Journal of Thrombosis and Haemostasis, **13** (Suppl. 1): S245–S251 DOI: 10.1111/jth.12940

INVITED REVIEW

Interventional therapy for venous thromboembolism

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To cite this article: Vedantham S. Interventional therapy for venous thromboembolism. *J Thromb Haemost* 2015; **13** (Suppl. 1): S245–S51.

Summary. Advances in image-guided, catheter-based interventions have shown great potential to improve outcomes in patients with venous thromboembolism. Catheter-directed thrombolysis has been shown in one randomized controlled trial to reduce the risk of post-thrombotic syndrome in patients with acute lower extremity deep vein thrombosis; data from a larger national institute of health trial are expected in early 2017. The use of catheter-directed thrombolysis is also being increasingly considered for patients with submassive or massive pulmonary embolism. Preliminary studies suggest that endovascular stent placement and ablative therapies may be used to reduce symptoms and improve quality of life in severely affected patients with established post-thrombotic syndrome. In this article, we summarize the risks and benefits of endovascular venous thromboembolism therapies as currently understood, highlight clinical situations where their benefit may outweigh risks, and describe ongoing and upcoming pivotal research initiatives with multidisciplinary participation.

Keywords: deep vein thrombosis; fibrinolysis; postthrombotic syndrome; pulmonary embolism; stent; venous thromboembolism.

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs yearly in over 1 in 1000 persons, and is a significant source of mortality and morbidity [1]. In 2008, the US Surgeon General issued a National Call to Action, estimated that between 100 000 and 180 000 deaths from PE occur yearly in the USA [2]. Acute DVT causes pain and swelling, and accounts for more than 250 000 hospitalizations yearly in the USA. Patients with VTE are also prone to the development of long-term complications. Recurrent VTE episodes occur in a substantial minority of patients, and approximately 40% of patients with a symptomatic first-episode DVT will develop the post-thrombotic syndrome (PTS) within 2 years of the DVT episode [3–5]. Cardiopulmonary dysfunction or reduced exercise tolerance develops in many PE survivors, with 4% developing full-blown chronic thromboembolic pulmonary hypertension (CTPH) [6].

Physicians who care for patients with severe manifestations of VTE are often faced with difficult decisions concerning escalation to more aggressive therapies that incorporate the use of endovascular procedures to mitigate short-term and long-term VTE risks. The purpose of this article was to summarize the current evidence pertaining to the use of interventional therapies for DVT, PE, and PTS.

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Thrombolytic therapy for acute DVT

Anticoagulant therapy prevents PE, thrombus extension, and VTE recurrence, and is therefore the mainstay of VTE treatment. Despite the use of anticoagulant therapy, prospective contemporary studies indicate that PTS develops in approximately 40% of patients who suffer a first episode of symptomatic lower extremity DVT [4,5]. PTS is a chronic condition that typically causes daily limb pain/aching, fatigue, heaviness, and/or swelling, which worsens with upright position and activity. In severely affected patients, limiting venous claudication, stasis dermatitis, subcutaneous fibrosis, and/or skin ulceration may develop. It is therefore not surprising that a large multicenter prospective cohort study, the Venous Thrombosis Outcomes (VETO) study, found the presence and severity of PTS to be the leading predictors of patients' health-related quality of life 2 years after a DVT episode [7]. The direct medical costs of treating PTS and the indirect costs of the related work disability have been shown to result in a substantial economic burden [8]. As recurrent ipsilateral DVT is associated with a 2- to 6-fold increased risk of PTS, anticoagulation should be viewed as a key PTS prevention measure [9]. However, it is clear that despite anticoagulation many DVT patients will still develop PTS.

The anatomic extent of DVT is an important predictor of a patient's subsequent risk of developing PTS.

Importantly, patients with 'iliofemoral' DVT (defined as DVT involving the common femoral vein and/or iliac vein, with or without involvement of other veins as well) experience recurrent VTE twice as frequently as patients with less extensive proximal DVT and have 2-year PTS rates of 50% or greater, despite the use of anticoagulation therapy [4,10]. These patients are also more likely to develop severe PTS manifestations such as disabling venous claudication and venous ulcers [11]. Although the daily use of elastic compression stockings (ECS) was previously thought to decrease the risk of PTS, a large, placebo-controlled, double-blind, multicenter randomized controlled trial (the SOX Trial) recently found no difference in PTS in patients using elastic compression stockings vs. a sham stocking [12].

Catheter-directed thrombolysis (CDT) refers to the direct intrathrombus administration of a fibrinolytic drug via a catheter or device embedded within the thrombus using imaging guidance [13]. The theoretical advantages of intrathrombus infusion are several:

1 Clot removal efficacy is enhanced by the ability to achieve a high intrathrombus drug concentration and avoid bypass of the drug around occluded venous segments via collaterals;
2 the addition of mechanical thrombus disruption with some drug delivery methods may further enhance pharmacological dissolution of thrombus;
3 the improved efficacy may enable reduced thrombolytic drug dose, treatment time, hospital resource use, and bleeding complications;
4 catheter access into the venous system may enable treatment of underlying venous anatomic abnormalities, which may help to reduce the risk of recurrent DVT [14].

In actual practise, CDT can be performed to rapidly reduce thrombus burden, restore venous patency, and reduce venous congestion, which can achieve important therapeutic goals in selected patients:

1 save life, limb, or organ when used urgently in patients with DVT causing acute limb-threatening circulatory compromise (i.e. phlegmasia cerulea dolens) or progressive inferior vena caval thrombosis causing an elevated PE risk or visceral organ compromise [15];
2 enable faster relief of presenting symptoms in patients who exhibit clinical or anatomic progression despite the initial use of anticoagulant therapy;
3 possibly prevent late venous obstruction and valvular reflux, which are key contributors to the development of PTS [14].

However, because the use of fibrinolytic drugs significantly increases the risk of major bleeding, careful patient selection is important and should include consideration of the following factors:

1 Projected Risk of Bleeding—all patients in whom CDT is being considered must undergo careful evaluation for factors that may increase the risk of bleeding, including ongoing or recent active bleeding; recent major surgery trauma, pregnancy, or other invasive procedure; and the presence of lesions that could bleed in critical areas like the central nervous system. A very low threshold should be applied to exclude patients if there bleeding concerns.
2 Clinical Severity of DVT—urgent thrombolysis is indicated to prevent life-, limb-, or organ-threatening complications of acute DVT in situations such as phlegmasia cerulea dolens or extensive inferior vena caval thrombosis. Non-urgent thrombolysis may also be reasonable when there is an increase in clinical severity of DVT or severe physical limitation which are not relieved with anticoagulation alone.
3 Anatomic Extent of DVT—patients with acute iliofemoral DVT (symptom duration < 14 days) are at much-increased risk for PTS and recurrent VTE and therefore appear to represent the most appropriate candidates for CDT [6,14]. In contrast, patients with asymptomatic DVT or isolated calf vein or popliteal DVT should not undergo CDT as the benefit is not likely to outweigh the risks [14,16].

It is also important to consider the patient's life expectancy, baseline ambulatory capacity, and comorbidities, and the patient should be made aware of the risks, benefits, and alternatives.

The range of specific CDT methods is beyond the scope of this article to detail, but is briefly summarized. With traditional drug infusion-only CDT, successful lysis of the thrombus is expected in 80–90% of patients with symptom duration less than 14 days [14,16]. In a multicenter randomized controlled trial (the CaVenT Study) of patients with DVT involving the iliac and/or upper femoral venous system, CDT using recombinant tissue plasminogen activator (rt-PA) infusions (at 0.01 mg kg^{-1} h^{-1} for up to 4 days) with anticoagulant therapy was associated with a 26% relative reduction in the risk of PTS over 2 years (41.1% vs. 55.6%, $P = 0.04$) compared with anticoagulant therapy alone [17]. The amount of residual thrombus post-CDT correlated with venous patency rates at 24-month follow-up ($P = 0.04$), and venous patency at 6 and 24 months correlated with freedom from PTS ($P < 0.001$) [18]. In this study, 3.2% of patients receiving CDT had a major bleed, including one who required surgery and another who received a blood transfusion, but there were no intracranial bleeds or deaths. Limitations of this study include its modest sample size (efficacy outcomes reported in 189 patients) and geographical limitation (four treatment centers in Norway).

In recent years, a number of methods have been developed to enable faster delivery and intrathrombus dispersion of the fibrinolytic drug, with the purpose of enabling faster treatment with reduced drug exposure (and thereby reduced bleeding). Ultrasound-assisted CDT involves the

delivery of the fibrinolytic drug through a specialized catheter that also emits low-power ultrasound energy into the thrombus. However, a randomized trial and another retrospective comparative study did not find an added benefit to use of the ultrasound catheter compared with a standard multisidehole catheter [19,20]. Pharmacomechanical CDT (PCDT) involves the use of catheter-mounted thrombectomy devices along with intrathrombus delivery of fibrinolytic drugs. Retrospective comparative studies suggest that the use of PCDT is associated with reductions in drug dose and treatment time compared with infusion-only CDT [21,22]. Some PCDT methods can enable treatment of selected patients in a single procedure session, further minimizing patient exposure to the thrombolytic drug. However, there are no completed, high-quality randomized controlled trials evaluating PCDT. The NIH-sponsored ATTRACT Trial, which has completed accrual, is expected to provide rigorous data on the benefit-to-risk ratio of PCDT [23].

Endovascular treatment of established post-thrombotic syndrome

Once PTS has developed, some patients can accommodate the daily symptoms with relative ease, but a substantial minority of patients will suffer significant activity limitation and disability that cause major interference with life activities and/or quality of life. A broad range of noninvasive therapies [24] have been utilized for the management of these patients, falling into three general categories:

1. lifestyle modifications such as periodic leg elevation, exercise programs, smoking cessation, and weight loss;
2. medical therapy utilizing anticoagulant drugs, pentoxifylline, diuretics, venoactive medications, nonsteroidal anti-inflammatory drugs, and/or oral pain medications;
3. compressive strategies such as elastic compression stockings, home edema pumps, wearable intermittent compression devices, multilayer compression, and/or minor surgical procedures (e.g. debridement) for the care of associated venous ulcers.

However, none of these treatments has been shown in rigorous clinical studies to consistently provide major improvement to patients with moderate-to-severe PTS.

Although the pathogenesis of PTS is complex, the development of ambulatory venous hypertension (AVH) is the final pathway leading to edema, tissue hypoxia and injury, calf muscle pump dysfunction, subcutaneous fibrosis, and skin ulceration [25,26]. Two contributors to AVH after DVT are persistent venous obstruction (due to residual thrombus and fibrotic changes) and valvular reflux (due to damage of the venous valves from the inflammatory response to DVT) [27–33]. Although some venous changes are irreversible or complex to treat, two components that are directly involved in causing the disability of PTS are inherently amenable to endovascular correction:

1. iliac vein obstruction is associated with increased rates of recurrent DVT, large elevations in venous and compartmental pressures, progressive valvular deterioration, impaired response to compression therapy, and delayed venous ulcer healing.
2. saphenous vein reflux is also common in PTS and plays an important role in its clinical sequelae.

Patients with iliac vein obstruction, with or without saphenous reflux, are especially prone to the more debilitating manifestations of PTS such as severe short-distance venous claudication; massive edema that, because it involves the thigh as well as the calf, is more restrictive to activity and less amenable to relief with compression; and venous ulceration.

In recent years, endovascular techniques have been applied to selected patients with PTS in some clinical practises [34,35]. Although data from controlled clinical studies are currently lacking, case series and prospective cohort studies suggest that at least some subgroups of patients with PTS may benefit from the integration of endovascular therapy into the overall management strategy. For any patient, it is first important to consider whether the clinical severity of disease merits an aggressive treatment approach. As stents may be associated with recurrent thrombosis or other as yet unknown long-term risks, their implantation should be targeted to those patients in most need of benefit, and only after conveying the risks and uncertainties to the patient during the informed consent process. Although there is substantial diversity of clinical practise, we believe that most patients in whom an endovascular approach is being contemplated fall into CEAP Clinical Classes 4–6 (major skin changes and/or an ulcer), or CEAP Clinical Class 3 with massive edema or severe venous claudication.

A careful clinical assessment should first be performed which includes a directed medical history and a physical exam that includes inspection of both lower extremities; the groins, buttock, and perineal regions; and the pelvis and lower abdomen. The physical exam is usually supplemented with venous duplex ultrasound to evaluate for signs of obstruction of the iliac vein and/or common femoral vein, and valvular reflux in the great and small saphenous veins. The physician should verify that key elements of low-risk conservative therapy have been utilized—at a minimum, anticoagulation appropriate for the history of DVT and PTS, elastic compression stockings, pentoxifylline, education on risk factors, and professional wound care for venous ulcers. The details of provision of conservative PTS therapy are beyond the scope of this article, but are well covered in other resources [24].

In patients who have moderate-to-severe PTS and iliac vein obstruction, endovascular stent placement may be

used to restore iliac vein patency and reduce the degree of AVH. This procedure can be performed in outpatient fashion, with use of either conscious sedation or general anesthesia. Although there is currently no FDA-approved venous stent, currently most practitioners utilize overlapping self-expandable bare stents ranging from 14 to 18 mm in diameter, placed from a variety of percutaneous venous access sites (internal jugular vein, popliteal vein, common femoral vein) depending on the operator's preference and the anatomy of the venous obstruction.

In preliminary studies, stent placement in chronically occluded iliac veins reduced obstructive venous physiology, healed ulcers, and relieved symptoms in patients with PTS [36–50]. While there are no randomized controlled trials, the largest series found patients ($n = 464$) with moderate-to-severe PTS to have reduction in pain ($P < 0.0001$ using Visual Analog Scale—VAS), severe pain (41% to 11%), and severe swelling (36% to 18%); ulcer healing (68%); improvement in QOL; and venous pressure reduction after stent placement [44]. Another study showed improvement in claudication, outflow fraction, and calf pump function [47].

Patients who either have a patent iliac vein or who continue to experience lifestyle-limiting PTS symptoms after stent recanalization should undergo repeat duplex ultrasound to evaluate for saphenous vein reflux. If present, endovenous thermal ablation (EVTA) can be used to eliminate the refluxing superficial vein. The underlying mechanism of EVTA is to deliver sufficient thermal energy to the wall of an incompetent vein segment to produce irreversible occlusion, fibrosis, and ultimately resorption of the vein. The thermal energy is delivered by a radiofrequency catheter or a laser fiber that is placed into the target vein under ultrasound guidance [51,52]. The procedure is performed on an ambulatory basis with local anesthetic, with or without conscious sedation. The patients are fully ambulatory following treatment and recovery time is short. The procedure tends to be durable in patients with primary valvular insufficiency, but has not been robustly studied in patients with PTS.

In one study, single-stage percutaneous iliofemoral venous stenting was combined with great saphenous vein stripping or percutaneous great saphenous vein ablation performed by radiofrequency or laser in 99 limbs in 96 patients with PTS [34]. Cumulative primary, assisted primary, and secondary stent patency rates at 4 years were 83%, 97%, and 97%, respectively. After treatment, limb swelling and pain substantially improved. The rate of limbs with severe pain (> 5 on VAS) fell from 44% to 3% after intervention. Gross swelling (grade 3) decreased from 30% to 6% of limbs. Cumulative analysis showed sustained complete relief of pain (VAS = 0) and swelling (grade 0) after 4 years in 73% and 47% of limbs, respectively. Ulcers healed in 26 (68%) of 38 limbs. All quality of life categories significantly improved after treatment. No patients died, and the morbidity with EVTA was largely limited to ecchymosis and thrombophlebitis in the thigh area.

When considering these findings, one should bear in mind the nature of moderate-to-severe PTS as a condition that markedly impairs patients' quality of life yet lacks any consistently effective treatment approach. On the other hand, it should also be remembered that the above studies are relatively small, lack control groups, and have a number of methodological limitations that confer a high potential for bias. Rigorous prospective studies of PTS treatment by multidisciplinary investigator groups are needed. In addition to ongoing industry-sponsored clinical studies being performed with the purpose of obtaining FDA approval for venous stents, the National Heart Lung and Blood Institute has funded a planning grant for the development of the Chronic Venous Thrombosis-Relief with Adjunctive Catheter-Based Therapy (C-TRACT) Trial, which will compare medical vs. endovascular strategies of PTS management. It is hoped that other similar initiatives will come to fruition in short order.

Treatment of acute pulmonary embolism

Patients with acute PE initially undergo risk stratification into three general groups: (i) low-risk or 'ordinary' PE, for which patient outcomes are good with anticoagulation therapy along; (ii) high-risk or 'massive' PE, in which patients show signs of acute hemodynamic compromise; and (iii) intermediate risk or 'submassive' PE, in which patients are hemodynamically stable but show evidence of right ventricular dysfunction [6]. In modern practise, aggressive strategies are frequently used for patients with massive PE and are considered for patients with submassive PE because these patients are at higher risk for short-term morbidity and long-term quality of life impairment.

Systemic thrombolysis refers to the administration of a fibrinolytic drug through an intravenous line that is distant from the target vessel(s). Three meta-analyses have recently summarized the results of 16 randomized controlled trials that compared systemic thrombolysis to anticoagulation alone for the treatment of acute PE [53–55]. These trials suggest that systemic thrombolysis probably does reduce mortality and prevent hemodynamic decompensation in patients with massive PE, at the price of an increased risk of major and intracranial bleeding. While the results of systematic meta-analyses differ on whether systemic thrombolysis reduces mortality in patients with submassive PE, it clearly increases major bleeding 3-fold and intracranial bleeding about 5-fold. These offsetting risks and benefits have reduced the degree of enthusiasm for systemic thrombolysis for submassive PE.

On the other hand, several studies have demonstrated improved long-term cardiopulmonary physiology in PE patients who received thrombolysis. For example, the

double-blind, placebo-controlled, randomized TOPCOAT study found systemic thrombolysis recipients to be more likely to have normal right ventricular (RV) function, exercise capacity, and perception of physical wellness (assessed using the SF-36 QOL measure) at 3 months compared with patients treated with anticoagulation alone [56].

The idea that thrombolysis may offer important clinical benefits, combined with the reluctance to utilize full-dose systemic thrombolytic administration, has increased interest in catheter-directed techniques that utilize lower doses of thrombolytic agent, thereby potentially lowering the bleeding risk. In a systematic review of 594 patients from 35 studies who received a heterogeneous array of catheter-based therapies, clinical success was achieved in 87% of patients undergoing catheter-directed therapy with a relatively low frequency of major complications [57]. However, the data in this review were derived mainly from case series and small cohorts, precluding firm conclusions from being drawn.

In recent years, ultrasound-assisted CDT has undergone prospective evaluation for the treatment of patients with acute PE. In a randomized controlled trial of 59 patients with submassive PE, ultrasound-assisted CDT (using the EkoSonic® Endovascular System, Bothell, WA, USA) with 20 mg total dose rt-PA plus anticoagulation reduced the RV/LV diameter ratio from baseline to 24 h to a greater extent than anticoagulation alone [58]. No patients undergoing ultrasound-assisted CDT died, suffered recurrent VTE, or developed major bleeding. A subsequent prospective, single-arm, multicenter study of ultrasound-assisted CDT in 150 patients with acute massive or submassive PE found similar hemodynamic effects, with a major bleeding rate of 10% (of whom one patient had a severe GUSTO bleed) (Piazza *et al*., presented at American College of Cardiology Meeting on March 30, 2014). The EkoSonic® Endovascular System is now FDA-approved for the treatment of PE. However, data from larger randomized trials will be needed to determine whether ultrasound-assisted CDT or any catheter-based method should be routinely employed for the management of submassive PE on the basis of mortality reduction or prevention of long-term PE sequelae. In addition, it remains unclear whether the same clinical outcomes would be achieved with CDT delivered without the ultrasound energy.

At present, the use of catheter-directed therapy for acute PE may be considered for hemodynamically compromised patients or those with significant RV dysfunction when systemic thrombolysis has failed or as an alternative to systemic thrombolytic therapy, if local expertise is available [59]. For patients with absolute contraindications to thrombolysis, catheter-assisted embolectomy without thrombolysis may be used, but clinical efficacy is uncertain and probably lower than for drug-based CDT. If catheter-directed therapy is incorporated into local PE treatment algorithms, close monitoring of the actual outcomes achieved in local practises is recommended.

Conclusion

Endovascular therapy holds great promise to improve treatment outcomes in patients with acute DVT, established PTS, and acute submassive/massive PE. This domain of treatment and study is finally entering the realm of evidence-based medicine with conduct of pivotal randomized trials led by multidisciplinary investigator groups. Within 5–10 years, it is likely that clinical practise will be guided by these rigorous efforts to characterize the risk-to-benefit ratio of endovascular VTE therapies.

Disclosure of Conflict of Interests

The author reports grants from Covidien, Bayer Healthcare, and Volcano Inc; and non-financial support from BSN Medical and Genentech, outside the submitted work.

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