

Quality Improvement Guidelines for the Treatment of Lower Extremity Deep Vein Thrombosis with Use of Endovascular Thrombus Removal



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J Vasc Interv Radiol 2006; 17:435-448

Abbreviations: CDT = catheter-directed thrombolysis, DVT = deep vein thrombosis, FDA = Food and Drug Administration, IVC = inferior vena cava, PE = pulmonary embolus, PMT = percutaneous mechanical thrombectomy, PTS = post-thrombotic syndrome, PTT = partial thromboplastin time, VTE = venous thromboembolism

LOWER extremity deep vein thrombosis (DVT) is a serious medical condition that can result in death or major disability due to pulmonary embolism (PE), post-thrombotic syndrome (PTS), paradoxical embolization, or limb loss. Since the early 1990s, endovascular methods have been used by interventional radiologists to provide aggres-

sive treatment for lower extremity DVT (1). However, there currently exist no published guidelines for the appropriate utilization of these techniques. The Society of Interventional Radiology (SIR) strongly believes that active participation of the interventional radiologist in the patient selection, pretreatment evaluation, patient

selection, periprocedural monitoring, and postprocedural care of the DVT patient will improve the safety and effectiveness of these procedures.

METHODOLOGY AND LIMITATIONS

SIR creates its Standards of Practice documents with use of the following process: Standards documents of relevance and timeliness are conceptualized by the Standards of Practice Committee members. A recognized expert is identified to serve as the principal author, with additional authors assigned depending on the project's magnitude.

An in-depth literature search is performed with use of electronic medical literature databases. A critical review of peer-reviewed articles is performed with regard to the study methodology, results, and conclusions. The qualitative weight of these articles is assembled into an evidence table, which is used to write the document such that it contains evidence-based data with respect to content, rates, and thresholds. When the evidence of literature is weak, conflicting, or contradictory, consensus for the parameter is reached

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DOI: 10.1097/01.RVI.0000197348.57762.15

by a minimum of 12 Standards of Practice Committee members with use of a Modified Delphi Consensus Method (2). For the purpose of these documents, consensus is defined as 80% participant agreement on a value or parameter.

The draft document is critically reviewed by the Standards of Practice Committee members in either a telephone conference call or face-to-face meeting. The revised draft is then sent to the SIR membership for further input/criticism during a 30-day comment period. These comments are discussed by the Standards of Practice Committee members and appropriate revisions are made to create the finished Standards document. Before its publication, the document is endorsed by the SIR Executive Council.

The current guidelines are written to be used in quality improvement programs to assess the endovascular treatment of lower extremity DVT. The most important elements of care are (a) pretreatment evaluation and patient selection, (b) performance of the procedure, and (c) postprocedure follow-up care. The outcome measures or indicators for these processes are indications, success rates, and complication rates. Although practicing physicians should strive to achieve perfect outcomes, in practice all physicians will fall short of ideal outcomes to a variable extent. Therefore, in addition to quality improvement case reviews conducted after individual procedural failures or complications, outcome measure thresholds should be used to assess treatment safety and efficacy in ongoing quality improvement programs. For the purpose of these guidelines, a threshold is a specific level of an indicator which, when reached or crossed, should prompt a review of departmental policies and procedures to determine causes and to implement changes, if necessary. Thresholds may vary from those listed here; for example, patient referral patterns and selection factors may dictate a different threshold value for a particular indicator at a particular institution. Therefore, setting universal thresholds is very difficult and each department is urged to adjust the thresholds as needed to higher or lower values to meet its specific quality improvement program situation.

The SIR is committed to the basic

principles of outcomes-focused, evidence-based medicine. Ideally, every Standards of Practice Committee recommendation would be based on evidence derived from multiple prospective randomized trials of adequate statistical power. Unfortunately, there currently exist no published multicenter randomized trials of significant size that evaluate image-guided endovascular DVT therapies. In evaluating the existing publications, several major limitations are evident: (a) extreme variation in patient selection parameters, definitions of short-term efficacy, and definitions of complications; (b) reliance on surrogate measures of treatment success instead of scientifically rigorous assessment of clinically meaningful outcomes; and (c) absence of systematic assessment of long-term efficacy. For these reasons, the U.S. Food and Drug Administration (FDA) does not currently label any drug or device for endovascular DVT treatment. Streptokinase (administered systemically) did receive FDA approval for DVT in 1980, but a National Institutes of Health consensus panel later recommended against the use of systemic thrombolysis for DVT (3).

The SIR recognizes the potential pitfalls of developing evidence-based DVT standards and of making recommendations regarding the off-label use of drugs and devices based on studies of suboptimal design. However, these difficulties are far outweighed by the potential improvements in safety and treatment efficacy that may be gained by implementing the key lessons learned from the peer-reviewed scientific literature that has evaluated these procedures. The current document was drafted by the DVT Standards and DVT Research Committees of the SIR Venous Forum with further modification by the SIR Standards of Practice Committee and therefore reflects the consensus experience of interventional radiologists with extensive expertise in treating DVT using endovascular means. Given the limited scientific foundation, however, most of the recommendations presented in this document are intended to guide clinical practice rather than to mandate the use of specific methodologies. The authors fully anticipate that these guidelines will be appropriately revised

when future studies of greater scientific rigor are available.

DEFINITIONS

Disease Processes

Venous thromboembolism (VTE) refers to the single common disease entity with two principal manifestations: DVT and PE. A patient with a proved episode of DVT and/or PE is said to have had an episode of VTE.

Pulmonary embolism (PE) refers most commonly to the intravascular migration of a venous thrombus to the pulmonary arterial circulation. *Proved PE* refers to PE that is documented by a positive pulmonary angiogram, an unequivocally positive helical CT scan, a high probability ventilation-perfusion scan, surgical observation, or autopsy. *Proved PE* can be *symptomatic* (patient had clinical PE symptoms and/or signs such as chest pain, dyspnea, hemoptysis, palpitations, or tachycardia) or *asymptomatic* (PE was detected on an imaging study in a patient without suggestive symptoms). *Suspected PE* refers to PE that is suspected based on clinical symptoms and/or signs but for which definitive diagnosis has not been made by imaging or autopsy.

Deep vein thrombosis (DVT) refers to the presence of thrombus within a deep vein of the body as proved by diagnostic imaging.

Phlegmasia refers to a characteristic clinical picture in which DVT causes massive swelling of the entire extremity. Patients with *phlegmasia alba dolens* do not have associated cyanosis. Patients with *phlegmasia cerulea dolens* have more extensive thrombosis with associated cyanosis of the affected limb. This disorder can lead to arterial insufficiency, compartmental compression syndrome (compartment syndrome), and/or venous gangrene and has been associated with a high rate of limb amputation (4).

Duration of Symptoms

Acute DVT refers to venous thrombosis for which symptoms have been present for 14 days or less or for which imaging studies indicate that venous thrombosis occurred within the last 14 days.

Subacute DVT refers to venous

thrombosis for which symptoms have been present for 15 to 28 days or for which imaging studies indicate that venous thrombosis occurred within this time interval.

Chronic DVT refers to venous thrombosis for which symptoms have been present for more than 28 days or for which imaging findings document the presence of venous thrombosis more than 28 days before.

Acute-on-chronic DVT refers to venous thrombosis that has both chronic (> 28 d) and acute (\leq 14 d) components as indicated by symptom history or imaging findings.

Anatomical Extent of Disease

Proximal DVT refers to complete or partial thrombosis of the popliteal vein, femoral vein (formerly known as the superficial femoral vein), deep femoral vein, common femoral vein, iliac vein, and/or inferior vena cava (IVC). Proximal DVT is often complicated by PE. Proximal DVT can be further subclassified as follows:

Femoropopliteal DVT refers to complete or partial thrombosis of the popliteal vein, femoral vein, and/or deep femoral vein.

Iliofemoral DVT refers to complete or partial thrombosis of any part of the iliac vein and/or the common femoral vein, with or without associated femoropopliteal DVT.

Calf vein DVT refers to complete or partial thrombosis of one or more deep calf veins, including the anterior tibial veins, posterior tibial veins, peroneal veins, and/or deep muscular veins. Isolated calf vein DVT is rarely associated with symptomatic PE (5). When calf vein DVT propagates into the popliteal vein, it is considered proximal DVT.

Treatment Methods

Pharmacologic thrombolysis refers to administration of drugs with thrombolytic activity. Several different routes of administration can be used:

Systemic thrombolysis refers to pharmacologic thrombolytic agent delivery through an intravenous line located distant from the affected extremity.

Flow-directed thrombolysis refers to pharmacologic thrombolytic agent delivery through a pedal intravenous line placed within the affected extremity,

with or without the use of tourniquets to intermittently compress the saphenous system to direct the drug into the deep venous system.

Catheter-directed intrathrombus thrombolysis (CDT) refers to pharmacologic thrombolytic agent delivery through an infusion catheter and/or wire that is embedded within the thrombosed vein being treated. *Lacing* refers to the use of a catheter to disperse a bolus dose of the thrombolytic drug throughout the thrombus.

Percutaneous mechanical thrombectomy (PMT) refers to the percutaneous use of catheter-based mechanical devices that contribute to thrombus removal via fine (microscopic) thrombus fragmentation, maceration, and/or aspiration.

Pharmacomechanical thrombolysis refers to thrombus dissolution via any simultaneous use of pharmacologic thrombolysis and mechanical thrombectomy. *Pulse-spray pharmacomechanical thrombolysis* refers to a specific technique in which a thrombolytic drug is periodically forcefully injected into the thrombus (6).

Aspiration thrombectomy refers to the use of a syringe to aspirate thrombus from the clotted vein via a catheter or sheath.

Balloon maceration refers to the use of a catheter-mounted angioplasty balloon to produce gross (macroscopic) thrombus fragmentation or maceration.

Balloon angioplasty refers to inflation of a catheter-mounted angioplasty balloon with the specific intent of enlarging the venous lumen.

Stent placement refers to catheter-based deployment of a metallic endoprosthesis to enlarge and maintain the venous lumen.

Surgical thrombectomy refers to the use of open surgical techniques, including venotomy, to remove thrombus from the deep veins of the body.

Other Terms

Therapeutic-level heparin administration refers to the intravascular use of unfractionated heparin to raise the partial thromboplastin time (PTT) to 1.5 to 2.5 times control. *Subtherapeutic heparin* refers to the intravascular use of unfractionated heparin at lower doses to prevent pericatheter thrombosis (PTT < 1.5 times control).

Major bleeding is defined as intracranial bleeding or bleeding severe enough to result in death, surgery, cessation of therapy, or blood transfusion (7). *Minor bleeding* is defined as less severe bleeding manageable with local compression, sheath upsizing, and/or dose alterations of a pharmacologic thrombolytic agent, anticoagulant, or antiplatelet drug.

Progression of DVT is defined as imaging-proved extension of an existing DVT into at least one previously uninvolved venous segment.

Recurrent VTE is defined as the presence of a new proved PE or recurrent DVT in a patient with at least one prior episode of VTE.

Recurrent DVT is defined as imaging-proved DVT involving a new venous segment or a previously involved venous segment for which symptomatic and imaging improvement had been obtained in a patient with at least one prior episode of DVT.

Post-thrombotic syndrome (PTS) refers to a symptom complex that is commonly observed after one or more episodes of DVT. PTS is often characterized by limb edema, heaviness, pain, venous claudication, and limb hyperpigmentation, with a minority of patients developing severe manifestations such as venous ulceration.

PRETREATMENT ASSESSMENT

A careful medical history and directed physical examination will usually yield most of the information needed to determine the appropriateness of endovascular therapy. Patients should be queried about known VTE risk factors, details of prior VTE episodes and treatments, the duration and exact nature of preexisting and more recent limb symptoms, and common PE symptoms such as dyspnea, chest pain, palpitations, hemoptysis, and syncope. Identification of PE is important because systemic PE thrombolysis, surgical pulmonary thrombectomy, or endovascular pulmonary thrombectomy may be more appropriate for unstable PE patients and stable PE patients with echocardiographic right ventricular dysfunction ("submassive PE") (5,8).

Important comorbidities to identify

Table 1
Indications for Pharmacologic Catheter-Directed Thrombolysis

Indication*	Acceptable Bleeding Risk	Life Expectancy	Primary Goals
Phlegmasia cerulea dolens	Low-Moderate	Any	Limb salvage Survival
Acute/subacute IVC thrombosis	Low-Moderate	Any	PE prevention Preserve organs Symptom relief
Acute iliofemoral DVT	Low	Long	Prevent PTS
Acute femoropopliteal DVT	Low	Long	Prevent PTS
Subacute/chronic iliofemoral DVT	Low†	Long	Alleviate PTS Prevent PTS

* The suggested threshold for these indications is 95%.

† When thrombolytic therapy is being used.

include factors that might promote bleeding complications (such as active ongoing bleeding; previous or current intracranial disease; recent trauma, surgery, or percutaneous procedures; severe hepatic dysfunction; gastrointestinal bleeding history; and severe uncontrolled hypertension), pulmonary hypertension and other cardiopulmonary diseases, renal failure, and active infection. Prior to thrombolysis, patients with malignancies known to metastasize to the central nervous system should undergo brain imaging to exclude the presence of lesions that might bleed. The patient's medications and drug allergies should be reviewed, and particular note should be taken of medications that influence coagulation or platelet function. The patient's life expectancy and anticipated activity level are also important to factor into the global assessment of the patient's suitability for endovascular therapy.

Because VTE symptoms tend to be nonspecific, the clinical assessment should be supplemented with imaging confirmation. In patients with suggestive symptoms, the presence of PE is typically established with contrast-enhanced helical CT scanning or ventilation-perfusion scanning, although catheter angiography is occasionally needed.

The anatomical extent of DVT often influences decisions of whether to use endovascular therapy and can usually be determined noninvasively. In patients with calf swelling, compression duplex sonography can characterize

the extent of thrombus in the popliteal, femoral, and common femoral veins with high accuracy (9–11). The hallmark finding of DVT on duplex sonography is venous noncompressibility. Other findings may include visualized intraluminal material, absence of flow on augmentation, lack of respiratory variation, and/or incomplete color filling. One pitfall can occur when a duplicated femoral vein is present: DVT in the accessory vein may be missed if the duplication is not recognized (12). Duplex sonography has only 70% to 85% accuracy for calf vein thrombosis, but its presence rarely affects decisions of whether to use endovascular therapy (13–15). If thigh swelling is present or if the common femoral vein is abnormal on ultrasonogram, then imaging of the ilioacaval venous system may be performed to define the upper extent of the thrombus. Contrast-enhanced CT scanning, MR imaging, and duplex US are commonly used for this purpose. However, it must be noted that at the time of writing, no CT or MR imaging method of evaluating the ilioacaval veins had been validated for DVT diagnosis (16,17).

When endovascular therapy is planned, a baseline hematocrit, platelet count, INR, PTT, creatinine, and serum human chorionic gonadotropin level (in women of childbearing age) should be obtained prior to treatment. A preprocedure fibrinogen level, while not required, is also recommended to serve as a baseline for later comparison.

INDICATIONS AND CONTRAINDICATIONS

For any particular DVT patient, the decision to use endovascular therapy depends on a balanced assessment of the likelihood that the patient will experience treatment success, the degree to which this benefit would be clinically meaningful to the patient, and the likelihood that the patient will suffer a major complication. The challenge in making this clinical determination is heightened by the lack of conclusive randomized trial data that characterize the actual safety and efficacy of endovascular DVT interventions. Hence, at present, decisions concerning the use of endovascular DVT therapy should be highly individualized and based on a rigorous pretreatment assessment of the patient. The patient must be informed of all the risks of therapy, the possible lack of long-term benefits, and the existence of alternative treatment methods.

The evidence basis pertaining to the treatment of lower extremity DVT using pharmacologic catheter-directed intrathrombus thrombolysis (CDT) with adjunctive balloon angioplasty and/or stent placement is considered sufficient to support limited recommendations regarding thresholds for indications, success rates, and complications.

Indications for Treatment Using Catheter-Directed Thrombolysis

Acceptable indications for CDT for lower extremity DVT are described here and are summarized in **Table 1**. The suggested threshold for these indications is 95%.

1. **Phlegmasia cerulea dolens** in patients with low or moderate bleeding risk. The use of CDT for phlegmasia cerulea dolens is predicated on anecdotal evidence of immediate efficacy and the unsatisfactory performance of other therapies. Surgical thrombectomy can also be effective in rapidly restoring venous outflow but often results in incomplete thrombus removal, recurrent DVT, and systemic complications in these extremely ill patients (18). Multiple case reports and small series attest to the ability of CDT to provide limb salvage for these patients without exposing them to the risks of surgery (19,20). Given the high rates of

limb amputation and death observed with other therapies, the risks of CDT are clearly justified for most phlegmasia cerulea dolens patients (21). Patients thought to be at high risk for bleeding may be candidates for surgical thrombectomy. When phlegmasia cerulea dolens is present, endovascular or surgical thrombus removal should be performed on an emergency basis.

2. Acute or subacute IVC thrombosis causing moderate to severe pelvic congestion, moderate to severe limb symptoms, and/or compromise of venous drainage from visceral organs in patients with low or moderate bleeding risk. IVC syndrome can create major clinical problems beyond those experienced by patients with less extensive forms of DVT. First, the discomfort associated with acute IVC thrombosis can be quite severe, particularly when severe venous congestion involves the external genitalia. Second, extension of thrombus into the suprarenal IVC, renal veins, and/or hepatic veins can lead to acute renal failure or Budd-Chiari syndrome. Third, the presence of IVC thrombus can preclude the placement of an IVC filter for PE prophylaxis. For these reasons, treatment of IVC thrombosis via CDT is often justified to prevent PE, preserve visceral organ function, and obtain immediate symptom relief in patients at low or moderate bleeding risk. Patients thought to be at high risk for bleeding complications may be candidates for surgical thrombectomy.

3. Acute iliofemoral DVT in ambulatory patients with low bleeding risk and long life expectancy. Patients with acute iliofemoral DVT tend to be highly symptomatic and may be at particularly high risk for recurrent DVT, PTS, and late disability (22–24). CDT can remove venous thrombus, provide immediate symptom relief, and facilitate treatment of underlying venous stenoses (1).

The primary justification for using CDT to treat iliofemoral DVT is its potential to reduce the frequency and severity of PTS. This relationship has not been conclusively established but is supported by several compelling lines of indirect evidence: (a) Absence of venous thrombus on follow-up duplex ultrasonogram after an episode of DVT has been associated with a re-

duced rate of recurrent DVT, the major risk factor for PTS (25,26); (b) thrombus removal via surgical thrombectomy or systemic thrombolysis has been associated with reduced rates of PTS in randomized trials (27–31); (c) in a retrospective case-control study, acute iliofemoral DVT patients treated with successful CDT plus anticoagulation experienced reduced PTS and improved health-related quality of life at midterm follow-up compared with a matched control group who received anticoagulation alone (32); and d) a single-center randomized trial and another nonrandomized study found improved limb outcomes in iliofemoral DVT patients treated with CDT plus anticoagulation compared with patients who received anticoagulation alone at follow-up of 6 months and 5 years, respectively (33,34).

Therefore, CDT is an acceptable and possibly superior method of treating acute iliofemoral DVT in ambulatory patients with long life expectancy who are considered to be at low risk for bleeding. In patients at moderate or high risk of bleeding, surgical thrombectomy may be considered.

4. Acute femoropopliteal DVT in highly symptomatic ambulatory patients with low bleeding risk and long life expectancy. In patients with acute femoropopliteal DVT, the use of CDT is based on its potential to prevent or minimize PTS (35). This relationship has not been conclusively established, but earlier randomized trials of systemic thrombolysis did indicate a potential benefit in preventing PTS in these patients (27–29). The ability of CDT to remove venous thrombus and provide immediate symptom relief in patients with acute femoropopliteal DVT is similar to that observed in patients with acute iliofemoral DVT, but midterm venous patency rates have been lower in the femoropopliteal DVT patients (36). It must also be recognized that many femoropopliteal DVT patients do experience symptom resolution and have few or no manifestations of PTS when treated with anticoagulation and compression stockings alone (24,37,38).

Given the smaller margin for potential benefit, the lower observed midterm patency rates of CDT, and the risk of complications, the proper threshold for utilizing CDT in the

treatment of acute femoropopliteal DVT should probably be higher than that for more extensive forms of DVT. Patients with progression of DVT despite anticoagulant therapy and those with severe symptoms, long life-expectancy, and good performance status are the best candidates in this subgroup.

5. Subacute and chronic iliofemoral DVT in patients with moderate to severe pelvic and/or limb symptomatology and low bleeding risk. Because the iliac vein rarely recanalizes, patients with subacute or chronic iliofemoral DVT develop valvular reflux and have persistent venous obstruction, a combination that tends to be associated with the worst forms of PTS (39,40). For this reason, endovascular therapy is often used as a non-surgical alternative to venous bypass in highly symptomatic patients (41). In this setting, endovascular treatment is not expected to result in a normal limb, since it has usually sustained some degree of permanent venous damage. Instead, the primary goals of therapy are improvement in presenting symptoms, reduction of venous disability, and/or healing of existing venous ulcers. CDT rarely produces complete thrombolysis in subacute or chronic DVT patients and is instead typically used to complement stent placement or to remove the superimposed acute thrombus in patients with acute-on-chronic DVT. In many patients, particularly those in whom a predisposition to bleeding is identified during the pretreatment evaluation, stent placement may be performed without preceding CDT (42,43).

Although a minority of practitioners do report success using CDT to treat patients with isolated chronic femoropopliteal DVT, these patients constitute a comparatively poor anatomic subgroup for endovascular treatment (36). SIR encourages those practitioners who utilize endovascular therapy for chronic femoropopliteal DVT to frequently review their clinical treatment results and to alter their practices if the benefits cannot be shown to outweigh the risks incurred.

Contraindications to Endovascular Treatment

In general, CDT is contraindicated in any patient with a hemorrhagic dis-

Table 2
Contraindications to Pharmacologic Catheter-Directed Thrombolysis

Absolute Contraindications

Active internal bleeding or disseminated intravascular coagulation
Recent cerebrovascular event (including transient ischemic attacks), neurosurgery (intracranial, spinal), or intracranial trauma (< 3 months)
Absolute contraindication to anticoagulation
Strong Relative Contraindications
Recent cardiopulmonary resuscitation, major surgery, obstetrical delivery, organ biopsy, or major trauma (< 10 days); recent eye surgery (< 3 months)
Intracranial tumor, other intracranial lesion, or seizure disorder
Uncontrolled hypertension: systolic > 180 mm Hg, diastolic > 110 mm Hg
Recent major gastrointestinal bleeding (< 3 months)
Serious allergic or other reaction to thrombolytic agent, anticoagulant, or contrast media (not controlled by steroid/antihistamine pretreatment)
Severe thrombocytopenia
Known right-to-left cardiac or pulmonary shunt or left heart thrombus
Massive PE with hemodynamic compromise
Suspicion for infected venous thrombus
Other Relative Contraindications
Renal failure (serum creatinine > 2.0 mg/dL)
Pregnancy or lactation
Severe hepatic dysfunction
Bacterial endocarditis
Diabetic hemorrhagic retinopathy

order, an anatomical lesion that is prone to bleeding, or an absolute contraindication to anticoagulant therapy (7). A list of contraindications to CDT is provided in **Table 2**.

TREATMENT GUIDELINES

Venous Access

Venous access for endovascular DVT treatment should be obtained in percutaneous fashion in nearly all instances. Common sites include the popliteal veins, internal jugular veins, common femoral veins, and the tibial veins. Real-time ultrasound guidance

is highly recommended for internal jugular vein, popliteal vein, and posterior tibial vein punctures, because it provides visualization of adjacent arterial structures and minimizes the number of needle passes, leading to fewer access site bleeding complications (44). Common femoral vein access may be obtained using traditional manual palpation and puncture, although ultrasonography is still recommended when CDT is planned. The use of a micropuncture system is also highly recommended. If inadvertent puncture of a lower extremity artery occurs despite these precautions, a small dilator or sheath may be left in place in the artery during the thrombolytic infusion. Guide-wire and catheter manipulations must be carefully monitored with fluoroscopy.

In treating acute DVT using CDT, optimal results are expected when the entire thrombus-containing venous segment is treated. More than one venous access site is sometimes needed for this purpose. Clearance of thrombus from the popliteal vein often necessitates a tibial vein approach, adding to the complexity of the procedure. However, this extra effort is considered worthwhile in most instances because it improves inflow into the recanalized proximal venous segments and because it may help to preserve popliteal valve function (45).

Diagnostic Venography

Diagnostic venography represents the criterion standard imaging modality with which to image venous thrombus and should be routinely used to confirm the anatomical extent of DVT in patients undergoing CDT (13). The hallmark venographic finding of DVT is visualization of intraluminal filling defects. Other findings may include abrupt cut-off of a vein, lack of opacification, or intraluminal septations or webs. Venography of the lower extremity veins is typically performed via contrast injections through the diagnostic catheter, but this information may be supplemented as needed by traditional venographic images obtained after contrast injection through a pedal intravenous line.

Thrombolytic Drug Delivery

Once the need for CDT is confirmed, a vascular sheath is usually placed. For thrombolysis of acute proximal DVT, catheter-directed intrathrombus drug delivery through a multi-side-hole catheter/wire is the method of choice. Because the vast majority of CDT studies describe the use of continuous infusion for drug delivery, this approach is recommended (1). The use of daily pulse-spray infusions of thrombolytic drug into the thrombus through a multi-side-hole catheter is an alternative method of drug delivery (46). Systemic thrombolysis is associated with frequent bleeding complications and is not recommended for DVT treatment (47,48). Flow-directed thrombolysis can be useful when intrathrombus catheter placement cannot be achieved or as an adjunct to CDT, but the results of this technique have not yet been shown to differ substantially from those of systemic thrombolysis (49,50).

Choice of Thrombolytic Agent

There is no consensus on the optimal pharmacologic thrombolytic agent for endovascular DVT therapy. Streptokinase (administered systemically) is the only thrombolytic drug that has been approved by the U.S. FDA for DVT treatment, but its use is discouraged because of high rates of associated allergic reactions and bleeding complications (3). Urokinase and tissue plasminogen activator have received FDA approval for the treatment of PE, a different manifestation of VTE.

Urokinase, tissue plasminogen activator, reteplase, and tenecteplase have all been used successfully in small cohort studies reporting the use of CDT for DVT. Urokinase is the drug with which the greatest experience has been accumulated, and its safety and immediate efficacy have been concordant in single-center observational studies and a multicenter prospective registry (1,33,36,42,51–58) (**Table 3**). However, two comparative single-center experiences did not reveal major differences in safety or efficacy between urokinase and either tissue plasminogen activator (both studies) or reteplase (one study) (57,58). It must be noted that these studies did not possess the sta-

Table 3
Published Studies of Pharmacologic CDT for Acute DVT (>10 Patients)

Study	Year	Study Type	Patients (n)	Drug	Anatomical Success (%)	Clinical Success (%)	Major Bleeds (%)	Re-Thrombosis
Semba (1)	1994	Observational	21	UK	85	85	0	8% at 3 months
Bjarnason (51)	1997	Prospective Cohort	77	UK	79	79	7	24% at 1 month
Verhaeghe (78)	1997	Observational	25	TPA	76	76	24	21% at 1 month
Raju (52)	1998	Observational	24	UK	88	Not stated	8	Not stated
Mewissen (36)	1999	Prospective Registry	287 (473)	UK	83	Not stated	11	25% at 1 month
Patel (53)	2000	Observational	10	UK	100	100	0	10% at 1 month
O'Sullivan (42)	2000	Observational	39	UK	87	Not stated	0	6% at 1 month
Kasirajan (54)	2001	Observational	17	UK/TPA/RPA	82	82	0	24% at 12 months
Chang (46)	2001	Observational	10	TPA	100	100	0	10% at 6 months
Ouriel (60)	2001	Prospective Registry	11	RPA	91	Not stated	9	Not stated
Shortell (55)	2001	Observational	31	UK/TPA	80	Not stated	10	Not stated
AbuRahma (33)	2001	Prospective Controlled	51	UK/TPA	89	Not stated	11	6% at 1 month
Castaneda (61)	2002	Prospective Cohort	25	RPA	92	Not stated	4	Not stated
Vedantham (56)	2002	Observational	20	UK/TPA/RPA	89	82	14	Not stated
Razavi (62)	2002	Prospective Cohort	31	TNK	89	Not stated	6	Not stated
Elsharawy (34)	2002	Randomized Trial	35	SK	100	Not stated	0	Not stated
Sugimoto (57)	2003	Observational	54	UK/TPA	Not stated	85	0	Not stated
Grunwald (58)	2004	Observational	74	UK/TPA/RPA	98	Not stated	5	Not stated
Vedantham (59)	2004	Observational	18	RPA	100	96	6	9% at 1 month

RPA = reteplase; SK = streptokinase; TNK = tenecteplase; TPA = tissue plasminogen activator; UK = urokinase.

tistical power to exclude modest differences in success rates or complications between these agents. Hence, there are insufficient data with which to recommend one agent over another for CDT of DVT.

Commonly used dosing schemes for CDT of DVT have been primarily derived by extrapolation from studies performed in patients with peripheral arterial disease, supplemented by a few small dose-ranging studies that included DVT patients. Based on these studies and the clinical experiences of the committee members, use of the following initial continuous infusion doses are suggested for a typical patient with extensive unilateral lower extremity DVT not involving the IVC: urokinase 120,000 to 180,000 units/hour (1,33,36,42,51–58), tissue plasminogen activator 0.5 to 1.0 mg/hour (57,58), reteplase 0.25 to 0.75 units/hour (59–61), or tenecteplase 0.25 to 0.5 mg/hour (62). For best results, the drug should be diluted to allow infusion of higher fluid volumes (generally 25–100 mL/h), which maximizes dispersion of the drug within the thrombus. The use of a lacing dose or a “front-loaded” regimen in which a higher dose is used for the first few

hours of treatment is optional. Because the scientific basis underlying these guidelines is limited, physicians are encouraged to use individual judgment in adjusting doses based on individual patient considerations, including the clinical severity of the thrombotic process, the extent of thrombosis, and the estimated risk of bleeding.

Patient Monitoring during Thrombolysis

Patients receiving thrombolytic therapy require careful monitoring. In most clinical practices, this may occur in an intensive care unit or stepdown unit. Alternative arrangements are also acceptable but must include frequent patient contact by experienced nursing staff. Patients must be placed at bed rest and the catheter-bearing extremity should be relatively immobile. Many practitioners elevate the legs to facilitate venous drainage from the limb. Blood should be drawn for serial monitoring of hematocrit, platelet count, and PTT (if heparin is used) every 6 to 8 hours. Arterial punctures and intramuscular injections are contraindicated during thrombolysis. If a dire

clinical emergency necessitates an arterial puncture during or immediately after the thrombolytic infusion, a small catheter can be left in place in the artery temporarily and diligent attention should be paid to hemostasis at the puncture site.

Many practitioners attempt to identify patients at risk for bleeding complications by monitoring serial fibrinogen levels. This approach is based on common anecdotal experiences of many interventionalists tempered by suggestive evidence from studies of patients with peripheral arterial occlusion (63). Based on this evidence, although a conclusive relationship between fibrinogen levels and the development of bleeding complications has not been scientifically established, the consensus opinion of the committee members is that serial monitoring of fibrinogen levels during venous CDT does help to prevent complications. However, because bleeding complications are also observed in patients who are not fibrinogen depleted, practitioners are cautioned against excessive reliance on fibrinogen levels to the exclusion of other potential markers of impending bleeding, such as marked pericatheter oozing, minor sentinel

bleeds (eg, epistaxis), and elevated PTT levels.

Concomitant Anticoagulant Therapy

The use of concomitant administration of intravenous unfractionated heparin during CDT of DVT is recommended based on empirical data from the published literature. However, there are no scientific studies that directly address the question of heparin dosing for any thrombolytic agent. The optimal heparin dosing during CDT may differ among the different thrombolytic agents due to their individual biologic properties. Pending future studies, the consensus opinion of the committee members is that therapeutic-level heparin may be appropriate for most patients receiving urokinase, and that subtherapeutic-level heparin may be appropriate for most patients receiving alteplase, reteplase, and tenecteplase. The use of concomitant infusion of a glycoprotein IIb/IIIa inhibitor during CDT of DVT (instead of heparin) has also been reported in a small series, but insufficient data exist to comment on its potential utility (64). The use of low molecular weight heparin during DVT thrombolysis has not been studied.

Adjunctive Thrombus Removal Techniques

In patients undergoing CDT, follow-up venograms are typically obtained every 8 to 24 hours after the infusion is initiated. At this time, the infusion catheter can be repositioned to concentrate the thrombolytic agent in the areas that contain residual thrombus. The committee encourages the use of relatively short infusions to reduce the risk of bleeding complications. If prolonged infusions are required, more careful patient monitoring is recommended.

At each follow-up check, one or more of the following methods may be used to increase the surface area of residual thrombus and thereby accelerate the thrombolytic process: PMT devices, balloon maceration, or aspiration thrombectomy (65,66). Although these methods are thought by many to enable safer treatment with lower administered dose and treatment time, this has not been scientifically estab-

lished and an evidence-based endorsement of these techniques cannot therefore be provided. If a PMT device is used, a two safety issues should be borne in mind. First, the use of some PMT devices or balloon maceration may be more likely to produce clinical PE if they are not used in conjunction with a pharmacologic thrombolytic drug, which has preferably circulated for at least 6 to 12 hours (66,67). If a contraindication to pharmacologic CDT is present, then use of a retrievable IVC filter may be considered to prevent PE during treatment. Second, PMT devices may cause hemolysis, hemoglobinuria, and/or changes in fluid balance; this should be monitored and fluids or blood replaced accordingly.

Balloon Angioplasty and Stents

Catheter-directed thrombolysis enables detailed evaluation of the underlying vein to be performed during and after endovascular thrombus removal. Although there are no controlled studies that prove that endovascular treatment of obstructive lesions is beneficial, restoration of continuous venous flow may include the need for balloon angioplasty or stent placement to treat flow-limiting obstructive lesions after CDT in several situations:

1. **Iliocaval venous stenosis** thought to be flow-limiting. Although the precise degree of anatomic or hemodynamic abnormality that correlates with clinically significant venous obstruction has not been scientifically established, commonly used venographic criteria include anatomic diameter narrowing, visualization of flow stasis during injection, and opacification of collateral veins (68). Intravascular sonographic demonstration of intraluminal webs and extrinsic compression may also be helpful in certain instances (69).

Stents are preferred over balloon angioplasty for the treatment of iliac vein obstructive lesions because the fibrotic nature of venous stenosis often results in elastic recoil after balloon angioplasty (70). Also, in many cases, it is unclear whether a residual iliac vein obstructive lesion represents stenosis, residual thrombus, or a combination. Because stents expand the vein and trap residual thrombus against its

walls, they tend to be effective for lesions of either type.

It has traditionally been considered desirable to avoid placing stents within vascular segments that span mobile areas such as the hip joint. In clinical practice, however, it is often necessary to extend stents into the common femoral vein to achieve treatment success (42). Animal studies and clinical experience with human implantations indicate that common femoral vein stent placement is safe, and this is therefore considered acceptable practice (42,43,71). When stents are extended into the common femoral vein, the use of currently available self-expandable stents is preferred due to their longitudinal flexibility (71).

2. **One commonly encountered lesion is stenosis of the left common iliac vein in patients with left-sided iliofemoral DVT.** When observed in the absence of a compressing mass or other clear anatomical risk factor, this is often referred to as May-Thurner syndrome (72). The spur-like stenosis observed is thought to develop in response to chronic irritation of the left common iliac vein by the crossing right common iliac artery. Thrombosis often ensues when an inciting factor is present, such as a hypercoagulable disorder, recent trauma, or the initiation of oral contraceptive therapy. Multiple case reports and small series attest to the ability of CDT with subsequent stent placement to provide effective treatment for these patients with low rates of early rethrombosis (42,53). The differing early rethrombosis rates between previous surgical methods (in which the stenosis was not treated) and modern endovascular and surgical methods (in which stent placement is performed) provide support for the practice of aggressively treating flow-limiting venous stenoses (73).

2. **Femoropopliteal venous stenosis** thought to be flow-limiting. Because stents have not been extensively evaluated for treatment of femoral vein stenosis, balloon angioplasty is generally preferred for such lesions. Stent placement in the popliteal vein is not recommended (36).

3. **Residual infrarenal ilio caval venous thrombus** involving a short segment. As stated above, many iliac vein or IVC lesions identified after CDT have an indeterminate character in

terms of whether they represent stenosis or residual thrombus. For certain patients with residual thrombus involving a short segment of the iliac vein or IVC, the risks of stent placement may be preferred over the risks of continued thrombolytic infusion (59). Although this may be appropriate, there are no controlled data with which to firmly endorse this approach at present.

Periprocedural Use of Inferior Vena Cava Filters

The incidence of clinical PE during pharmacologic CDT does not appear to exceed that observed in patients who receive anticoagulant therapy alone (36). One potential explanation for this observation is that any small thrombus fragments released by catheter manipulations are simply dissolved by the circulating thrombolytic drug. In one randomized trial, placement of permanent IVC filters in anticoagulated patients with a first DVT episode doubled the rate of recurrent DVT and did not improve the 2-year survival rate (74). This study, while not directly applicable to DVT patients undergoing CDT, highlighted the potential long-term consequences of filter placement in VTE patient populations. Hence, routine placement of permanent IVC filters in patients undergoing CDT for DVT is not likely to be beneficial and may be harmful in the long run.

In making decisions regarding placement of retrievable IVC filters, the potential benefits must be balanced with the risks and costs inherent to filter placement and removal. Placement of a retrievable IVC filter may be a good compromise solution for certain patient subsets at particularly high risk of major morbidity due to clinical PE during CDT, such as patients with poor cardiopulmonary reserve and patients treated with PMT without concomitant pharmacologic CDT (75). Once CDT is completed, the filter can be removed as long as significant residual thrombus is not present within the filter or in the treated venous segments. However, it must be noted that insufficient data are present for meaningful evaluation of the use of retrievable filters in this setting.

IMMEDIATE POST-PROCEDURE FOLLOW-UP CARE

After thrombolysis is discontinued, the patient is typically given anticoagulation to therapeutic levels using unfractionated heparin. The use of low molecular weight heparins immediately after thrombolysis has not been studied. If unfractionated heparin is used, it may be either continued or halted briefly before venous sheath removal, but complete reversal of its effects is generally not desirable. If heparin is discontinued to permit sheath removal, it may be restarted soon after hemostasis is obtained. If anatomical success was obtained, significant improvement in symptoms can be expected over the course of the next 3 to 5 days. If anatomical success was achieved but clinical success is not apparent, then repeat imaging of the venous system may be indicated to evaluate for early rethrombosis. Many patients can be transitioned to long-term anticoagulant therapy as outpatients using a short course of low molecular weight heparin as a bridge.

LONG-TERM FOLLOW-UP CARE

Patients treated for DVT with endovascular thrombus removal must have diligent long-term clinical follow-up for the best clinical outcomes to be obtained. Two major elements of standard DVT care should be instituted. One element is transition to outpatient therapy with a vitamin K antagonist, a low molecular weight heparin, or another appropriate anticoagulant (5). Appropriate INR monitoring must be arranged when vitamin K antagonists are used. The other element is use of graduated compression stockings to prevent PTS (37,38). If a stent was placed, use of an antiplatelet agent for 1 to 3 months may be appropriate, although there are no scientific data to support this practice. Hematologic testing for an underlying thrombophilic condition is an important part of postprocedure care and is appropriate in young DVT patients (< 50 y) and in patients with recurrent DVT despite anticoagulant therapy, DVT in an unusual site (eg, cerebral or mesenteric vessels), unexplained recurrent fetal loss, DVT during pregnancy or during

the first year of oral contraceptive therapy, or a family history of DVT (two or more first-degree relatives with DVT) (76).

During follow-up, significant changes in daily symptom pattern should prompt rapid clinical evaluation and/or imaging of the venous system to evaluate for restenosis or recurrent DVT. If rethrombosis has occurred, then selected patients may be retreated with repeat CDT if there is no contraindication. If restenosis has occurred, retreatment using balloon angioplasty or placement of additional stents may often be performed.

SUCCESS RATES

The major goals of endovascular DVT therapy for acute DVT are several: (a) elimination of thrombus and re-establishment of venous patency; (b) provision of immediate symptom resolution; (c) prevention of recurrent DVT, valvular dysfunction, and PTS; (d) prevention of PE; and (e) preservation of limb and visceral organ function.

There currently exist no large multicenter randomized trials that have quantified the actual efficacy of CDT for DVT. Analysis of the available literature is limited by marked heterogeneity of patient cohorts in terms of DVT risk factors, age, gender, extent of DVT, duration of symptoms, thrombolytic drug used, specific methodology of treatment, and method of endpoint evaluation. Anatomical success has been defined in published studies as either restoration of in-line flow with venous patency, or removal of 50% or more of the thrombus burden (complete plus partial thrombolysis). In most studies, clinical success has been defined as the presence of anatomical success and significant improvement in presenting symptoms.

A pooled analysis of 19 published peer-reviewed studies in which patients with acute DVT were treated with pharmacologic CDT with or without PMT was performed (Table 3) (1,32–34,42,46,51–62,77,78). Studies describing endovascular treatment of fewer than 10 patients, predominantly chronic DVT populations, or the use of stand-alone PMT without pharmacologic CDT were excluded. The populations studied included 1046 patients with mean age 46 years (range, 14–94 y), of

Table 4
Success Rates of Pharmacologic Catheter-Directed Thrombolysis

Success Measure	Reported Range (%)	Pooled Mean (%)	Suggested Threshold (%)
Anatomical success* (acute and chronic DVT)	61–100	88	75
Anatomic success (acute DVT only)	81–100	92	80
Immediate clinical success (acute and chronic DVT)	76–100	85	75
Early rethrombosis† (at 30 days)	6–25	20	30

* Populations with greater proportions of chronic DVT patients are expected to have less favorable results, and these thresholds should be adjusted accordingly.

† The rate of early rethrombosis is expected to vary according to the risk profiles of different DVT populations, and these thresholds should be adjusted accordingly.

Table 5
SIR Classification of Complications by Outcome

Minor Complications
No therapy, no consequence
Nominal therapy, no consequence; includes overnight admission for observation only.
Major Complications
Require therapy, minor hospitalization (<48 hours)
Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours)
Permanent adverse sequelae
Death

Table 6
Complications of Pharmacologic Catheter-Directed Thrombolysis

Complication	Reported Range (%)	Pooled Mean (%)	Suggested Threshold (%)
Death	0–1	0.3	1
Intracranial bleed	0–1	0.2	1
Major bleed	0–24	8.3	15
Symptomatic PE	0–1	0.9	2
All major complications	0–24	9.3	18

which 58% were female (range, 33–100%). Acute DVT (including acute DVT superimposed on chronic DVT) was treated in 88% (range, 50–100%) of the reported patients. Most patients (66%) treated had iliofemoral DVT. The following thrombolytic drugs were used for catheter-directed infusion: urokinase (75%), tissue plasminogen activator (12%), reteplase (8%), tenecteplase (3%), and streptokinase (2%). Adjunctive PMT was used in 6% of patients. Stents were placed in 46% of patients and IVC filters were placed periprocedurally in 1% of patients.

Anatomical success and/or immediate clinical success were analyzed for 860 limbs. Anatomical success defined as restoration of venous patency

was observed in 88% (range, 76–100%) of patients. Anatomical success defined as greater than 50% thrombus removal was also observed in 88% (range, 61–100%) of patients. In studies that reported results separately for acute DVT versus chronic DVT, anatomical success was observed in 92% (range, 81–100%) of acute DVT patients. The degree of thrombolysis observed was complete (> 95% clot removal) in 44%, partial (50–95% clot removal) in 44%, and minimal/none (< 50% clot removal) in 12%. Immediate clinical success was observed in 85% (76–100%) of patients. The frequency of rethrombosis was 20% (range, 6–25%) in studies reporting on this parameter. Based on this analysis,

the suggested threshold values for early success of CDT in acute DVT populations are presented in **Table 4**.

Insufficient data are present with which to establish evidence-based standards for the incidences of late recurrent DVT, valvular dysfunction, PTS, and other measures of long-term treatment success. It is hoped that future versions of this document will be able to present evidence-based recommendations for these parameters.

COMPLICATIONS

Complications are stratified on the basis of outcome, per SIR reporting standards (**Table 5**). Published rates for individual types of complications are highly dependent on patient selection and may therefore vary from those reported in the literature. It is also recognized that a single complication can cause a rate to cross above a complication-specific threshold when only a small volume of patients are treated, for example early in a quality improvement program. In this situation, the overall major complication threshold may be more appropriate to use. The rates and thresholds presented here reflect a pooled analysis of 19 available published studies, as described in the previous section.

Major bleeding is the most frequent major complication of CDT and is observed in approximately 8% of patients undergoing treatment. However, it must be noted that the range of major bleeding rates (0–24%) is relatively wide, presumably due to differences in the respective patient populations, small sample size in the single-center studies, and variability in reporting criteria. For this reason, a threshold value of 15% is suggested for this parameter.

Intracranial bleeding, retroperitoneal bleeding, PE, and death represent the most clinically significant complications of CDT. However, analysis of the published literature indicates that each of these complications is rare. Suggested thresholds for these indicators and for the overall major complication rate are presented in **Table 6**.

CONCLUSION

The use of endovascular methods to treat lower extremity DVT is feasible and has shown potential to speed

symptomatic relief and prevent PTS-related disability. The quality improvement guidelines presented here are intended to improve the interventionalist's ability to coordinate the patient selection process, to perform these procedures in the safest possible manner, and to obtain the best clinical results.

Acknowledgments: Dr. Suresh Vedantham authored the first draft of this document and served as topic leader during the subsequent revisions of the draft. Drs. John F. Cardella and Robert Morgan chair the Standards of Practice Committees for SIR and CIRSE, respectively. Dr. David Sacks is Councilor of the SIR Standards Division. All other authors are listed alphabetically. Other members of the Standards of Practice Committee and SIR who participated in the development of this clinical practice guideline are (listed alphabetically) Gangi Afshin, Prof. MD, PhD, John "Fritz" Angle, MD, Curtis W. Bakal, MD, Stephen Balter, PhD, Timothy W.I. Clark, MD, MSc, Patricia E. Cole, PhD, MD, Peter Drescher, MD, Neil J. Freeman, MD, Jeffrey D. Georgia, MD, Debra Ann Gervais, MD, S. Nahum Goldberg, MD, Ziv Haskal, MD, David M. Hovsepian, MD, Neil M. Kilnani, MD, Sanjoy Kundu, MD, Curtis A. Lewis, MD, MBA, Patrick C. Malloy, MD, J. Kevin McGraw, MD, Philip M. Meyers, MD, Kenneth Murphy, MD, Albert A. Nemcek, Jr., MD, Reed Ali Omary, MD, MS, Jean-Pierre Pelage MD, PhD, Goffette Pierre, MD, Anne C. Roberts, MD, Gary P. Siskin, MD, Harry R. Smouse, MD, Thomas M. Vesely, MD, Louis K. Wagner, PhD.

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The clinical practice guidelines of the Society of Interventional Radiology attempt to define practice principles that generally should assist in producing high-quality medical care. These guidelines are voluntary and are not rules. A physician may deviate from these guidelines as necessitated by the individual patient and available resources. These practice guidelines should not be deemed inclusive of all proper methods of care or exclusive of other methods of care that are reasonably directed toward the same result. Other sources of information may be used in conjunction with these principles to produce a process leading to high-quality medical care. The ultimate judgment regarding the conduct of any specific procedure or course of management must be made by the physician, who should consider all circumstances relevant to the individual clinical situation. Adherence to the SIR Quality Improvement Program will not assure a successful outcome in every situation. It is prudent to document the rationale for any deviation from the suggested practice guidelines in the department policies and procedure manual or in the patient's medical record.

CME TEST QUESTIONS

The following Questions 1–3 are based on both articles in this issue by Vedantham et al; question 4 refers specifically to the second article. Examination available at <http://directory.sirweb.org/jvircme>

1. The Revised CEAP Classification of Chronic Lower Extremity Venous Disease is based on all of the following factors *except*:
 - a. Clinical signs of chronic venous insufficiency
 - b. Etiology
 - c. Anatomic distribution of involvement
 - d. Pathologic findings on skin biopsy

2. Which of the following has not been proven to be an independent risk factor for deep venous thrombosis (DVT)?
 - a. Prior history of DVT
 - b. Recent surgery or trauma
 - c. Iliac vein stenosis
 - d. Malignancy

3. Deep veins of the thigh include which of the following?
 - a. Superficial femoral vein and deep femoral vein
 - b. Greater saphenous vein and deep femoral vein
 - c. Sural veins and deep femoral vein
 - d. Femoral vein and deep femoral vein

4. Based on current Society of Interventional Radiology recommendations (*J Vasc Intervent Radiol* 2005;16[1]:1–4), all of the following scenarios are considered acceptable indications for catheter-directed thrombolysis for lower extremity deep venous thrombosis *except*:
 - a. Forty-year-old woman with metastatic angiosarcoma to the cerebellum who develops phlegmasia cerulea dolens
 - b. Fifty-year-old man with a 3-week history of inferior vena cava thrombosis causing hepatic venous outflow obstruction, resulting in ascites and moderate elevation of INR to 1.5
 - c. Thirty-year-old, otherwise healthy woman who develops acute iliofemoral deep venous thrombosis due to May-Thurner syndrome.
 - d. Twenty-year-old man with Factor V Lieden mutation and recent (3 weeks ago) knee surgery who develops phlegmasia cerulea dolens.