Deep vein thromboses (DVTs) cause significant morbidity and mortality in the general population. Oral anticoagulation therapy may reduce thrombus propagation but does not cause clot lysis and therefore does not prevent postthrombotic syndrome (PTS). Catheter-directed thrombolysis (CDT) can be used to treat DVTs as an adjunct to medical therapy, but there is no consensus defining exact indications. Current evidence suggests that CDT can reduce clot burden and DVT recurrence and consequently prevents the formation of PTS compared with systemic anticoagulation. Appropriate indications include younger individuals with acute proximal thromboses, a long life expectancy, and relatively few comorbidities. Limb-threatening thromboses may also be treated with CDT, although the subsequent mortality remains high. A number of randomized controlled trials are currently under way comparing the longer-term outcomes of CDT compared with anticoagulation alone. Initial reports suggest that venous patency and valvular function are better maintained after CDT. The effectiveness of combined pharmacomechanical thrombectomy and the role of vena cava filters need to be investigated further before strong recommendations can be made. The reported short-term outcomes following catheter-based intervention for DVT are encouraging in selected patients. Further evidence is required to establish long-term benefits and cost-effectiveness.

**Key Words:** anticoagulants • thrombolysis • thrombosis • catheter directed thrombolysis
years after proximal DVT, up to 50% of patients will have evidence of PTS. A reason for this is that oral anticoagulation does not precipitate thrombolysis but stops thrombus propagation and protects against recurrence. It is thought that chronic venous hypertension secondary to valvular destruction leads to PTS. Therefore, if valvular function can be effectively restored through early clot lysis, there might be benefits in terms of a reduced incidence of PTS.

Systemic thrombolysis had been investigated in trials to achieve this early lysis, but it was associated with unacceptably high rates of serious bleeding complications, such as retroperitoneal hematoma and intracranial hemorrhage, with relatively modest rates of thrombus clearance. Catheter-directed thrombolysis (CDT) involves a more localized delivery of thrombolytic agents directly into the thrombus. This may be more effective in achieving local resolution and restoring venous patency while significantly reducing the risks of bleeding complications.

A Cochrane review compared thrombolysis with standard anticoagulation across 12 randomized controlled trials (RCTs) comprising 700 patients. The majority of these studies included only patients treated with systemic thrombolysis. Clot lysis was seen more frequently in early (relative risk, 4.14; 95% CI, 1.22 to 14.01) and late (relative risk, 2.71; 95% CI, 1.84 to 3.99) follow-up. The incidence of PTS was reduced significantly (relative risk, 0.66; 95% CI, 0.47 to 0.94). A 50% reduction of relative risk (although not statistically significant) in the formation of lower limb ulcers was demonstrated. Bleeding complications were significantly higher (relative risk, 1.73; 95% CI, 1.04 to 2.88). The suggestion was that thrombolysis offered potential advantages but that indications were not clearly defined. In addition to 2 RCTs, there are several institutional cases series reporting the use of CDT and mechanical thrombectomy (Table 1). They display considerable variation in design and the combination of therapies used, but all convey the message that improvements in quality of life have also been demonstrated. Defining which groups of patients will benefit most from the use of this newer technology is one of the major challenges facing exponents of this technique.

### Achieving Venous Patency

A 3-point scale has been proposed to define outcomes of therapy for DVT (Table 2), with grades II and III signifying at least 50% luminal patency postlysis. This is classed as a satisfactory therapeutic outcome. A recent report describing

### Table 2. Grade of Lysis Following Treatment of DVT (Adapted From Protack et al)

<table>
<thead>
<tr>
<th>Grade of lysis</th>
<th>CDT (87) \pm angiplasty ± stent ± PMT</th>
<th>Streptokinase</th>
<th>Immediate: grade III in 69 (79%), II in 162 (52%), I in 54 (17%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Immediate: grade III in 11 (61%), control 0 (0%)</td>
<td>Immediate: 5 (18%) complete lysis, 20 (72%) partial</td>
<td>Immediate: grade III in 30 (95%), II in 63 (96%), I in 4 (8%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>Immediate: grade III in 46 (87%), II in 19 (26%), I in 4 (8%)</td>
<td>Immediate: grade III lysis in 41 (85%)</td>
<td>Immediate: grade III in 95 (92%), II in 10 (11%), I in 1 (1%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>Immediate: grade III lysis in 14 (89%), II in 2 (11%)</td>
<td>Immediate: grade III lysis in 181 (60%)</td>
<td>Immediate: grade III lysis in 181 (60%)</td>
</tr>
</tbody>
</table>

All patients were treated postprocedure with standard anticoagulation unless otherwise stated. Grade III lysis, complete; grade II lysis, 50% to 99%; grade I lysis, <50%.

*Timing not available.
short-term follow-up results from the ongoing Norwegian CaVenT randomized control trial showed favorable patency rates when CDT was compared with anticoagulation and compression stockings.\textsuperscript{13} Grade II–III lysis was achieved in 40% of patients immediately postprocedure. After 6-months, iliofemoral patency was found in 64% of the CDT group and compared with 35% of the control group, giving an absolute risk reduction of 28% (95% CI: 9.7% to 46.7%; \( P = 0.004 \)). Venous obstruction was present in 20% of the CDT group and 49% of controls, representing an absolute risk reduction of 29% (95% CI: 20.0% to 38.0%; \( P = 0.004 \)). Recently, a Scandinavian group has reported 50-month follow-up data on a series of 103 limbs treated by DCT in a group of 101 highly selected patients. More than 82% of patients had patent veins with competent valves and no skin symptoms.\textsuperscript{14}

Timing of CDT

The success of venous recanalization, preservation of valve function, and symptom relief may depend on the timing of therapy postthrombosis. These factors influence effectiveness of intervention and the subsequent incidence of PTS. Freshly formed thromboses respond better to thrombolysis than established, organized thromboses. It has been suggested that 10 days may be the optimal interval from onset of symptoms during which to instigate treatment\textsuperscript{15}; however, the ATTRACT trial in the United States has used 14 days and the CaVenT trial has used 21 days as the cut-off for recruitment.\textsuperscript{16,17} This interval requires further definition through the results of these trials to determine the optimal time frame for intervention that will prevent valvular destruction and venous hypertension, which may result in an increase of the likelihood of longer-term sequelae.\textsuperscript{18–20}

Percutaneous Mechanical Thrombectomy

Combining CDT and percutaneous mechanical thrombectomy (PMT) devices has been attempted to try to improve early mechanical thrombus removal and promote lysis of remaining clot. Several devices exist to perform PMT, but the optimum design and outcomes are not known, despite encouraging early reports and case series. Devices 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).\textsuperscript{21} A series of 43 patients with DVTs undergoing PMT within an average of 14 days of symptom onset recently reported short-term results with successful lysis 63% of clots after 1 session of PMT (greater than 50% clot lysis). One-third of patients had iliac stents deployed in conjunction with mechanical therapy. Freedom from DVT recurrence and reintervention was maintained in 95% of patients after 9 months. The ATTRACT trial will report on the merits of combined therapy in the future.\textsuperscript{16}

Potential Complications

Many of the reported complications following CDT were related to hemorrhage, as may be expected. The US National Venous Registry reported infrequent but severe peri- and postprocedural complications that included intracranial hemorrhage (<1%); retroperitoneal hematoma (1%); and muscu-

<table>
<thead>
<tr>
<th>Table 3. A typical Protocol for Performing Thrombolysis in Cases of DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is identified; if on LMWH, (^*) this is stopped for 8 hours</td>
</tr>
<tr>
<td>Oral anticoagulants are stopped, ensuring international normalized ratio (INR) &lt;1.5</td>
</tr>
<tr>
<td>5000-U bolus of UFH administered</td>
</tr>
<tr>
<td>Infusion of UFH at 15 U/kg, keeping activated partial thromboplastin time (APTT) at 1.2–1.7 times normal</td>
</tr>
<tr>
<td>Appropriate venous access obtained under ultrasound guidance with local anesthetic</td>
</tr>
<tr>
<td>Wire/catheter is introduced above proximal thrombus, and venography is performed</td>
</tr>
<tr>
<td>20 mg of Alteplase administered in 500 mL of 0.9% NaCl at a rate of 0.01 mg/kg/hour to a maximum of 20 mg in 24 hours</td>
</tr>
<tr>
<td>During infusion, observation of hemodynamic stability and puncture site is performed</td>
</tr>
<tr>
<td>Clotting studies are performed daily with daily venography</td>
</tr>
<tr>
<td>Maximum time of therapy should be &lt;96 hours</td>
</tr>
<tr>
<td>Balloon angioplasty/placement of venous stents may be performed if necessary</td>
</tr>
<tr>
<td>Catheters are removed, and manual pressure is used to control bleeding</td>
</tr>
<tr>
<td>Pressure dressing applied for a further 2 hours, with an additional dose of LMWH given 1 hour after catheters are removed</td>
</tr>
<tr>
<td>Anticoagulation is then established</td>
</tr>
</tbody>
</table>

\( \* \) LMWH, low–molecular weight heparin, UFH, unfractionated heparin.

Ioskeletal, genitourinary, and gastrointestinal bleeds (3%).\textsuperscript{22} Most incidents of bleeding were relatively minor, such as that associated with the access site. Catheterization of access veins under ultrasound guidance has been shown to reduce these complications by avoiding multiple vessel punctures.\textsuperscript{23} In addition, aiming for the minimum infusion time to achieve the best results and minimizing the dose of thrombolytic agent reduces both local and systemic bleeding complications. The mechanical thrombectomy device might play a role in achieving this balance.

Some centers have reported an increased incidence of pulmonary embolism following percutaneous treatments, but this has not been supported by registry reports or trials data.\textsuperscript{24,25} Finally, with regard to mortality, the reported rate of mortality for patients undergoing CDT is less than 1%. Currently, patients are highly selected for CDT, so the true postprocedural mortality is unknown. This said, it is likely to remain less than 1% in routine practice.

Controversies

The practice of CDT remains variable between centers. The choice of thrombolytic agent, the use of adjunctive venous stenting, and inferior vena cava (IVC) filters are areas in which this variability becomes most apparent.

Endogenous serine protease inhibitors such as urokinase and recombinant tissue plasminogen activator (r-TPA) have replaced streptokinase as the agent of choice in systemic thrombolysis. r-TPA is the most effective and is likely to be associated with fewer side effects. Consequently, the major RCTs under way are using Alteplase in their protocols (Table 3),
and this is being used with increasing regularity in clinical practice.

The use of IVC filters as an adjunct to CDT remains controversial. Many series report their use in selected cases. Situations where they may prove useful include those in which standard indications would apply, such as a patient developing a thrombosis while on effective anticoagulation or the presence of a contraindication to anticoagulation. Filters should not be used routinely, as CDT has not been shown to increase the rate of pulmonary embolism (PE). There remains insufficient evidence to determine whether IVC filters should be used for free-floating thrombus or thrombus extending into the IVC. We recommend that use of filters be decided through multidisciplinary team discussion on an individual case-by-case basis, and where possible, temporary filters should preferentially be used. In practice, we rarely use them.

Endovascular venous stent placement in conjunction with thrombolysis may improve patency rates in selected cases, particularly if abnormal anatomy is the underlying cause of DVTs. May-Thurner syndrome is the most common of these conditions; in this syndrome, the left common iliac vein is compressed by the overlying right common iliac artery, leading to both extrinsic compression and vessel damage because of the repeated trauma of the arterial pulse. Other causes include pelvic tumors, osteophytes, chronic urinary retention, iliac artery aneurysms, endometriosis, pregnancy, and uterine masses.26

A review of case series with 5 or more patients revealed an initial technical success rate of 87% to 100% and 1 year patency of between 80% and 100% (Table 4). Patent venous outflow at 2 years has been reported after combined CDT and stenting in 1 study.27–29 In 1 small series of May-Thurner patients, all those treated by CDT alone had evidence of righthemobrosis on follow-up venogram, whereas only 11% of patients treated with CDT and stenting developed stent occlusion.28,30 Further research has shown that the use of thrombolysis without stent placement, in cases of May-Thurner, can lead to restenosis in up to 75% of patients in the short term.28,31 It should be noted that venous stents can induce long-term DVT recurrence because of low luminal flow rates. This may outweigh the apparent short-term benefits, but additional data are required. At present, not enough data exist to determine the exact indications for deployment of stents, but once again, the results of the randomized trials appear critical to provide clear answers.

Cost-Effectiveness and Quality of Life
Systemic anticoagulation with subcutaneous low–molecular weight heparin is easy to initiate, relatively convenient for patients, and inexpensive. As anticoagulation is still required after CDT, the procedural costs associated with CDT along with an inpatient admission will always be greater than for the outpatient management of oral anticoagulation alone.

This apparent drawback must be considered in the context of the economic burden of PTS and venous ulceration, not simply because of the utilization of hospital and community healthcare resources (which cost more than £400 million per year in the United Kingdom alone) but also in terms of lost opportunity costs. One study suggested that 81% of patients suffered loss of financial productivity post-DVT. This is of considerable interest in light of the fact that more than 50% of patients with proximal DVT are of working age.15

Health-related quality of life in patients receiving CDT has been shown to be improved in comparison with those treated with systemic anticoagulation alone at 16 and 22 months posttreatment.32 In addition, patients with proximal DVTs treated by CDT reported better functional scores and fewer symptoms of PTS than those undergoing systemic anticoagulation.12 These findings will be of importance in the cost-effectiveness analyses of the ongoing randomized trials.

Recommendations for Management
This review of the relevant literature suggests CDT can achieve superior clot lysis in the acute setting, with better long-term venous patency rates in comparison with anticoag-

Table 5. Possible Indications for DVT Thrombolysis

<table>
<thead>
<tr>
<th>Extensive thrombosis with high risk of pulmonary embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT (iliofemoral or femoral vein)</td>
</tr>
<tr>
<td>Threatened limb viability</td>
</tr>
<tr>
<td>Underlying predisposing anatomic anomaly</td>
</tr>
<tr>
<td>Good physiological reserve (18–75 years old)</td>
</tr>
<tr>
<td>Life expectancy over 6 months</td>
</tr>
<tr>
<td>Recent onset of symptoms (&lt;14 days)</td>
</tr>
<tr>
<td>Absence of contraindications to thrombolysis</td>
</tr>
</tbody>
</table>

Table 4. A Summary of Series Reporting Use of CDT and Venous Stent Placement in Patients With May-Thurner Syndrome

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>Pathology</th>
<th>Therapy</th>
<th>Initial Technical</th>
<th>Short-Term Patency</th>
<th>Long-Term Patency</th>
<th>Major Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Sullivan et al (2000)28</td>
<td>39</td>
<td>M-T with DVT (19) and symptomatic (20)</td>
<td>Urokinase and stent (35 stented)</td>
<td>34/39 (87%)</td>
<td>&gt;90% at 1 year of stented patients</td>
<td>Not reported</td>
<td>2</td>
</tr>
<tr>
<td>Patel et al (2000)29</td>
<td>10</td>
<td>M-T with acute iliofemoral DVT</td>
<td>Urokinase and stent</td>
<td>10/10 (100%)</td>
<td>10/10 (100%) at 1 year</td>
<td>Not reported</td>
<td>0</td>
</tr>
<tr>
<td>Heijmen et al (2001)40</td>
<td>6</td>
<td>M-T, symptomatic</td>
<td>Angioplasty and stent</td>
<td>6/6 (100%)</td>
<td>5/6 (83%) at 1 year</td>
<td>Not reported</td>
<td>0</td>
</tr>
<tr>
<td>Kwak et al (2005)29</td>
<td>22</td>
<td>M-T with DVT (+6 other causes of venous compression)</td>
<td>Urokinase and stent</td>
<td>26/27 (96%)</td>
<td>Primary 95% Secondary 100% At 1 year</td>
<td>Primary 95% Secondary</td>
<td>100% At 2 years</td>
</tr>
<tr>
<td>Kim et al (2006)29</td>
<td>21</td>
<td>M-T with DVT</td>
<td>Thrombectomy and stenting</td>
<td>18 urokinase and stent; 3 stent alone</td>
<td>20/21 (95%)</td>
<td>18/21 (85%) at 6 months</td>
<td>Not reported</td>
</tr>
<tr>
<td>Husmann et al (2007)30</td>
<td>11</td>
<td>M-T with DVT</td>
<td>Thrombectomy and stenting</td>
<td>11/11 (100%)</td>
<td>10/11 (91%) up to 22 months</td>
<td>Not reported</td>
<td>0</td>
</tr>
</tbody>
</table>
ulation alone. This may avoid the clinical sequelae of PTS and venous ulceration. The indications for CDT are based on a number of small RCTs, registry data, and institutional series and a variety of expert opinions.

Current guidelines from the American College of Chest Physicians suggest that CDT should be used in those with life expectancy >1 year, good functional status, extensive iliofemoral thrombosis, and presenting soon after the onset of symptoms >14 days (level 2B evidence). The guidelines also advocate the use of venous angioplasty and stenting in the presence of reversible causes of thrombosis and discuss the efficacy of dual therapy with pharmacomechanical therapy.12

Those most likely to benefit from CDT (Table 5) are individuals with a long life expectancy, as the reductions in PTS and ulceration are likely to be the most important benefits. These outcomes have a measurable incidence at 2 years postthrombosis, and so the differences in outcomes between medically treated patients and those with CDT might be most easily interpreted at this stage. Those patients of working age are likely to derive the most benefits at the lowest risk of intervention.

Higher rates of PTS are seen with more proximal thrombi and in the absence of contraindications, CDT should be considered in these cases. This would include both iliofemoral and femoral vein thromboses. Adjunctive venous stenting is appropriate in cases in which there is an underlying anatomic abnormality.

Unfortunately, some groups of patients with proximal thrombosis would currently be excluded from management by CDT using currently published criteria (Table 6). This may include trauma victims or patients who have undergone recent surgery, although these patients may stand to gain most significantly from effective treatment of extensive thrombosis. The role for mechanical thrombectomy devices might lie in these patient subgroups. In individual cases, a combination of the focused delivery of thrombolytic agent with or without the addition of mechanical therapy may be not only safe but also highly effective.

Oncology patients are at high risk of thromboembolism, and the mortality in this group is significantly higher than that of the general population following DVT. Life expectancy and the risk of hemorrhage (ie, likelihood of brain or liver metastases) must be considered and assessed before CDT. A full assessment would realistically include a current head and chest-abdomen-pelvis computed tomography scan to identify metastases. The current inclusion criteria for CDT may need to be broadened if more patient groups such as this are to benefit, but this is not likely to occur until the full benefit of CDT has been quantified in more selected subgroups of patients.

Given the high associated mortality of phlegmasia caerulea dolens and the lack of an effective alternative, CDT is probably justified in this patient group, despite a high mortality due to the underlying disease, and may lead to effective limb salvage in up to 100% of cases.12

Extensive, free-floating or IVC thromboses may be at high risk of causing pulmonary embolism. Timely reduction of clot burden using CDT would seem to offer a better chance of avoiding such events than simply relying on systemic anticoagulation to prevent their propagation. Whether IVC filters should be used remains an area of considerable debate.

The outcome of the CaVenT, ATTRACT, and the proposed United Kingdom–based RCTs should provide further guidance regarding exclusion and inclusion criteria for CDT (Table 7). Detailed health-economic analyses of the use of CDT and thrombectomy devices are required to establish the cost-effectiveness of this treatment. Finally, encouraging results regarding CDT in the management of DVTs should not detract from meticulous DVT prophylaxis in all at-risk patients.

Conclusions
Venous thromboembolism is common and has a significant socioeconomic impact. The present therapeutic strategy in the form of oral anticoagulation does not prevent the PTS and venous ulceration, even when combined with elastic compression stockings.

CDT is effective in achieving clot lysis in acute thrombosis, and this may help to prevent PTS and subsequent ulceration. The incidence of serious complications is acceptable following these procedures. Patient selection is of importance to achieve maximum benefit at the lowest risk.
and the reports of several ongoing RCTs are awaited to help define who will benefit most. Based on these trial results, the cost-effectiveness of CDT will be effectively determined. This is needed before the routine use of CDT can be advocated.

**Disclosures**

None.

**References**


Indications for Catheter-Directed Thrombolysis in the Management of Acute Proximal Deep Venous Thrombosis
Benjamin O. Patterson, Robert Hinchliffe, Ian M. Loftus, Matt M. Thompson and Peter J.E. Holt

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