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Narrative Review

# Is there a role for intervention radiology for the treatment of lower limb deep vein thrombosis in the era of direct oral anticoagulants? A comprehensive review

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ABSTRACT

Despite recent advances in the treatment of Deep Vein Thrombosis (DVT) provided by Direct Oral Anticoagulants (DOAC), a substantial proportion of lower limb DVT patients will develop some degree of post-thrombotic syndrome (PTS) within 2 years.

Systemic thrombolysis, although effective in reducing the risk of PTS and leg ulceration, is associated with a high risk of major bleeding, making it unsuitable for the vast majority of patients.

A local approach, aimed at delivering the fibrinolytic drug directly into, or near to, the thrombus surface, is attractive because of the possibility of lowering of the administered drug dose, thus reducing the bleeding risks.

However, even after the recent publication of the ATTRACT trial, only weak evidence is available about the efficacy and safety of Catheter Directed Thrombolysis (CDT), either alone (pharmacological technique) or in combination with additional endovascular approaches (pharmacomechanical technique, PMT) including percutaneous mechanical thrombectomy, angioplasty with or without stenting and ultrasound-assisted CDT.

The present review is aimed at providing the physicians with a comprehensive evaluation of the current evidence about this relevant topic, in order to build a reliable conceptual framework for a more appropriate use of this resource.

## 1. Introduction

Anticoagulation with unfractionated (UFH) or low-molecular weight heparin (LMWH) followed by anti-vitamin K oral anticoagulants (AVK) has been established as the standard therapy for the treatment of acute Deep Vein Thrombosis (DVT), aimed at prevention of thrombus propagation, pulmonary embolism (PE) and disease recurrence [1].

Recently, the risk/benefit profile of the anticoagulant treatment has been further improved by the introduction of direct oral anticoagulants (DOACs), which have been demonstrated to be at least as effective as, and safer than, AVK for the initial and long-term treatment of Venous Thromboembolism (VTE) [2,3].

Despite optimal anticoagulant therapy, up to 40% of lower limb DVT patients will develop some degree of post-thrombotic syndrome (PTS) within 2 years [4]. PTS typical symptoms include pain, itching, heaviness, pain during ambulation, edema, varicose veins, hyper-pigmentation and in the worst scenario skin breakdown with ulceration. Depending on the severity of these symptoms, PTS may cause major long-term quality-of-life impairment. Although not exactly quantified, the direct and indirect costs of PTS can be assumed as relevant, because PTS not only often requires high-intensity medical care, but also hampers employability [4].

Among other factors, location of thrombosis is an independent predictor of PTS, because iliofemoral DVT is associated with significantly higher recurrence rates and more chronic complications compared to patients with infrainguinal DVT alone [5,6].

Anticoagulation alone does not treat the obstructing thrombus itself and lacks fibrinolytic activity, and systemic thrombolysis has been considered an attractive strategy for the treatment of DVT. However, this treatment, although effective in reducing the risk of PTS and leg ulceration, has been demonstrated to carry a significantly higher risk of major bleeding [7].

A different strategy to achieve pharmacological thrombolysis is to deliver the fibrinolytic drug directly into, or near to, the thrombus

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surface, in order to enhance its effects while reducing the dose, thus reducing the bleeding risks.

Such an approach has a strong pathophysiological background, as the conversion of plasminogen into plasmin by tissue-type plasminogen activator occurs efficiently only on the fibrin surface, where activator and plasminogen are assembled. Moreover, free plasmin in the blood is very rapidly inactivated by α2-antiplasmin, but plasmin generated at the fibrin surface is partially protected from inactivation [8].

Catheter Directed Thrombolysis (CDT) has emerged as an alternative/adjunct treatment for DVT since the early 1990s as an "early thrombus removal technique" [9].

CDT can be used alone (pharmacological technique), but it is often associated with additional endovascular approaches (pharmacomechanical technique, PMT) including percutaneous mechanical thrombectomy, angioplasty with or without stenting and ultrasound-assisted CDT [10].

However, the evidence about the efficacy and the safety of such techniques is scarce, and their use is often based on the personal experience of the attending physician, with a conspicuous heterogeneity among the clinical behaviors [11].

On these premises, we decided to perform a comprehensive review of the available evidence about CDT and PMT in patients with lower limb, acute DVT, aimed at providing a reliable conceptual framework for a more appropriate use of this resource.

The MEDLINE electronic database was searched without temporal limits using English language as a restriction. The Medical Subject Heading and key words used were: "Deep Vein Thrombosis", "Anticoagulant Drugs", "Thrombolytic Therapy", "Mechanical Thrombolysis", "Rivaroxaban", "Apixaban", "Edoxaban", "Dabigatran", "Warfarin". We also screened the reference lists of the most relevant review articles for additional studies not captured in our initial literature search.

### 1.1. Catheter-directed thrombolysis (CDT)

CDT is the most commonly used endovascular therapy and involves the delivery of the thrombolytic agent through a multiple–side-holes infusion catheter positioned within the thrombosed vein. Commonly used thrombolytic agents include recombinant tissue plasminogen activator -the most used lytic drug (rt-PA, alteplase) but also streptokinase and urokinase [12].

This technique allows to attain higher local drug concentrations inside the thrombus and to lower the total administered dose of the thrombolytic agent respect to its systemic administration.

Since the first reports of CDT [9], more evidence about the efficacy and the safety of this treatment has been provided by a multicenter registry [13] and by prospective [14] and retrospective [15,16] observational studies. Only two randomized controlled trials (RCT) have compared CDT plus anticoagulation versus anticoagulation alone in the treatment of proximal lower limb DVT [17–19].

The trial from Elsharawy et al. was a single blind trial including 35 patients with iliofemoral DVT randomized to CDT with streptokinase or to with intravenous heparin. Warfarin begun the same evening in both groups [17]. The primary end-points of complete clot lysis and absence of reflux at 6 months were achieved in 13 (72%) patients in the treatment group vs. 2 patients (12%) in the control arm ($p < 0.001$). No major bleeding or death were recorded in both groups.

The CavenT trial [18,19], was a large RCT which randomized 209 adult patients with a first-time iliofemoral DVT to conventional anticoagulant treatment alone or additional CDT in an intention-to-treat analysis. The primary outcomes were venous patency rates after 6 months and frequency of post-thrombotic syndrome defined by Villalta score [20] after 2 years.

At completion of 24 months' follow-up, 37 (41·1%, 95% CI 31·5–51·4) patients allocated to additional CDT presented with PTS compared with 55 (55·6%, 95% CI 45·7–65·0) in the control group ($p = 0·047$); absolute risk reduction (ARR) = 14·4% (95% CI 0·2–27·9). 20 bleeding complications related to CDT were reported; three major (one abdominal wall hematoma necessitating blood transfusion, one compartment syndrome of the calf needing surgery, and one inguinal puncture site hematoma) and five clinically relevant. No bleeding complications in patients allocated to control were reported during the same period. There were no deaths, pulmonary embolisms, or cerebral hemorrhages related to CDT [20].

The Authors concluded that CDT reduced PTS compared with anticoagulation alone, at the cost of a small additional risk of bleeding, lower than that reported with systemic thrombolytic treatment. The same group reported later the results of the predefined secondary outcomes of this trial, i.e. PTS development, patency and reflux, and quality of life 5 years after the index DVT [21].

They found that CDT reduced the risk of PTS 43% of pts. allocated to CDT vs 71% to anticoagulation alone ($p < 0.0001$, ARR = 28%, 95% CI 14–42, number needed to treat = 4, 95% CI 2–7) as well as its severity, but did not improve the quality of life.

The trial from Elsharawy et al. [17] and the CavenT trial [18] are the only RCT evaluating CDT included in the already cited meta-analysis by the Cochrane Collaboration group comparing any kind of thrombolysis (systemic, loco-regional and catheter-directed) plus anticoagulation to anticoagulation alone for lower limb acute DVT [7]. Among the 224 pts. included, 58 (out of 116) patients receiving standard anticoagulation had complete clot lysis compared to 81 (out of 108) in the CDT group (RR 2.52. 95% CI 0.52 to 224); 55 (out of 99) patients in the standard anticoagulation group developed intermediate PTS (6 months to under 5 years after treatment) compared to 37 (out of 90) in the CDT group (RR 0.74, 95% CI 0.55 to 1.0). 63 (out of 89) patients in the control group developed late PTS (5-year follow-up after treatment) compared to 37 (out of 87) in the CDT group (RR 0.60, 95% CI 0.45 to 0.79). Regarding the safety, no bleeding complications were recorded in the control group up to 1 month after treatment compared to 3 major bleeding in the CDT group (RR 7.69, 95% CI 0.40 to 224). No significant effect on mortality was detected.

The Authors concluded that systemic thrombolysis and CDT had similar levels of effectiveness (quality of evidence: moderate because of the wide confidence intervals around the estimate of the effect). This meta-analysis was updated in 2016 with no change to conclusions [21].

A further meta-analyses published in 2015 included 3 RCTs [17–19], 1 prospective study [14] and 2 retrospective studies [15,16] [22]. The primary outcomes considered were PTS and major bleeding complications, and the secondary outcomes included iliofemoral patency rate, deep venous function, mortality, pulmonary embolism, and recurrent DVT.

The Authors found that patients treated with CDT had a significantly higher rate of patency at 30 days and 6 months (respectively, OR = 91, 95% CI 19.28 to 429.46, $p < 0.05$ and OR = 5.77, 95% CI 1.99 to 16.73, $p < 0.05$). Compared with standard anticoagulation treatment, additional CDT was associated with a lower rate of PTS (OR = 0.4; 95% CI 0.19 to 0.96), and a lower rate of venous obstruction (OR = 0.20; 95% CI 0.09 to 0.44). No difference between the two treatments was found in terms of mortality, pulmonary embolism, or recurrent DVT. CDT group showed a significant increase in major bleeding events (OR 2.06, 95% CI 1.62 to 2.62, $p < 0.05$).

The Authors concluded that additional CDT therapy seems to be more effective than standard anticoagulation treatment alone in improving the venous patency and preventing venous obstruction and PTS, but at cost of an increased risk of major bleeding. CDT was not found to offer benefits in terms of mortality, recurrent DVT, or pulmonary embolism.

### 1.2. Pharmacomechanical techniques (PMT)

This term refers to the various techniques aimed at mechanically removing the thrombus from the venous system, often performed along