Indications for Thrombolysis in Deep Venous Thrombosis


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Abstract Objectives: Deep venous thromboses (DVTs) are a significant cause of morbidity and mortality in the general and inpatient population. Current anticoagulation therapy is efficient in reducing thrombus propagation but does not contribute to clot lysis or prevention of post-thrombotic limb syndrome. Catheter directed thrombolysis (CDT) is an alternative method for treating DVTs but there is no consensus regarding indications for its use.

Data sources: PubMed and Cochrane library were searched for all articles on deep vein thrombosis and thrombolysis.

Review method: Articles presenting data on DVT thrombolysis, DVT anticoagulation, mechanical thrombectomy, venous stenting and May-Thurner’s syndrome were considered for inclusion in the review.

Results: CDT reduced clot burden, DVT recurrence and may prevent the formation of post-thrombotic syndrome. Indications for its use include younger individuals with a long life expectancy and few co-morbidities, limb-threatening thromboses and proximal ilio-femoral DVTs. There is a marked lack of randomised controlled trials comparing CDT-related mortality and long term outcomes compared to anticoagulation alone. The effectiveness of combined pharmaco-mechanic thrombectomy, although promising, need to be further investigated, as is the role of caval filters in preventing DVT-associated pulmonary emboli.

Conclusions: These results suggest that the outcome of CDT in DVT management are encouraging in selected patient cohorts, but further evidence is required to establish longer term benefits and cost-effectiveness.

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**Objectives**

Deep venous thromboses (DVTs) affect around 56–122 individuals per 100,000 in the general population per year. In the USA, DVTs are responsible for 50,000–200,000 deaths annually, at the same time representing the third commonest cardiovascular pathology in the UK after coronary artery disease and stroke. Significant complications associated with DVTs include pulmonary emboli which cause 10% of inpatient deaths, phlegmasia caerulea dolens (PCD) leading to limb-threatening venous gangrene and severe morbidity secondary to chronic venous hypertension and post-thrombotic syndrome (PTS).

PCD is characterised by limb cyanosis and swelling as a result of thrombosis at a capillary level. This is of clinical importance as it has an associated mortality of 20–41%, and many survivors ultimately develop venous ulceration and limb loss.

PTS is caused by chronic venous hypertension secondary to venous reflux, venous obstruction and valvular dysfunction, with clinical sequelae of leg pain, oedema, venous trophic changes and chronic ulceration. It is estimated that up to 80% of patients with a DVT may go on to develop symptoms of PTS, whilst 4–15% progress to leg ulceration.

Standard treatment of DVTs involves anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UH), followed by long term therapy with vitamin K antagonists, such as warfarin. This has been shown to effectively reduce the risk of thrombus propagation or recurrence, pulmonary embolism and death. Nevertheless, anticoagulants have little impact on reducing thrombus size in the short term, being ineffective in the management of PCD. Furthermore, their inability to cause thrombus dissolution may not prevent the development of post-thrombotic limb syndrome in the long term in many patients.

The feasibility of more invasive techniques aimed at reducing thrombus burden has gained increasing interest in recent years. Initially, systemic thrombolysis (with urokinase, streptokinase or tissue plasminogen activator) demonstrated adequate clot lysis, but exposed patients to unacceptable side-effects, including intracranial haemorrhage, and significant retroperitoneal haematomas. Catheter directed thrombolysis (CDT) involves a focused delivery of plasminogen activating agents directly into the thrombus. This may be more effective in local thrombolysis and restoring venous patency, whilst reducing the risks associated with systemic therapy.

If CDT presents an effective treatment option for the management of DVT, then patient selection is of critical importance in identifying those who would benefit most.

The objective of the article was to review current indications for DVT thrombolysis.

**Data Sources and Review Methodology**

A PubMed and Cochrane Library search for ‘deep vein thrombosis’ and ‘thrombolysis’ was performed. 46 articles were selected as relevant for the review. These included articles addressing the management of May-Thurner’s syndrome, DVT anticoagulation with heparin and warfarin, as well as mechanical thrombectomy. Details of article selection are shown in Fig. 1.

**Results**

**Short term outcome**

**Lysis and patency rates**

Clot lysis may be quantified and stratified according to the percentage of venous luminal patency restored (Table 1). Lysis grades II and III describe greater than 50% of the lumen as being patent post-lysis and may be considered to be a satisfactory therapeutic outcome. Current evidence demonstrated that CDT achieved superior clot lysis when compared to a regime of combined heparin and warfarin therapy (72% vs. 12% patency rate at 6 months), with grade II and III lysis being achievable in both acute iliofemoral DVTs (87% of patients) and femoro-popliteal DVTs (79% of patients). This suggested a potential for treating thromboses at both proximal and distal sites. In addition, venous patency post CDT has been shown to be maintained at 6 months post therapy, suggesting longer term advantages over standard anticoagulation (CDT 72% vs. anticoagulation 12%). Furthermore, about one third of CDT-managed DVTs achieved complete clot lysis, which was associated with a reduction in the risk of recurrent thrombosis related to residual thrombus.

**Phlegmasia caerulea dolens**

Despite a lack of randomised controlled trials, CDT is an accepted treatment option for PCD. In the light of limited alternative therapeutic options and a 20–40% associated mortality, CDT assisted by percutaneous or surgical thrombectomy may be attempted to prevent limb amputation or death. Nevertheless, the literature comprised single patient reports or single centre case series, with only one published randomised controlled trial and one large venous registry series. The relative lack of evidence prevented a definitive conclusion from being drawn regarding significant treatment benefits in PCD, but in general the literature was supportive of the role of CDT in acute limb salvage. Considering the lack of alternative therapeutic options and little evidence against the use of CDT for this condition, it would seem pragmatic to support this treatment pathway.

**QUORUM Flowchart**

Potentially relevant abstracts identified from PubMed searches (n=179)

128 excluded as abstracts unsuitable

Articles retrieved for analysis and evaluation (n=51)

5 excluded as did not address review

Articles included in review (n=46) of which 1 randomised controlled trial

![Figure 1](image-url) Flowchart demonstrating article selection process.
Timing of CDT
The speed of intervention in acute thrombotic events is of clinical relevance as there is a potential for reversal of occlusion, relief of symptoms, and preservation of valve function, which may maximise the potential for reducing the risk of PTS. It is known that acute thrombi respond better to thrombolysis compared to established DVTs (86% vs. 68% significant grade II or III lysis; 34% vs. 19% grade III lysis) due to thrombus organisation over time. Current evidence suggested that the optimal window for DVT thrombolysis was within 10 days from onset of symptoms. Following this period, thrombus organisation and prolonged venous hypertension led to worse outcomes and reduce the likelihood of clot lysis. However, there has been no formal definition of an acute or chronic DVT from a CDT perspective and the interventional window of 10 days post-onset is arbitrary.

Pharmacomechanical therapy
More recent studies have looked at combining CDT and percutaneous mechanical thrombectomy (PMT). A variety of devices have been developed to be used alone or in conjunction with CDT in order to provide a more refined method of thrombectomy. Their underlying principle involves isolation of the thrombus between proximal and distal balloons, local delivery of a thrombolytic agent followed by mechanical dissolution of the clot using various physical methods. These include rotating sinusoidal dispersion wires (Trellis-8, Bacchus Vascular Inc, Santa Clara, CA), pulsatile saline jets (Angiojet,Possis Medical Inc, Minneapolis, MN) and low-energy high-frequency ultrasound (Ekos, Bothell, WA). Efferent parts of the catheter are then used to remove the macerated thrombus before the proximal balloon is deflated, theoretically reducing the risk of pulmonary emboli. Success rates in 80–90% of patients have been reported for combined therapy, with associated reductions in ITU stay and overall hospital length of stay. In particular, ultrasound-accelerated thrombolysis has been shown to require shorter infusion time and lower average drug dose compared to catheter directed thrombolysis alone. The role of combined CDT and PMT requires further investigation to confirm: a. the effectiveness of PMT and CDT compared to CDT alone in a randomised trial environment; b. The impact of PMT on reduced dose of thrombolytic agent used and infusion time; c. the impact of PMT on incidence of thrombolysis related pulmonary embolism.

Complications
Despite the reported effectiveness of CDT in achieving clot lysis, the endovascular delivery of a thrombolytic agent may still be associated with significant local and systemic morbidity and mortality.

Bleeding
Most CDT-associated complications were local or systemic haemorrhagic complications. CDT-related bleeding was reported to occur in 5–11% of patients, higher rates being associated with prolonged infusion time and high doses of thrombolytic agent used. Furthermore, data from the USA National Venous Registry reported infrequent, but significant CDT-associated complications, including intracranial haemorrhage (<1%), retroperitoneal haematoma (1%), musculoskeletal, genitourinary and gastrointestinal bleeds (3%).

Despite the possibility of major haemorrhagic complications, most of the incidents recorded were associated with puncture site bleeding. The routine use of ultrasound-guided venous catheterisation can address this issue by avoiding the risk of multiple punctures, whether arterial or venous. Further reductions in complication rates may be achieved by limiting the thrombolytic agent infusion time and dose, in addition to strict enforcement of patient exclusion criteria (Table 2). Unfortunately these exclude a large percentage of patients who have developed DVTs secondary to surgical interventions or trauma, making thrombolysis a relative therapeutic contraindication.

Pulmonary emboli
There is debate as to whether CDT increases the risk of PE in the process of clot lysis. PEs occur in up to 30% of general patients suffering with acute DVTs, many having subclinical presentations. In CDT-treated DVTs, PEs have been reported in as many as 4.5% of patients, although most studies suggest a rate closer to 1%. By comparison, current data suggests that acute DVTs treated with LMWH have a symptomatic PE incidence of less than 2%.

Mortality
Limited data exist regarding CDT-related mortality compared to anticoagulation alone, although rates of 0–0.4% have been suggested. One study however, suggests a 90-day all-cause mortality of 4%, but insufficient evidence was available to implicate CDT. It is likely that mortality is a poor outcome measure for this technique, and that patient reported outcome measures (PROMs), radiological lysis rates and ultimately the development of PTS might prove more reliable indicators.

Long term outcome
Recurrent DVTs and the development of PTS are the two most significant long term consequences of venous thrombosis managed with anticoagulation alone.

### Table 1 Grade of DVT lysis

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<thead>
<tr>
<th>Grade</th>
<th>Lysis</th>
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<tr>
<td>I</td>
<td>&lt;50%</td>
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<tr>
<td>II</td>
<td>50–99%</td>
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<tr>
<td>III</td>
<td>Complete</td>
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Adapted from Protack et al.

### Table 2 Contraindications for thrombolysis

1. Bleeding diathesis/thrombocytopenia
2. Organ specific bleeding risk (recent MI, CVA, GI bleed, surgery or trauma)
3. Renal or hepatic failure
4. Malignancy (e.g. brain metastases increase risk of bleeding)
5. Pregnancy
Post-thrombotic limb syndrome
PTS is caused by long standing venous obstruction or occlusion, leading to venous reflux, valvular damage and chronic venous hypertension. This manifests as ‘bursting’ limb pain, venous claudication and ulceration, with the attendant morbidity and loss of function. 90% of DVT patients treated with anticoagulation alone develop some symptoms of venous hypertension at 5 years. Furthermore, 15% develop venous claudication whilst another 4–15% progress to ulceration.6–9 This reflects the fact that clot lysis occurs in only 4–12% of patients on anticoagulants alone,34 making the development of venous hypertension almost inevitable with this treatment option.

Furthermore, persistent, partially treated venous thrombi are associated with an increased rate of DVT recurrence,1 which may be avoided by thrombolysis at the time of initial presentation. It is evident therefore, that the long term outcome of anticoagulant therapy is poor with respect to preventing DVT-associated morbidity, principally due to its inability to achieve satisfactory clot lysis.

Large ilio-femoral DVTs are most likely to lead to PTS due to significant proximal residual clot burden and mechanical stress on venous valves causing destruction and loss of function. Considering that 70–80% of clinically significant DVTs25,32 involve the proximal veins, the ability of CDT to re-establish venous patency in ilio-femoral thrombosis (87% patency at 6 months, vs. 79% patency in femoral-popliteal DVTs) provides a strong argument for its use in the appropriate clinical settings.

Long term venous patency
The ability of CDT to achieve sustainable venous patency is crucial in determining its role in preventing PTS. It has been shown that that up to 75%23 of the CDT-treated limbs demonstrated complete clot lysis at 1 year and that patency was maintained at 3 years follow-up.11 In addition, CDT has been shown to reduce long term venous reflux13 compared to anticoagulation alone, reflecting its ability to preserve valve function and protect against the development of PTS. DVT recurrence rates have also been reported to be low at 6 months (CDT and warfarin vs. anticoagulation alone: 72% vs. 12% patency rates)10 and 3 years (75% of patients free of recurrent DVT).11

The inadequate long term outcome of anticoagulation therapy, combined with the encouraging patency rates of CDT suggests that thrombolysis may have a role in reducing PTS and chronic complications of DVTs. However, the lack of large randomised controlled trials demonstrating this effect has so far prevented the use of CDT as a first line therapy. Further answers may be provided by the Norwegian CaVenT randomised controlled trial (RCT), which has been setup to investigate the role of CDT vs. conventional therapy in acute ilio-femoral vein thrombosis.36

Controversies
Comparison of the benefits and limitations of CDT is made difficult by the heterogeneity of vascular approaches to the thrombus, thrombolytic agent used, type of infusion catheter employed and concomitant use of endovenous stenting.

Choice of lytic agent
Traditionally streptokinase was used for both local and systemic thrombolysis, but was associated with an increased antigenicity and risk of haemorrhage. Consequently, it has been abandoned in favour of endogenous serine protease inhibitors such as urokinase and tissue plasminogen activator.37 In vitro work comparing streptokinase (SK), urokinase (uPA) and tissue plasminogen activator (tPA) demonstrated an advantage of uPA in terms of a more rapid time to clot lysis and an improved fibrinolytic specificity over SK or tPA.38 The clinical relevance of uPA was supported by the National Multicentre Venous Registry where 52% and 31% patients treated with uPA achieved grades II and III lysis, respectively.14 Associated major bleeding complications and intracranial haemorrhages occurred in 12.4% and 0.6% of patients in the uPA group compared with 22% and 2.8% of patients in the tPA group, respectively.39 Nevertheless, others report the rates of intracranial bleeds, PEs and overall CDT-associated mortality to be close to 0%.25,40

Venous access
Regarding venous access, Meissner recommended that an antegrade approach should be used in conjunction with uPA.12 The National Registry described a variety of access sites for CDT access, including the popliteal vein (42%), the common femoral vein (28%), the internal jugular vein (21%) and the pedal vein (19%). In all cases, ultrasound (US) guided vascular access was recommended in order to avoid multiple venous punctures14 and subsequent haematoma formation.

Venous stents
CDT has the potential advantage of being complemented by the deployment of augmented by the deployment of endovascular venous stents should thrombolysis alone fail or an underlying anatomical abnormalities be identified. Reported one year patency rates vary between 53–75% without stenting and 54–89% with stent deployment.14,25,40 More evidence however is needed to establish whether these achieve any additional patency benefit, routinely, or whether their use should be limited to selected cases only.

Caval filters
Caval Filters have been developed to reduce the risk of PEs in patients with DVTs. However, they have been shown to be associated with an increased risk of recurrent DVTs (20.8% vs. 11.6%),41,42 although the association with increase recurrent DVT risk was based on unmatched patient groups in terms of underlying pathology. Furthermore, it is important to consider the morbidity associated with the additional interventions of filter insertion and retrieval.

The ability of caval filters to reduce the incidence of PEs has not been clearly established. Case series have shown that patients undergoing CDT may have PE-free survival for up to 3 years in the absence of IVC filters, raising important questions regarding the role of caval filtration in CDT.11,18 Furthermore, a distinction must be made between PE caused by thromboembolism during CDT and late embolism as a result of residual thrombus dislodgement independent of CDT. Consequently, the rationale for the use of caval filtration in CDT must depend specifically on the incidence of CDT-associated PEs, although there is a lack of consensus regarding this.
The short and long term morbidity of IVC filtration in the context of CDT requires further research before a firm conclusion can be reached. The role of retrievable filters must also be addressed, as these may provide short term protection in the peri-CDT period in those with the highest risk, whilst potentially avoiding longer term complications such as increased risk of recurrent DVT.

**CDT and thrombosis secondary to anatomical or structural anomalies**

DVTs secondary to an underlying anatomical or structural cause, such as outflow obstruction through the iliac veins, have been shown to respond poorly to standard ‘passive’ anticoagulation therapy due to the inability of LMWH to achieve satisfactory clot lysis.\(^{43}\)

Due to the reported high incidence of iliac venous compression,\(^{44}\) venography and CDT provide a unique opportunity to distinguish between haemodynamically significant iliac vein compression and normal anatomical variants with no clinical consequences. A standard practice of venography prior to CDT is currently allowing an increasing number of iliac vein compression syndromes to be diagnosed and treated, which has reduced the rate of recurrent thromboses.

A variety of causes for iliac vein compression have been identified including pelvic tumours, osteophytes, chronic urinary retention, iliac artery aneurysms, endometriosis, pregnancy and other uterine masses, such as fibroids.\(^{44}\) The most commonly documented anatomical variant is May-Thurner syndrome, in which the left common iliac vein is compressed by the overlying right common iliac artery. Venous obstruction is caused not only by direct extraluminal compression, but also by intimal changes induced by vibratory irritation from the overlying pulsatile artery.\(^{44}\)

In the absence of endovenous imaging of patients with DVT, a diagnosis of iliac vein compression is not possible. However, DVT patients managed with CDT should have concomitant venography, providing an additional diagnostic advantage in identifying those anomalies permitting the definitive treatment of the venous occlusion by balloon angioplasty and endovascular stent placement following CDT. In this situation a good outcome may be expected from combined CDT and stenting, with up to 95% technical success and patent venous outflow at 2 years’ follow-up.\(^{43,45,46}\) To highlight this point, in one small series of May-Thurner patients, whilst 11% of patients treated with CDT and stents developed stent occlusion, all patients treated by CDT alone had evidence of re-thrombosis on follow-up venogram.\(^{45,47}\) Furthermore, the use of thrombectomy and anticoagulation alone in the treatment of May-Thurner’s syndrome may lead to re-thrombosis in almost three quarters of sufferers, highlighting the therapeutic potential of CDT and stent insertion.\(^{45,48}\)

**Cost-effectiveness and quality of life**

There is a consensus that anticoagulation therapy with subcutaneous LMWH is a fast, convenient and inexpensive therapy that can be started in hospital and may be continued in the community by district nursing or patient self-administration. By contrast, CDT requires repeat venography which is invasive and increases in-hospital costs. In addition, CDT may be administered in critical care setting, with average stay of 12–48 h. Nevertheless, this must be balanced against the economic burden of PTS and venous ulceration, with 81% of patients reporting loss of financial productivity post DVT.\(^{49}\)

There is a documented increase in health-related quality of life in patients receiving CDT at 16 and 22 weeks post treatment compared to anticoagulation alone.\(^{20}\) Patients with ilio-femoral DVTs treated by CDT reported superior overall physical function and fewer symptoms of PTS or health distress compared to those receiving standard therapy alone.\(^{20}\)

**Recommendations for management**

Current guidelines from the American College of Chest Physicians (ACCP) suggest that CDT should be used in selected patients (good life expectancy >1 year, good functional status) with extensive venous thrombosis (ilio-femoral involvement) that have an acute presentation (<14 days).\(^{50}\) The guidelines also advocate the use of venous angioplasty and stenting in the presence of reversible causes of thrombosis and highlight the importance of using CDT and PMT over CDT alone.\(^{50}\)

The available data reviewed in our review suggested that CDT was effective in achieving superior clot lysis in the acute setting, with improved long-term patency rates over anticoagulation alone. Clinically, this may translate into relief of DVT symptoms, an effective management of limb-threatening thrombosis, and protection against the development of PTS. There remains a paucity of data on the long term outcome of CDT in terms of PTS and this lack of evidence combined with rare, but significant associated complications highlight the importance of adhering to strict patient selection guidelines for CDT. The combination of CDT with PMT, venous stenting and IVC filtration may provide superior results in selected groups of patients and should be further investigated.

The patients most likely to benefit (Table 3) are individuals with a long life expectancy, significant ilio-femoral thrombosis and those with early presenting DVTs (<14 days). Patients with a suspected underlying anatomical abnormality may also benefit from the diagnostic and therapeutic potential of CDT. This population is likely to benefit from aggressive therapy with subsequent gains in quality of life.

Exclusion criteria for thrombolysis limit the use of CDT in those patient groups most likely to develop DVTs, such as

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<tr>
<td>1. Extensive thrombosis with high risk of pulmonary embolisation</td>
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<tr>
<td>2. Ilio-femoral or IVC thrombosis</td>
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<td>3. Acute limb compromise</td>
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<td>4. Anatomical cause for DVT</td>
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<td>5. Good physiological reserve (20–70 years)</td>
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<td>6. Life expectancy over 6 months</td>
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<td>7. Short onset of symptoms (&lt;14 days)</td>
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<td>8. Failure of standard LMWH therapy</td>
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<td>9. No contraindications for thrombolysis</td>
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those with extensive trauma or post-operative patients. As such the target group may include those with out of hospital DVTs or those with non-operative DVTs (e.g. sepsis). The outcome of the CaVenT RCT should provide further guidance regarding exclusion and inclusion criteria for CDT. More detailed cost-effectiveness analyses comparing CDT vs. anticoagulation alone are required to establish a health economic evidence base for this treatment. Finally, encouraging results regarding CDT in the management of DVTs should not shift clinical focus from meticulous DVT prophylaxis in all high risk patients.

Conclusions

In selected patients CDT with or without the concomitant use of venous stenting can improve both short and mid-term outcomes from proximal DVT. These techniques may be particularly useful where an anatomical anomaly underlies thrombus formation, or where there is limb-threatening ischaemia. Patient selection will be critical to the success of these techniques. Further randomised controlled trials are needed to establish the role of thrombolysis in the management of DVTs.

Conflict of Interest

No conflict of interests declared.

References


