Acute Deep Vein Thrombosis Cases in the Real World

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Abstract

Keywords

- deep vein thrombosis (dvt)
- postthrombotic syndrome (pts)
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- catheter-directed thrombolysis (cdt)
- pharmacomechanical cdt (pcdt)
- venous thromboembolism (vte)

Practicing interventional radiologists (IRs) are routinely faced with challenging decisions that pertain to the management of patients with acute deep vein thrombosis (DVT). In this article, we describe five questions that are commonly posed by interventionalists and discuss both the indirect published evidence as well as our own experience in dealing with these issues. Our aim is to address procedural and, perhaps more importantly, nonprocedural-related knowledge domains with which the IR physician is less familiar and are often not directly addressed by published data or evidence-based clinical practice guidelines. This discussion is meant to facilitate a stronger understanding of the published literature as it pertains to the justifiable indications for endovascular thrombolytic therapy, the optimal use of anticoagulant therapy, and the reasonable use of adjuncts such as inferior vena cava filters and elastic compression stockings. Our goal is to provide a framework for practicing IRs to help them make the best clinical decisions for their individual patients and, ultimately, achieve optimal DVT treatment outcomes.

Objectives: Upon completion of this article, the reader should be able to list the current evidence, published literature, and the on-going challenges that pertain to the management of patients with acute deep vein thrombosis (DVT).

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Practicing interventional radiologists are routinely faced with challenging decisions pertaining to the management of patients with acute deep vein thrombosis (DVT). These questions may encompass both procedural and nonprocedural knowledge domains with which the physician is less

familiar and often are not directly addressed by published data or evidence-based clinical practice guidelines. In this article, we describe five questions that are commonly posed by interventionalists who care for patients with DVT. We describe the indirect published evidence that may bear on these issues, with the goal of providing the interventional radiologist with a stronger framework from which to make the best possible decisions for individual patients.

Clinical Question 1

"I was recently referred a 25-year-old man with a first-episode left lower extremity DVT that involved only the femoral vein and popliteal vein. The lower extremity pain and swelling began approximately 8 days previously. The common femoral vein and iliac vein were not involved. Is this a good indication for catheter-directed thrombolytic therapy?"

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Answer and Discussion

For any DVT patient, the decision to use endovascular therapy hinges on a balanced assessment of several key factors to determine the patient's likelihood of treatment success. The anatomical extent of thrombosis, the clinical severity of DVT manifestations, and the patient's projected risk of experiencing a bleeding complication must be assessed and weighed.^{1,2} The presence of comorbidities and the patient's baseline activity level, ambulatory capacity, and life expectancy should all be considered in determining a patient's suitability for aggressive DVT therapy.

A first observation to be made in this scenario is that this patient's DVT is limited to the femoropopliteal venous segments. Although any patient with proximal DVT is at risk for developing the postthrombotic syndrome (PTS), the available literature suggests that most patients with femoropopliteal DVT do well with a combination of anticoagulant therapy and elastic compression stockings.³⁻⁶ Ultrasound studies have shown that most anticoagulated patients with femoropopliteal DVT ultimately experience venous recanalization, although valvular reflux may develop.⁷ Also, the studies^{8,9} comparing endovascular thrombolysis plus anticoagulation versus anticoagulation alone had methodological limitations and largely focused on patients with acute iliofemoral DVT (IFDVT, defined as DVT involving the iliac vein and/or common femoral vein).^{10,11}

Therefore, given the small risk of bleeding complications with thrombolytic therapy and the lack of published data confirming the presence of a patient benefit, the clinical threshold for intervening in this scenario should be high. Specifically, assuming the patient does not have acute limb-threatening circulatory compromise, three questions should be asked: (1) Is the patient entirely free of identifiable risk factors for bleeding and other comorbidities that would increase the risk of procedure-related complications? (2) Is the patient experiencing severe lower extremity pain, swelling, and/or inability to ambulate despite the use of therapeutic-level anticoagulant therapy for at least 3 to 5 days? (3) Is the patient actively requesting that a more aggressive approach be taken? In general, only if the answer to all three questions is yes should endovascular thrombolytic therapy be offered to the patient. If it is offered, the informed consent process should include a balanced discussion of the possible benefits, the possible lack of benefits, the risks, and alternatives including that of simply switching to another anticoagulant regimen. For example, in some patients, the use of low molecular weight heparin (LMWH) monotherapy for a prolonged period may be effective in relieving persistent symptoms of acute DVT, presumably due to the anti-inflammatory properties of these agents and the more consistent anticoagulant effect they provide compared with oral warfarin therapy.

It is important to note that patients with asymptomatic DVT, isolated calf DVT, or chronic femoropopliteal DVT are poor thrombolysis candidates. The first two categories of patients do not develop life-limiting PTS at a rate that outweighs the risks of an aggressive approach, and catheter-

directed thrombolysis is ineffective for removal of organized thrombus.^{12,13}

Finally, it is important to remember that the equation is likely to be substantially different for patients with acute IFDVT. These patients have been shown to experience a higher rate of recurrent DVT, PTS, and late disability than patients with DVT of lesser anatomical extent.¹⁴⁻¹⁶ Although there is as yet no adequately designed study that has definitively shown endovascular thrombolysis to be of benefit, the preponderance of the available data supports its judicious use in this population. In particular, four separate studies (each with key methodological limitations) have been concordant in finding reduced PTS and/or improved quality of life (QOL) with the use of endovascular thrombolysis.^{8,9,17,18} Therefore, the guidelines of the American College of Chest Physicians,¹⁹ the American Heart Association (AHA),¹¹ and the Society of Interventional Radiology (SIR)^{1,20} all suggest that it may be reasonable to offer selected patients with acute IFDVT endovascular thrombolysis as first-line adjunctive therapy.

Of note, both patients with IFDVT and those with DVT limited to the femoropopliteal venous segments are included in two ongoing multicenter randomized trials that are evaluating the use of catheter-directed thrombolysis (CDT) and pharmacomechanical CDT (PCDT) for PTS prevention in patients with proximal DVT.^{21,22} Therefore, within several years, the risk-benefit ratio of CDT/PCDT in these two different cohorts should be better understood.

Clinical Question 2

"I just completed catheter-directed thrombolysis in a patient with proximal DVT. For how long should I continue my patient on anticoagulant therapy?"

Answer and Discussion

The optimal duration of anticoagulation for DVT has been the subject of extensive study in contemporary randomized trials. In practice, this decision is made by balancing the estimated risks of recurrent venous thromboembolism (VTE) against those of treatment-induced bleeding complications in the individual patient.¹⁹ It is accepted that nearly a third of patients with symptomatic DVT will present with recurrent VTE episodes at some future date.³ A key concept for interventional radiologists to understand is the fact that patients who develop a DVT due to a major provocation such as recent major surgery or major trauma are much less prone to develop recurrent VTE than patients who develop DVT in the course of normal daily living ("unprovoked DVT").²³⁻²⁶ This distinction carries important implications regarding disease prognosis and treatment duration. When considering the optimal treatment duration for anticoagulant therapy for DVT, most patients may be grouped into one of three main categories¹: first-episode DVT related to a major reversible risk factor (i.e., recent surgery or trauma),² recurrent DVT or unprovoked DVT,³ and DVT in patients with cancer.

In most patients with first-episode DVT related to a major reversible risk factor, anticoagulation may be safely stopped after 3 months.^{19,27-30} However, in actual clinical practice, one

finds that treatment is often extended to 6 months for proximal leg or pelvic DVT. Reassessment of the transient, provoking risk factor can then be made and treatment altered accordingly.

In the absence of known reversible risk factors, patients with recurrent DVT or unprovoked DVT should be considered for treatment of indefinite duration, with periodic reassessment of the risk and benefit of anticoagulation.^{31–35} This is largely based on data from the randomized PREVENT (Prevention of Recurrent Venous Thromboembolism) Trial, in which indefinite-duration warfarin was compared with placebo in patients with idiopathic VTE who had received 6 months of anticoagulation before randomization.³² This trial was terminated early because of a highly significant (64%) reduction in recurrent VTE among the patients receiving long-term warfarin.

For most cancer patients with DVT, first-line therapy should be weight-based LMWH for at least 3 to 6 months, or for as long as the cancer or its treatment (e.g., chemotherapy) is ongoing. This is based on randomized trial data that clearly demonstrate LMWH to be superior to oral warfarin in preventing recurrent VTE.^{36–38}

The use of direct thrombin inhibitors for the initial and long-term treatment of DVT has also shown significant promise, with one study suggesting that dabigatran may provide comparable outcomes to warfarin therapy.³⁹ Although as of this writing no direct thrombin inhibitors are approved by the U.S. Food and Drug Administration for the treatment of DVT, several clinical trials are in progress.

Recent studies suggest using ultrasound findings of residual thrombus to determine whether to continue anticoagulation beyond 3 to 6 months may reduce recurrent VTE in patients with proximal DVT.^{40–42} Specifically, Palareti et al reported a reduction (12% versus 17%) in recurrent VTE events in one trial testing such an approach. Another tool that may aid the decision process (and that is less costly than ultrasound) is the D-dimer test. Data from the multicenter PROLONG Study show that patients with an abnormal D-dimer level 1 month following discontinuation of anticoagulation have a significantly increased risk of recurrent VTE, which is reduced by the resumption of anticoagulation.⁴³

The preceding information is given to provide the interventional radiologist with a context within which to place decisions on anticoagulant therapy in patients who have undergone endovascular thrombolytic therapy for DVT. It should be noted that observational studies have noted high rates of early rethrombosis following CDT. In one pooled analysis of 19 published peer-reviewed CDT studies, the mean frequency of rethrombosis at 30 days follow-up was 20% (range: 6 to 25%).¹ However, in prospective studies, the rate of recurrent DVT after CDT/PCDT has been quite low. For example, a single-center randomized trial found recurrent DVT to be reduced with use of CDT/PCDT plus anticoagulation compared with anticoagulation alone (2.3% versus 14.8%; $p = 0.003$).¹⁸ This apparent discrepancy may reflect the fact that patients in randomized trials are more likely to have garden-variety first-episode DVT, whereas patients who receive CDT/PCDT in clinical practice (and who are reported in observational studies) tend to be referred for aggressive therapy

only when there is physician concern about greater thrombus extent (IFDVT) or lack of response to initial anticoagulant therapy.

It must be presumed that catheter manipulations create venous endothelial trauma that is a potent procoagulant factor. There currently exist no data comparing different anticoagulant strategies in the early weeks and months after CDT. However, the authors often leave CDT recipients on LMWH for a longer period of time (several weeks) prior to converting to warfarin. This approach may be influenced by other factors including the quality of the anatomical result obtained. Whatever approach is chosen, it is imperative for the interventional radiologist to ensure that the patient remains fully therapeutic on some form of anticoagulation during the early weeks after CDT when his or her care is being transitioned back to a primary medical physician.

Clinical Question 3

“Should I use fully therapeutic heparin or “subtherapeutic” heparin dosing during CDT/PCDT?”

Answer and Discussion

Before and after CDT/PCDT, patients should receive therapeutic-level anticoagulation with similar dosing, monitoring, and duration as DVT patients who are not undergoing thrombolysis.¹⁹

During CDT infusions, however, many physicians have evolved toward the use of reduced-dose unfractionated heparin (UFH) over therapeutic-level UFH. We believe that this practice is reasonably supported by indirect findings from clinical studies. First, in arterial thrombolysis trials, a supra-therapeutic UFH level has been shown to correlate with thrombolysis-related bleeding.^{44,45} In one study in which recombinant urokinase was the thrombolytic drug, the target UFH level was reduced to a subtherapeutic level midstudy, and a reduction in major bleeding events was subsequently observed.⁴⁵ In contrast, a relatively low rate of major bleeding was observed in an article reporting findings from the first 100 patients randomized in the CaVenT Trial, in which reduced-dose UFH was used along with recombinant tissue plasminogen activator (rt-PA) CDT for proximal DVT.²¹ The use of subtherapeutic UFH during DVT thrombolysis is supported by current guidelines of the AHA and the SIR.^{1,11} The optimal UFH dosing during CDT may also differ among the different thrombolytic agents due to their individual biological properties. That said, there are no scientific studies that specifically address the question of UFH dosing for any particular thrombolytic agent or technique.

It should be noted that the optimal degree of anticoagulant effect may differ substantially for patients who are being treated with a strategy of single-session PCDT. In this situation, the catheter and device manipulations tend to be more robust and the procedure itself may last for anywhere between 1 and 3 hours. Because greater endothelial damage may occur, and as the potential for thrombus migration and embolization may be slightly higher, we generally use fully therapeutic UFH during single-session PCDT and, for that

matter, at follow-up sessions after infusion CDT in which adjunctive techniques are used. If all of the thrombus is not removed at the session and an overnight infusion is needed, the UFH dose is reduced to subtherapeutic levels. It may be particularly important to fully anticoagulate the patient in low-inflow situations, such as when the popliteal vein and/or its major tributaries are thrombosed.

The use of LMWHs and antiplatelet therapies during or after DVT thrombolysis has not been directly studied. We and others have used LMWH as a substitute for UFH during PCDT and anecdotally have not noticed any reduction in anticoagulant efficacy. We believe this practice is safe even during continuous rt-PA infusions because even though LMWH will result in fully therapeutic anticoagulation its use is not associated with the broader and unpredictable swings in partial thromboplastin times that are often observed with the use of UFH.

Clinical Question 4

“Should I place a retrievable inferior vena cava filter (IVC) filter for periprocedure pulmonary embolism (PE) prevention prior to performing CDT or PCDT?”

Answer and Discussion

In a large prospective registry of 473 proximal DVT patients undergoing infusion CDT (without percutaneous mechanical thrombectomy), symptomatic PE occurred in only six patients (1.3%), of whom one died (0.2%).¹³ The relative rarity of major PE in CDT recipients may partly arise from the ability of the thrombolytic drug to quickly dissolve any circulating thrombus fragments. When one considers that two thirds of the patients in the registry just described had IFDVT, the 1.3% PE rate is not likely to be substantially higher than the PE rate that would have been observed in a similar cohort of patients who received anticoagulation alone. Therefore, given that IVC filters impose costs and risks such as migration and late recurrent DVT, we do not advocate IVC filters for most patients undergoing traditional infusion CDT.^{46–48}

However, for patients being treated with single-session PCDT methods (which can involve more upfront clot manipulation), there are sparse data to support or refute the use of IVC filters; limited evidence suggests that major PE can occur as a PCDT complication.^{49–51} Therefore, it may be reasonable to use a retrievable IVC filter prior to initiation of single-session PCDT, especially when ilio caval thrombus is present. This decision may be further individualized by considering the patient's overall clinical status, with a lower threshold for IVC filter utilization used in patients with pulmonary hypertension or other cardiopulmonary comorbidities. When an IVC filter is placed, it is imperative that the interventional radiologist share in the responsibility for ensuring that it is removed at the first clinically appropriate opportunity.¹¹

Clinical Question 5

“After performing CDT for a 30-year-old woman with iliofemoral DVT, I saw her in follow-up at 1 month. She says that

she bought a pair of compression hose at the local medical supply store. She is asking how often she should wear the stockings. How should I advise her?”

Answer and Discussion

Graduated elastic compression stockings (ECS) are considered a mainstay treatment in the management of acute DVT and prevention of PTS.¹⁹ By augmenting the calf muscle pump, ECS effectively reduce the cross-sectional area of the limb, leading to increased linear velocity of venous blood flow, decreased vein wall distention, and improved valve function. This reduction in venous hypertension and reflux leads to decreased edema and better tissue microcirculation.

Three European single-center RCTs found that the daily use of sized-to-fit, 30 to 40 mm Hg knee-high ECS for 2 years after the diagnosis of first-episode proximal DVT reduces the risk of PTS by ~50%.^{4–6} It should be noted that these studies were limited by the lack of a placebo control, blinding, and/or separate delineation of outcomes for patients with IFDVT. For this reason, a double-blind, placebo-controlled, multicenter randomized trial (the SOX trial) is being performed to definitively address the issue of whether ECS truly prevent PTS.⁵²

Nevertheless, given the strength of the currently available evidence and the recommendations of current practice guidelines,^{11,19} interventional radiologists should strongly encourage the use of ECS along with anticoagulant therapy after CDT/PCDT. It is important to understand that the hose purchased by patients in their local store may not be properly sized, and that they typically will not provide a compressive force (most such hose fall into the 3 to 15 mm Hg range) that is comparable with prescription ECS. Therefore, the patient described here should have his or her legs carefully measured and should be prescribed 30 to 40 mm Hg ECS for routine daytime use. The patient should be educated that the stockings are not merely provided to reduce ongoing symptoms, but that they are an important element in the long-term prevention of PTS, which, once established, often produces irreversible impairment of quality of life.

With specific regard to IFDVT patients following CDT, there are no studies that directly address the comparative efficacy of knee-high versus thigh-high compression stockings. In these patients, we usually start by encouraging the use of thigh-high stockings if the patient can tolerate them. If not, the use of knee-high stockings may be recommended.

The main contraindication to the use of ECS is lower extremity arterial insufficiency. In patients with documented significant peripheral arterial disease, ECS should be avoided. Because many elderly patients with atherosclerotic risk factors may have mild arterial insufficiency, the elderly patient should be reminded only to wear them in the daytime when the leg is dependent.

Conclusion

The interventional radiologist is most likely to achieve optimal DVT treatment outcomes with a strong understanding of the published literature as it pertains to the justifiable

indications for endovascular thrombolytic therapy, the optimal use of anticoagulant therapy, and the reasonable use of adjuncts such as IVC filters and elastic compression stockings.

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