriovenous fistula plus anticoagulation versus anticoagulation alone.\textsuperscript{43} At 5 years, there were slightly more asymptomatic patients (37% versus 18%) and less frequent severe postthrombotic sequelae (16% versus 27%) in the surgical group (differences not significant); the iliac vein was more frequently normal after thrombectomy (\(P < .05\)), but outflow capacity (61 versus 45 mL/min per 100 mL) was not significantly better.\textsuperscript{44} At 10 years’ follow-up, the researchers continued to report less severe sequelae for the surgical patients, with less common occlusions of the iliac vein (17% versus 59%; \(P < .05\)), although measures of venous physiology did not show any significant differences.\textsuperscript{45} Despite the small sample size of this single-center study and the nonsignificance of some outcomes, the results have still been considered as providing provisional support for the concept of early thrombus removal as a means of preventing postthrombotic syndrome.\textsuperscript{12,28,46}

Support for the open-vein hypothesis also comes from earlier trials of systemic thrombolytic therapy (the fibrinolytic drug administered by way of an intravenous line at some distance

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**Factors apparent at DVT diagnosis thrombosis**

Previous ipsilateral DVT

Extent of index DVT

Proximal DVT

Older age (in some studies\textsuperscript{33,34})

Male sex (weak predictor in one study\textsuperscript{39})

High body mass index

Thrombophilia

**Factors that become manifest during long-term follow-up**

Presence of DVT symptoms and clinical signs at 1 mo after initial treatment

Poor quality of early anticoagulant therapy (eg, >50% of time with subtherapeutic INR)

Presence of residual thrombus on ultrasonography

Increased D-dimer 3 weeks after withdrawal of oral VKA anticoagulant (in one study\textsuperscript{39})

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**Figure 1.** Risk factors for postthrombotic syndrome.\textsuperscript{32,35,39}
from the affected limb), which receives a grade of 2C in the ACCP guidelines (Table 1), where again catheter-directed thrombolysis when available is considered the preferred option. The guidelines identify 3 randomized trials of systemic thrombolytic therapy versus anticoagulation alone, in which the thrombolysis was associated with reduced incidence of postthrombotic syndrome at 1 year (urokinase), 1.6 years (streptokinase), and 6.5 years (streptokinase). In a Cochrane analysis of 12 randomized controlled trials of thrombolysis versus anticoagulation for acute deep venous thrombosis, significantly less postthrombotic syndrome occurred in patients who received thrombolysis (relative risk 0.66; 95% CI 0.47 to 0.94). However, of 688 patients in this analysis, those receiving thrombolysis had significantly more bleeding complications (relative risk 1.73; 95% CI 1.04 to 2.88). But these investigators observe that in the trials they examined, the incidence of bleeding appeared to be reduced over time with the introduction of stricter selection criteria, an impression underscored by the ACCP guidelines, referring to exploration of alternatives to the prolonged infusions of streptokinase used predominantly in the earlier studies.

With comparative procedural advantages and the potential for lower required dosages of fibrinolytic drugs, catheter-directed thrombolysis has demonstrated the potential to dissolve thrombus and prevent postthrombotic syndrome while preserving valve function. Historically, use of catheter-directed thrombolysis has involved systemic exposure to thrombolytic drugs during periods ranging from 20 to 48 hours and has required multiday ICU stays, with risk of embolization and reported rates of major bleeding of 11% and higher (compared with the rates of 2% to 4% for anticoagulation alone), mostly related to catheter-access complications. Analysis of the results of 312 urokinase infusions in 303 limbs of 287 lower-limb deep venous thrombosis patients in the National Venous Registry determined that the degree of lysis achieved was predictive of 1-year patency: 79% for grade III lysis, 58% for grade II lysis, and 32% for grade I lysis (P<.001). In 19 catheter-directed thrombolysis studies of heterogeneous design tabulated in the most recent ACCP guidelines, significant lysis was observed in 79% of 945 limbs treated with catheter-directed thrombolysis, and in a comparison of 68 iliofemoral deep venous thrombosis patients treated with catheter-directed thrombolysis, versus 30 patients treated with anticoagulation alone, quality of life was better in the catheter-directed thrombolysis patients and correlated with the extent of lysis. In the first reported randomized controlled trial of catheter-directed thrombolysis (plus anticoagulation) versus anticoagulation alone, a single-center study of 35 patients with acute iliofemoral deep venous thrombosis, 6-month patency was significantly improved (72% versus 12%; P<.001) in the 18 patients treated with intrathrombus pulse-spray streptokinase, as was the preservation of normal venous valve function (89% versus 59%; P=.04).

No major bleeding or death was reported in this trial. More contemporary endovascular treatments use thrombolytic drugs with greater fibrin specificity and lower allergenicity (such as tissue plasminogen activator instead of streptokinase) that are catheter directed for intrathrombus delivery (preventing drug efflux through collateral veins, which enables dosage reduction and limits systemic fibrinolysis) and then dispersed mechanically within the clot to accelerate lysis.

These techniques, used concomitantly with a standardized anticoagulation regimen in the posttreatment period, yield early venous patency rates exceeding 80% (versus the 10% to 15% typically achieved with anticoagulation alone) and significantly affect the onset and severity of postthrombotic syndrome. According to the endovascular technical advances, the accumulated operator experience, and more appropriate patient selection, bleeding complication rates, according to the ACCP, had been cut by more than 50% since the beginning of the century.

The recently published interim results of the open, randomized, controlled, multicenter Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis trial extend the evidence for the open vein hypothesis and improve the basis for the ACCP recommendations about catheter-directed thrombolysis. At 6 months’ interim analysis in this 2-year trial, 50 patients with acute (<21 days) iliac or iliofemoral deep venous thrombosis who were treated with catheter-directed thrombolysis (including those who underwent adjunctive angioplasty and stenting) plus standard treatment (anticoagulation and pressure hose) had better patency than 53 patients who received the standard treatment alone (64.0% versus 35.8%; absolute risk reduction 28.2%; 95% CI 9.7% to 46.7%; P=.004), although the groups did not differ in terms of femoral venous insufficiency. Major procedure-related bleeding occurred in only 1 catheter-directed thrombolysis patient. Whereas most previous reported studies of thrombolytic treatment used streptokinase or urokinase, the thrombotic in the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis trial was recombinant tissue plasminogen activator (alteplase), which has strong affinity for fibrin, is nonimmunogenic, and can be given as a continuous intravenous infusion.

Pharmacomechanical Endovascular Interventions

A distinct evolution of endovascular thrombolysis involves augmentation with local mechanical thrombus fragmentation, with or without aspiration, during the basic catheter-directed thrombolysis procedure. (The ACCP guidelines counsel against treatment with percutaneous mechanical thrombectomy alone without concomitant catheter-directed thrombolysis because that approach has been associated with a higher incidence of pulmonary embolism.) In retrospective comparisons of this “pharmacomechanical” catheter-directed
thrombolysis versus catheter-directed thrombolysis alone, the rates of thrombolysis (70% to 80%) and of major bleeding (5% to 8%) were similar, but pharmacomechanical catheter-directed thrombolysis was associated with shorter treatment times and lower lytic doses, shorter ICU and hospital stays, and reduced costs.12,67,68 Another concept, recently under investigation as an alternative to mechanical thrombus fragmentation, involves the incorporation of ultrasonographic transducers into the infusion catheter to speed clot lysis by altering the structure of the thrombus. A few published reports suggest the safety and efficacy of this technology, with overall thrombolytic infusion time reduced to the range of 24 hours.40,69,70

The latest refinements in pharmacomechanical treatment use single-use disposable catheters and allow the combination of catheter-directed thrombolysis and mechanical thrombus fragmentation/aspiration to be completed in a single treatment session, often eliminating the need for postprocedural ICU monitoring while further limiting lytic exposure. The AngioJet Rheolytic Thrombectomy System (Possis Medical, Minneapolis, MN) uses high-velocity saline-solution jets to fracture thrombus and then enable aspiration by creating a localized negative pressure zone at the catheter tip. With the incorporation of a “Power Pulse” capacity, the AngioJet can first deliver and then disperse a thrombolytic drug.28 In one retrospective study of 24 patients receiving this treatment, grade II or III lysis (that is, ≥50% thrombus removal) was achieved in 19 patients (79.2%).66 In a second retrospective study, grade II or III lysis was achieved in 39 (75%) of 52 AngioJet Power Pulse procedures, with adjunctive venous balloon angioplasty or stenting performed in 43 (82%), and the mean ICU (0.6 day) and hospital (4.6 days) stays represented significant reductions compared with that of a control cohort receiving basic catheter-directed thrombolysis.68

Available since 2005, the Trellis Peripheral Infusion System (Covidien, Mansfield, MA), featuring a multilumen catheter with 2 occluding balloons, effectively supports single-session thrombolysis.28 With the Trellis, in a procedure that has been referred to as isolated segmental pharmacomechanical thrombolysis,61 the thrombus is isolated on a segment-by-segment basis between occluding balloons, the lytic infusion then occurs in the isolated segment, then the lytic is mechanically mixed (by means of a rotating sinusoidal stainless steel wire attached to an oscillation drive unit) to further the breakup of thrombus, and finally both the thrombus and lytic are aspirated. The segmental isolation is intended to reduce the thrombolytic dosing. The mechanical mixing promotes quicker interfacing of drug with thrombus than does simple passive delivery (without the potentially damaging effects of high-energy percutaneous mechanical thrombectomy). The aspiration phase both reduces systemic exposure to the lytic drug and removes fibrinolysis debris.

Data from a voluntary manufacturer-sponsored registry of 2,203 cases of extremity deep venous thrombosis treated with the Trellis device in 2,203 patients between October 2005 and November 2009 demonstrate that grade II or III lysis (that is, ≥50% thrombus removal) was achieved in 95.5% of the treated limbs across all clot chronicities at the conclusion of the procedure, and adjunctive angioplasty or stent placement then was performed in 75% of cases.71 The Trellis procedures, including adjunctive and bilateral procedures when applicable, were performed in a single setting in 83.3% of cases, with the average Trellis use time 22.3 minutes (SD 9.4 minutes). No major bleeding complications, symptomatic pulmonary embolism, or other significant adverse events were reported during the registry procedures. Although the registry included no formal recording of postprocedural follow-up, several case series reported independently from the registry have demonstrated the ability of the procedure to rapidly and safely restore venous patency in patients with acute deep venous thrombosis and to quickly resolve acute clinical symptoms.57,59,61,62,72,73

The AngioJet and Trellis pharmacomechanical devices both figure in the recently published 6-month outcomes from the single-center randomized controlled Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO) trial of endovascular intervention plus anticoagulation and compression stockings versus anticoagulation and compression stockings alone for 183 patients with acute proximal deep venous thrombosis.74 The expressed goal of the percutaneous intervention in TORPEDO was to restore streamline flow from the popliteal vein to the unobstructed portion of the inferior vena cava filter that was initially placed in all endovascular patients. The intervention consisted of one of, or a combination of, the following: pharmacomechanical thrombectomy, balloon venoplasty, stenting, or local low-dose thrombolytic therapy (tissue plasminogen activator). The particular approach was determined by the venography results. For acute deep venous thrombosis with otherwise preserved venous anatomy, the percutaneous thrombectomy could be performed with the AngioJet, the Trellis, or manual aspiration with an 8-F guide catheter. No preference was given to any catheter-directed thrombolysis or pharmacomechanical device, with the use of any particular device based on operator discretion and device availability. The indication for thrombolysis was greater than 30% residual thrombus after initial thrombectomy. The protocol also covered in detail the adjunctive use of balloon venoplasty and stent placement. On the primary 6-month efficacy endpoints, recurrent deep venous thrombosis developed in 2.3% of the endovascular patients versus 14.8% of the control patients (P = .003), and postthrombotic syndrome developed in 3.4% of the endovascular patients versus 27.2% of the controls (P <.001) (Table 2). Bleeding was reported in only 2 of the endovascular patients and 1 of the controls. A total of 47 stents were placed in 27 of the endovascular patients, and there were no stent fractures or occlusions at 6 months.

The National Heart, Lung, and Blood Institute–sponsored Acute Venous Thrombosis: Thrombus Removal With...
Adjunctive Catheter-Directed Thrombolysis trial seeks to demonstrate the safety and efficacy of these new endovascular techniques. Currently recruiting patients, with completion and reporting targeted for 2016, the trial has been designed to evaluate whether pharmacomechanical catheter-directed thrombolysis, including the intrathrombus administration of the tissue plasminogen activator alteplase, can limit the incidence of postthrombotic syndrome in patients with symptomatic proximal deep venous thrombosis compared with optimal standard anticoagulation therapy alone. The drug is being administered at a maximum allowable dose of 35 mg during a period of up to 24 hours. Three methods of drug delivery are being used: (1) the Trellis-8 Peripheral Infusion System, with a maximum first-session dose of 25 mg; (2) the AngioJet Rheolytic Thrombectomy System, also with a maximum first-session dose of 25 mg; and (3) conventional catheter-directed thrombolysis infusion for up to 24 hours at 0.01 mg/kg per hour (maximum 1.0 mg per hour) through a multisidehole infusion catheter when patients present with thrombotic occlusion below the knee (no inflow). Before and after these treatments, the patients randomized to these treatments will receive the same standard anticoagulation therapy as in the control arm: unfractionated heparin (enoxaparin, dalteparin, or tinzaparin) for at least 5 days, overlapped with long-term oral warfarin (target international normalized ratio 2.0 to 3.0), with concomitant prescription of elastic compression stockings. The primary outcome measure of the trial is the incidence of postthrombotic syndrome within 24 months after randomization; multiple secondary outcome measures include the severity of postthrombotic syndrome, the resolution of presenting deep venous thrombosis symptoms, the prevalence of valvular reflux and residual thrombus, the degree of clot lysis, cost-effectiveness within 24 months of randomization, major bleeding, symptomatic pulmonary embolism, recurrent venous thromboembolism, and death at 10 days and 24 months.

**Recommendations for Consideration of Referral**

The ACCP guidelines recommend referral for consideration of catheter-directed thrombolysis in selected patients with extensive acute proximal deep venous thrombosis who have low risk of bleeding. (According to the 2009 quality improvement guidelines from the Society of Interventional Radiology, catheter-directed thrombolysis is contraindicated in any patient with a hemorrhagic disorder, an anatomic lesion that is prone to bleeding, or an absolute contraindication to anticoagulant therapy.) It has been suggested that among patients who might be expected to realize substantial benefit from active thrombolysis are those with significant iliofemoral clot burden, those with acute phlegmasia (symptom onset <10 days) requiring aggressive and urgent intervention to decrease compartment pressures and resolve ischemia, and patients with occluded veins as a result of May-Thurner (iliac vein compression) syndrome. There are other types of patients for whom consideration for referral from the ED for possible endovascular therapy should perhaps be greater. For example, for young patients with acute deep venous thrombosis but otherwise in good health and with normal life expectancy, prompt clot resolution may provide disproportionate benefit by returning them more quickly to work. Furthermore, because it can be assumed that such patients will have a longer post–deep venous thrombosis life span than older deep venous thrombosis patients, greater benefit might be derived from the reduction of the likelihood of postthrombotic syndrome, which can occur many years after the index deep venous thrombosis. In addition, older patients with terminal disease, for whom pulmonary embolism could foreshorten remaining quality life span, might be candidates for aggressive clot removal. Such a strategy could allow resumption of plans to arrange one’s affairs or to see family as planned when the terminal diagnosis was made. Finally, a pharmacomechanical approach could be considered as a more definitive alternative to inferior vena cava filter placement in patients with contraindications to anticoagulation, although this approach deserves prospective study and would have to be balanced with the small but finite risk of extralot lysis.

The intent of the evolved pharmacomechanical approach to catheter-directed thrombolysis is to most effectively prevent postthrombotic syndrome and recurrent deep venous thrombosis through the long term by promptly eliminating thrombus burden while building on the success of catheter-directed thrombolysis by reducing overall procedure time, as well as the duration and quantity of exposure to the lytic agent. Although endovascular balloon sequestration of clot and thrombolytic therapy does not completely eliminate the
possibility of systemic circulation of lytic agent, the likelihood of bleeding complications with this approach seems to be low. Registry data have demonstrated a reduced need for multiple procedural passes and for follow-up ICU monitoring, reduced cost, and a very low incidence of bleeding and other complications such as those associated with earlier uses of catheter-directed thrombolysis. In the TORPEDO trial, the incidence and severity of postthrombotic syndrome were significantly reduced at 6 months after endovascular reduction of thrombus burden. Rapid restoration of patency may equate with better valve function and less likely development of venous insufficiency, whereas complete or near-complete recanalization of the involved vein can reduce the incidence of chronic venous hypertension and edema associated with postthrombotic syndrome. Successful thrombolysis can also expose underlying lesions requiring adjunctive angioplasty or stenting procedures to sustain patency. Although prompt recognition of deep venous thrombosis and initiation of anticoagulation therapy remain the mainstays of ED management, ongoing collaboration among emergency physicians, vascular specialists, and interventional radiologists may improve appropriate and timely use of these treatment approaches in the overall management of deep venous thrombosis (Figure 2).

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treatment of deep venous thrombosis in the emergency 
Short abstract for Pollack, YMEM 

The standard of care for treatment of deep venous thrombosis in the emergency department (ED), supported by the 2008 American College of Chest Physicians guidelines, involves initiation of anticoagulation with low-molecular-weight heparin, pentasaccharide, or unfractionated heparin. For selected appropriate patients with extensive acute proximal deep venous thrombosis, the American College of Chest Physicians guidelines now recommend thrombolysis in addition to anticoagulation to reduce not only the risk of pulmonary embolism but also the risk of subsequent postthrombotic syndrome and recurrent deep venous thrombosis. I review the grounds for use of adjunctive thrombolysis in patients with acute proximal deep venous thrombosis and begin to identify types of deep venous thrombosis patients encountered in the ED who might benefit most from multidisciplinary consideration of early referral for possible endovascular therapy.