

THROMBOLYSIS & IVC FILTERS

Introduction to Thrombolysis

Catheter-directed thrombolytic techniques can be invaluable in managing patients with the most severe forms of venous thrombosis. They have also shown promise to improve clinical outcomes in the larger population of patients with venous thromboembolic disease. However, the proper indications for thrombolytic therapy have not been conclusively established and the wide range of thrombolytic techniques offered can be confusing. The purpose of this document is to provide a straightforward approach to patient selection, procedure performance, and post-procedure monitoring that can be easily adopted by IRs starting to perform venous thrombolysis.

Patient Selection

At present, the proper indications for catheter-directed thrombolysis (CDT) in the treatment of lower extremity DVT are controversial.

- (1) Patient selection should take into account the anatomic extent of thrombosis, symptom duration and severity.
- (2) Patient's likelihood of having a bleeding complication.

Absolute contraindications to CDT include:

- A. active internal bleeding
- B. disseminated intravascular coagulation
- C. recent (< 3 months) cerebrovascular event, neurosurgery, or intracranial trauma
- D. presence of an absolute contraindication to anticoagulation.

Strong relative contraindications include:

- A. recent CPR
- B. recent major surgery, delivery, biopsy, trauma
- C. bleeding event
- D. intracranial lesion or seizure
- E. uncontrolled hypertension
- F. thrombocytopenia
- G. known right-to-left cardiopulmonary shunt
- H. renal failure
- I. severe hepatic dysfunction
- J. septic thrombophlebitis
- K. diabetic hemorrhagic retinopathy.

A. Lower Extremity and Inferior Vena Caval DVT:

A multicentre CDT registry clearly demonstrated that CDT is more effective in removing acute thrombus compared with chronic organized thrombus (3). There are two primary reasons to perform CDT in patients with acute DVT:

- 1) to prevent major immediate adverse clinical sequelae such as death, limb loss, pulmonary embolism, and renal failure in patients with phlegmasia or acute IVC thrombosis
- 2) to prevent post-thrombotic syndrome in patients with acute proximal DVT of lesser severity (iliofemoral and femoropopliteal).

It is, however, important to recognize that the ability of CDT to prevent PTS has not been conclusively established in randomized trials. Therefore, patients evaluated for CDT with the primary goal of post-thrombotic syndrome (PTS) prevention should be informed of the long-term risks of PTS; the risks, benefits, and alternatives to CDT; and the lack of conclusive evidence in favor of (or against) CDT's ability to prevent PTS.

B. Upper Extremity DVT:

Post-thrombotic syndrome of the upper extremity, particularly when within the dominant arm, can also significantly impair quality of life (4). For this reason, patients with symptomatic, acute axillosubclavian DVT may also be candidates for CDT. In general, the etiology of thrombosis plays a major role in determining the optimal therapeutic approach. Primary axillosubclavian vein thrombosis is typically caused by compression of the subclavian vein from surrounding ligamentous and muscular structures in the thoracic outlet. These patients are often young and otherwise healthy and need more drastic measures.

Modern treatment features a combined interventional-surgical approach: CDT to eliminate the acute thrombus, followed by surgical thoracic outlet decompression to prevent recurrence. Angioplasty and stent placement are not performed in order to avoid further traumatizing the subclavian vein, and because stents tend to fracture in this location. Treatment of patients with secondary axillosubclavian venous thrombosis is largely dependent upon the degree of symptoms and overall patient condition. In general, symptomatic younger patients without major co-morbidities that would elevate bleeding risk are candidates for CDT. Because many such cases are related to stenosis caused by prior central venous catheters and other devices, balloon angioplasty may play a role in treatment as well.

Procedural Technique

The following is a brief description of the basic CDT technique for acute DVT (5):

- A. **Venous Access:** When thrombolytic therapy is planned, venous access should be obtained using ultrasound guidance in order to avoid inadvertent arterial punctures. When possible, a lower extremity vein should be selected at a site lower than the most distal extent of thrombosis. For many patients with iliofemoral DVT, the popliteal vein provides a suitable access sites; however, patients with thrombus involving the popliteal vein and upper calf veins may be better treated with access into the small saphenous vein or posterior tibial vein. The internal jugular vein is another option.
- B. **Catheter Venography:** Once venous access is obtained, diagnostic venography is performed to accurately define the extent of thrombosis.

- C. Retrievable IVC Filter is placed
- D. Initiation of Thrombolysis: A multisidehole catheter is embedded within the thrombus and the thrombolytic drug is infused in drip fashion. The patient is simultaneously anticoagulated using heparin infusion. The patient is monitored in an ICU or stepdown unit, and serial laboratory values are obtained every 6 hours. Specifically, the hematocrit, partial thromboplastin time, and fibrinogen are monitored for change and dose adjustments made accordingly.
- F. Follow-Up Checks: At 6-18 hour intervals, the patient is brought back to the interventional suite and repeat venography performed to define the extent of thrombolysis. At each follow-up check, one of several findings is seen:
 - a) Complete thrombolysis with no venous stenosis – therapy is deemed successful, the thrombolytic infusion is terminated, and the patient is anticoagulated.
 - b) Complete thrombolysis with a venous stenosis identified – iliac vein stenoses are typically treated with endovascular stent placement and femoral vein stenoses are typically treated with balloon angioplasty
 - c) Incomplete thrombolysis – an angioplasty balloon is used to macerate the thrombus, the infusion catheter is repositioned within the residual thrombus, and the infusion is continued.

If no thrombolysis is seen within 24-48 hours, therapy is discontinued.

Choice of Thrombolytic Drug:

Although UK is the drug most commonly used in published CDT studies, its intermittent unavailability has prompted the use of alternative drugs including tissue plasminogen activator (TPA), reteplase (RPA), and tenecteplase (TNK). To date, no studies have demonstrated differences in safety or efficacy of these agents using current dosing regimens (Appendix).

Concomitant Anticoagulation: Although there is no direct evidence available to support use of any anticoagulation regimen over another, the current consensus is for full-dose therapeutic-level heparin (PTT 1.5 – 2.5x control) when using UK. On the other hand, subtherapeutic heparin (300-500 units/hr, PTT < 1.5x control) is suggested when using TPA, RPA, and TNK.

Percutaneous Mechanical Thrombectomy (PMT): To date, no stand-alone PMT method has proven effective in DVT treatment without associated pharmacologic thrombolytic therapy. However, the combination of pharmacologic CDT with PMT, known as pharmacomechanical thrombolysis, has shown potential to speed thrombolysis, reduce the required drug dose, and reduce complication rates.

Several different pharmacomechanical methods have been used:

- a) Thrombolytic drug infusion followed by PMT to macerate or remove thrombus.
- b) Initial PMT to debulk the thrombus and create a flow channel, followed by thrombolytic drug infusion.

- c) Recently, several pharmacomechanical techniques have been introduced to enable on-table, single session DVT treatment. These techniques involve vigorous pulse-spray injection of a bolus dose of thrombolytic drug into the thrombus, with concomitant/subsequent PMT device use to macerate and/or aspirate residual thrombus. To date, mid-term results of the single-session treatment methods have not been published.

Appendix: CDT Dosing

The following represent acceptable dosing regimens for CDT of DVT.

1. Urokinase: 120,000 – 200,000 units/hr – Dissolve 1 million units UK in 500 ml normal saline (= 2000 units/ml). Infuse at 60-100 ml/hr.
2. Tissue Plasminogen Activator: 0.5 – 1.0 mg/hr – Dissolve 10 units TPA in 1000 ml normal saline (= 0.01 mg/ml). Infuse at 50-100 ml/hr.
3. Reteplase: 0.25 – 0.75 units/hr – Dissolve 10 units reteplase in 1000 ml normal saline (= 0.01 units/ml). Infuse at 25-75 ml/hr.
4. Tenecteplase: 0.25 – 0.5 mg/hr – Dissolve 5 mg TNK in 500 ml normal saline (= 0.01 mg/ml). Infuse at 25-50 ml/hr.

Post-Procedure Care

Patients must transition to long-term anticoagulant therapy. He/she may ambulate soon after sheath removal and can usually be discharged from the hospital within 1-2 days afterwards. Typically patients are placed on oral warfarin and are given low-molecular weight heparin during the transition period – this is discontinued when the patient reaches the desired therapeutic range (INR 2.0 – 3.0 for most first-episode DVT patients, 2.5 – 3.5 for selected subgroups of patients).

Patients receiving stents are often also placed on anti-platelet therapy for several months. Patients also undergo risk factor evaluation to determine the appropriate duration of anticoagulant therapy, per American College of Chest Physicians guidelines – this may be done with hematology consultation in many instances. Patients with lower extremity DVT should be asked to wear a Class II (30-40 mmHg) graduated compression stocking to the affected limb for prevention of PTS – two randomized trials have shown that this intervention may decrease PTS rates by 50%. Patients and their physicians should be educated about the need to inform the interventionalist should symptoms recur, since re-stenosis can sometimes be treated with repeat balloon angioplasty or stent placement before re-thrombosis occurs.

Introduction to IVC Filters

Although systemic anticoagulation remains the cornerstone of venous thromboembolism treatment, not all patients are candidates for this therapy, some fail the therapy, and some patients on anticoagulation suffer complications from the treatment. Fortunately, inferior vena cava (IVC) filtration is available for these selected patients as an adjunctive treatment for venous thromboembolism, or as an effective prophylactic measure in selected high-risk patients.

Indications for Infrarenal IVC Filtration

The three classic indications for IVC filtration include the presence of venous thromboembolic disease (pulmonary embolus or IVC, iliac, or femoropopliteal deep venous thrombosis) combined with one of the following:

- (a) contraindication to anticoagulation
- (b) complication of anticoagulation
- (c) failure of anticoagulation (including recurrent PE despite adequate anticoagulation and inability to achieve therapeutic systemic anticoagulation).

The contraindications to anticoagulation have been cited as a bleeding complication of anticoagulation, known recent hemorrhage, recent major trauma or surgery, hemorrhagic stroke, thrombocytopenia, heparin-associated thrombocytopenia thrombosis syndrome, and a known central nervous system neoplasm, aneurysm, or vascular malformation.

Additional well-accepted indications include:

- A. massive pulmonary embolism with residual deep venous thrombus (DVT) in a patient at risk for further PE; free floating iliofemoral or IVC thrombus.
- B. Severe cardiopulmonary disease and deep venous thrombosis (e.g. cor pulmonale with pulmonary hypertension); and poor compliance with anticoagulant medications.

“Extended” indications include prophylactic IVC filter placement in selected, high-risk patients without documented PE or deep venous thrombosis.

- A. Severe trauma victims with closed head injury, spinal cord injury, and/or multiple long bone or pelvic fractures.
- B. Other high-risk patients include those that are immobilized or subjected to prolonged intensive care.
- C. Prophylactic filters preoperatively in patients who have multiple risk factors for venous thromboembolism.
- D. Filtration for protection during iliofemoral DVT thrombolysis for prevention of significant PE.

Indications for Suprarenal IVC Filtration

- A. Renal vein thrombosis.
- B. IVC thrombosis extending up to or above the level of the renal veins, renal cell carcinoma with renal vein or IVC involvement, thrombus extending above a previously placed infrarenal filter.
- C. Pulmonary embolism after gonadal vein thrombosis.
- D. Anatomic variants, such as a duplicated IVC and low insertion of the renal veins.
- E. Pregnant women.

Contraindications to IVC Filtration

Absolute contraindications:

Complete thrombosis of the IVC.

Uncorrectable Coagulopathy.

Bacteremia/Sepsis are relative contraindications, and clinical judgement must be used.

Success and Efficacy of IVC Filtration

The technical success for IVC filter placement should be equal to or exceed 97% in experienced hands.

The primary indicator of efficacy of an IVC filter is the recurrent PE rate. Generally speaking, all available IVC filters have comparable recurrent symptomatic PE rates, which range roughly between 2 and 5%. However, it is important to understand that the true incidence of recurrent PE following IVC filtration is probably higher, since most asymptomatic PE remain undiagnosed.

Decousus et al. compared IVC filters to a control group. This study showed a significant benefit of filters at 12-day follow-up, with the control group experiencing a more than four-fold increase in PE rate compared to the filter group (4.8% without filter vs. 1.1% with filter). This difference was even greater when only patients with PE at enrollment were considered (8.6% without filter vs. 1.1% with filter). However, there was no significant difference in mortality between these two groups. In addition, at 2-year follow-up, there was no significant difference between the two groups with respect to PE rate, but the filter group did experience more recurrent deep venous thrombosis than the control group (20.8% and 11.6%, respectively). These findings persisted in a subsequent paper reporting on 8-year follow-up of these patients. There was a significantly lower rate of symptomatic PE in the filter group compared with the no filter group (6.2% vs. 15.1%, $p=0.008$) while there was a slightly higher rate of DVT (35.7% vs. 27.5%, $p=0.042$).

General IVC Filter Placement Procedure

Prior to placement of an IVC filter, objective documentation of venous thromboembolism is essentially best performed with either ultrasonography, radionuclide scintigraphy, contrast enhanced computed tomography.

The procedure may be performed via a jugular, femoral, subclavian, or sometimes an upper extremity peripheral vein route.

Inferior vena cavography is performed to analyse the status of the IVC with regard to patency and the presence or absence of thrombus, to include measurements of the diameter of the IVC and the location of the renal veins, and to exclude the presence of a venous anomaly such as a megacava, duplicated IVC, and circumaortic or retroaortic left renal vein.

Complications of IVC Filtration

Complications of IVC filter placement vary among the specific filters, but for simplicity, they can be considered collectively for all filters as a group.

Thromboembolic events following IVC filter placement, such as recurrent PE.

IVC thrombosis

Recurrent deep venous thrombosis at the access site are not uncommon, with occurrence rates reported to be, 0.5-6%, 2-30%, 20.8%, and 2-28%, respectively. Most partial IVC thrombosis complications, often diagnosed incidentally on ultrasound or CT examinations, remain asymptomatic, and might be better interpreted as evidence of efficient embolus trapping by the filter. Complete IVC thrombosis can result in phlegmasia cerulea dolens, which can sometimes be treated with venous thrombolysis. Filter migration (0-18%) and embolisation to the right heart or pulmonary arteries (2-5%) occasionally occur spontaneously, but may be precipitated by entrapped exchange guide-wires used during bed-side central venous catheter placement procedures. Both guide-wire entrapment and filter embolisation have been successfully treated using Interventional Radiology transcatheter techniques.

IVC penetration, which may or may not cause a retroperitoneal hematoma or perforation into the aorta or gastrointestinal tract, has been documented to be as high as 41% in one series, but clinically significant penetration is believed to be a rare event. Filter fracture, which can be a late occurring event, can be detected on plain radiographs, and has been reported to occur with a rate of 2-10%.

Retrievable Filters

Because of the risk of the above-mentioned long-term complications of IVC filtration, retrievable filters have been introduced. Currently available temporary or retrievable filters might be better classified as “optional” filters, since they can function as permanent or temporary filters. An IVC filter that gives the option for use as a permanent or temporary filter is an attractive alternative for patients with a time-limited need for IVC filtration. This would include patients such as severely injured trauma patients at high risk for pulmonary thromboembolism and patients with venous thromboembolism and a temporary contraindication for anticoagulation, who subsequently can undergo anticoagulation. These patients may only require a filter for the short term, and could benefit by having the filter removed percutaneously at a later time.

The Günther Tulip Retrievable Filter has been used in Europe since 1992, and was introduced in the U.S. in 2000. It is manufactured from conichrome, a non-ferromagnetic alloy and thus it is MRI compatible up to 1.5 T.

The Recovery Retrievable Filter received FDA clearance as a permanent filter in 2002 and was redesigned in 2005 and renamed G2. Since there is no indicated retrieval time limit, extended implantations have occurred, with some filters successfully removed up to six months post insertion. Both of these filters are MRI-compatible and MRI-safe, and do not cause an artifact on MRI.

Selected References for IVC Filters;

1. Grassi CJ, Swan TL, Cardella JF, et al. Quality improvement guidelines for percutaneous permanent inferior vena cava filter placement for the prevention of pulmonary embolism. *J Vasc Interv Radiol* 2003; 14:S271-S275.

2. Kaufman JA, Kinney TB, Streiff MB, et al. Guidelines for the use of retrievable and convertible vena cava filters: report from the Society of Interventional Radiology multidisciplinary consensus conference. *J Vasc Interv Radiol* 2006; 17:449-459.
3. Participants in the vena caval filter consensus conference. Recommended reporting standards for vena caval filter placement and patient follow-up. *J Vasc Interv Radiol* 2003; 14:S427-S432.
4. Millward SF, Grassi CJ, Kinney TB, et al. Reporting standards for inferior vena caval filter placement and patient follow-up: supplement for temporary and retrievable/optional filters. *J Vasc Interv Radiol* 2005; 16:441-443.
5. Kinney TB. Update on inferior vena cava filters. *J Vasc Interv Radiol* 2003; 14:425-440.
6. Millward SF, Oliva VL, Bell SD, et al. Günther tulip retrievable vena cava filter: results from the registry of the Canadian Interventional Radiology Association. *J Vasc Interv Radiol* 2001;12:1053-1058.
7. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl JMed* 1998; 338:409-415.
8. The PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC randomized study. *Circulation* 2005;112:416-422.
9. Asch MR. Initial experience in humans with a new retrievable inferior vena cava filter. *Radiology* 2002; 225:835-844.
10. Ferris EJ, McCowan TC, Carver DK, McFarland DR. Percutaneous inferior vena cava filters: follow-up of seven designs in 320 patients. *Radiology* 1993; 188:851-856.
11. Becker DM, Philbrick JT, Selby JB. Inferior vena cava filters: indications, safety, effectiveness. *Arch Intern Med* 1992; 152:1985-1994.
12. Athanasoulis CA. Complications of vena cava filters. *Radiology* 1993; 188:614-615.
13. Ascher E, Hingorani A, Tsemekhin B, et al. Lessons learned from a 6-year clinical experience with superior vena cava Greenfield filters. *J Vasc Surg* 2000; 32:881-887.
14. Rogers FB, Strindberg G, Shackford SR, et al. Five-year follow-up of prophylactic vena cava filters in high-risk trauma patients. *Arch Surg* 1998; 133:406-412.
15. Pasquale M, Fabian TC, and the EAST Ad Hoc Committee on Practice Management Guideline Development. Practice management guidelines for trauma from the Eastern Association for the Surgery of Trauma. *J Trauma* 1998; 44:941-956.
16. Ray CE, Kaufman JA. Complications of inferior vena cava filters. *Abdom Imaging* 1996;21:368-374.
17. Wojtowycz MM, Stoehr T, Crummy AB, et al. The Bird's Nest inferior vena cava filter: review of a single-center experience. *J Vasc Interv Radiol* 1997; 8:171-179.

18. Morris CS, Rogers FB, Najarian KE, Bhave AD, Shackford SR. Current trends in vena caval filtration with the introduction of a retrievable filter at a level I trauma center. *J Trauma* 2004;57:32-6.
19. Nunn CR, Neuzil D, Naslund T, et al. Cost-effective method for bedside insertion of vena caval filters in trauma patients. *J Trauma* 1997; 43:752-8.
20. Rosenthal D, Wellons ED, Levitt AB, Shuler FW, O'Conner RE, Henderson VJ. Role of prophylactic temporary inferior vena cava filters placed at the ICU bedside under intravascular ultrasound guidance in patients with multiple trauma. *J Vasc Surg* 2004; 40:958-64.

Selected references for Thrombolysis:

1. Buller HR, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:401S-428S.
2. Vedantham S, Thorpe PE, Cardella JF, et al. Quality improvement guidelines for the treatment of lower extremity deep vein thrombosis with use of endovascular thrombus removal. *J Vasc Interv Radiol* 2006, in press.
3. Mewissen WM, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicentre registry. *Radiology* 1999; 211:39-49.
4. Kahn SR, Elman EA, Bornias C, Blostein M, Wells PS. Post-thrombotic syndrome, functional disability and quality of life after upper extremity deep venous thrombosis in adults. *Thromb Haemost* 2005; 93(3):499-502.
5. Semba CP, Dake MD. Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. *Radiology* 1994; 191:487-494.
6. Grunwald MR, Hofmann LV. Comparison of urokinase, alteplase, and reteplase for catheter-directed thrombolysis of deep venous thrombosis. *J Vasc Interv Radiol* 2004; 15:347-352.
7. Sugimoto K, Hoffman LV, Razavi MK, Kee ST, Sze DY, Dake MD, et al. The safety, efficacy, and pharmacoeconomics of low-dose alteplase compared with urokinase for catheter-directed thrombolysis of arterial and venous occlusions. *J Vasc Surg* 2003; 37(3):512-517.
8. Vedantham S, Vesely TM, Parti N, Darcy M, Hovsepian DM, Picus D. Lower extremity venous thrombolysis with adjunctive mechanical thrombectomy. *J Vasc Interv Radiol* 2002; 13(10):1001-1008.
9. Vedantham S, Vesely TM, Sicard GA, et al. Pharmacomechanical thrombolysis and early stent placement for iliofemoral deep vein thrombosis. *J Vasc Interv Radiol* 2004; 15:565-574.

10. Kasirajan K, Gray B, Ouriel K. Percutaneous Angiojet thrombectomy in the management of extensive deep venous thrombosis. *J Vasc Interv Radiol* 2001; 12:179-185.
11. Spencer E, Garby KB. Initial results with a new device, the Trellis, using isolated thrombolysis for treatment of lower extremity DVT. *J Vasc Interv Radiol Suppl* 2004; 15(2 Pt 2):S152.
12. McNamara TO, Dong PR, Gomes A. New device/method for clearing iliofemoral venous thrombosis in the post operative period. *J Vasc Interv Radiol Suppl* 2004; 15(2 Pt 2):S153-S154.
13. Cynamon J, Dym J, Fitzpatrick D, et al. Power pulse spray for treatment of acute DVT: a multicenter retrospective study. *J Vasc Interv Radiol Suppl* 2005; 16 (2 Pt 2):S13.
14. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome. *Ann Intern Med* 2004; 141(4):249-256.
15. Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; 349:759-762.

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