"Early thrombus removal" in iliac-femoral deep vein thrombosis for prevention of post-thrombotic syndrome

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The post-thrombotic syndrome (PTS) is a long-term complication of deep vein thrombosis (DVT) of the lower limbs occurring in 40–50% of patients (1). Impaired thrombus resolution with persistent obstruction is involved in the pathogenesis of PTS, similarly to chronic thromboembolic pulmonary hypertension (CTEPH), which however develops only in a small minority of subjects after pulmonary embolism (PE) (2). Both PTS and CTEPH are associated with substantial morbidity and high healthcare expenses (2). PTS epidemiology reflects that of venous thromboembolism (VTE), which is estimated to affect 104–183 subjects per 100,000 person-years among Caucasians (3,4), encompassing PE and DVT, with an incidence ranging from 29 to 78 and 45 to 117, per 100,000 person-years, respectively (5,6). PTS can occur in severe forms in 10% and with the development of leg ulcers in 1–3% of patients (1). Leg ulcers tend to recur and pose a relevant mobility and health care burden (7).

PTS pathophysiology involves presumably two main mechanisms: vein outflow obstruction due to residual thrombus or venous scarring and venous reflux due to venous valve damage produced by inflammatory response to thrombosis (8). As a result, venous hypertension ensues with persistent high venous pressure with walking or exercise (contrary to the healthy state) and with venous claudication and ankle swelling. Venous hypertension is associated with an inflammatory response, with increased vascular permeability, leukocyte recruitment, tissue hypoxia due to a fibrin cuff forming around capillaries, all leading to damage to the skin with typical changes defined as lipodermatosclerosis and ulceration (9).

Several factors have been demonstrated to be associated with the risk of developing PTS. The anatomical extension with the involvement of iliac and femoral veins can increase the risk by 2-fold when compared to calf DVT, ipsilateral recurrent DVT is associated with a 4–6-fold increase, by promoting further damage of previously compromised venous valves or worsening obstruction of venous flow. Persistent DVT symptoms/signs 1 month after the acute phase are also associated with the risk of subsequent PTS (10).

Pharmacological strategies for prevention and treatment of acute and chronic phases of both DVT and PE have been explored by a very large number of randomized clinical trials in the past 30 years. These trials have demonstrated the efficacy and safety of anticoagulants, such as low molecular weight heparin (LMWH), vitamin K antagonists (VKA) and more recently direct oral anticoagulants (DOACs), for both the primary and secondary prevention of DVT and PE (11,12). These trials however have not usually considered PTS or CTEPH among their outcomes (13). As a result, there are limited evidence-based approaches for prevention and treatment of chronic complications such as PTS and CTEPH.

Preventing DVT is obviously a relevant step for also preventing PTS, but after DVT occurrence, an adequate quality of anticoagulant treatment and prevention of recurrence, especially of ipsilateral DVT, are other useful steps. Two studies have shown that an insufficient quality of anticoagulation treatment with VKA as expressed by a subtherapeutic international normalized ratio (INR) that is an INR below <2.0 for more than 20–50% of the time in the first 3 months of treatment is associated with a 2–3-fold increased risk of PTS (14,15). No effect on PTS development is associated with the quality of anticoagulation beyond the first 3 months or with the duration of anticoagulation (16). It is plausible that the first four weeks of anticoagulation are crucial for vein recanalization as continued thrombin generation in this time frame may retard clot lysis with resulting connective tissue growth and persistent fibrotic occlusion and venous damage (10). DOACS are now available for DVT treatment and they have a potential advantage over VKA for preventing PTS as they might produce a sustained and less variable anticoagulant activity, especially in the initial acute phase, thus favouring vein recanalization. A post-hoc analysis of the Einstein DVT trial showed a non-statistically significant difference in the cumulative PTS incidence rates at 60 months of follow-up between rivaroxaban arm (29%) and enoxaparin/VKA arm (40%) (17).

Anticoagulants do not dissolve thrombi, but only limit their extension allowing the fibrinolytic system to slowly degrade their fibrin mesh over time. Another approach, the so called "early thrombus removal", has been proposed since the 90's as an adjunctive to anticoagulation. Such an approach involves immediate thrombus dissolution or removal with the aim to obtain an "open vein" and thus to limit valvular damage and vein scarring thus potentially preventing PTS development. Such an adjunctive approach can be performed with the infusion of thrombolytics locally into the thrombus, by catheter directed thrombolysis (CDT). CDT can be performed with different techniques such as multiple–side-holes infusion catheter with continuous infusion/pulse-spray infusion of fibrinolytic drug [streptokinase, urokinase, tissue type Plasminogen Activator (t-PA)] delivered into, or near to, the thrombus, to potentiate thrombolysis with reduced doses, with lower bleeding risks. Another approach for early thrombus removal is pharmaco-mechanical thrombectomy (PMT) by which the fibrinolytic drug is delivered directly into the thrombus with concomitant thrombus removal by aspiration or maceration, the latter being performed by different devices such as rotating motorized systems, rheolytic instruments, ultrasound enhanced devices. Adjunctive therapy can be performed in case of persistent obstructive lesions such as intravenous procedures balloon dilatation and stenting. PMT has many theoretical advantages over CDT in particular shorter treatment times with shorter hospital stay, thrombolytic lower dosages with less systemic side effects, more complete thrombus removal, incremental cost effectiveness ratio, fewer venographies. In spite of these theoretical advantages, few randomized clinical trials comparing early thrombus removal by CDT or PMT with standard anticoagulation are available.

In a meta-analysis of RCTs comparing thrombolysis by any route (systemic, loco-regional and catheter-directed) plus anticoagulation versus anticoagulation alone for acute DVT, the Cochrane Collaboration group included only two randomized clinical trials (RCT) evaluating CDT in 224 pts affected by femoral and iliac-femoral DVT. These two studies, albeit in a very limited sample, showed that CDT achieved more effective complete lysis, with improved venous patency with a reduction of PTS at 5 years [relative risk (RR): 0.60; 95% confidence intervals (CI): 0.45–0.79], when compared with standard anticoagulation, albeit with increased bleeding in the CDT group (RR: 7.69; 95% CI: 0.40–224) (18). A more recent meta-analysis drew similar conclusions indicating that CDT decreases the incidence of PTS when treating iliac-femoral DVT, while PMT does not (19).

The largest RCT on PMT was the National Institutes of Health sponsored, phase III, multicenter open-label, assessor-blinded, parallel two-arm, ATTRACT controlled clinical trial (Acute venous thrombosis: thrombus removal with adjunctive catheter-directed thrombolysis). The aim of the ATTRACT study was to determine whether the use of pharmaco-mechanical catheter-directed thrombolysis (PCDT) adjunctive to standard anticoagulation compared with standard anticoagulation alone for above-the-knee DVT prevents PTS over a follow-up of 2 years (20).

The ATTRACT study was performed in 56 centers in USA. The thrombolytic drug for PCDT was recombinant tissue plasminogen activator (rt-PA- alteplase, Activase®, Genentech, South San Francisco, CA, USA) which was infused into the thrombus using one of three methods: a standard multi-sidehole catheter ("infusion-first"); the AngioJet Rheolytic Thrombectomy System (Boston Scientific, Malborough, MA, USA) ("power pulse-spray" or "rapid lysis" method); or the Trellis Peripheral Infusion System [Covidien, Inc., Mansfield, MA, USA (now

Medtronic), "isolated thrombolysis"]. Rt-PA dosing limits were: (I) 0.01 mg/kg/hr, not to exceed 1.0 mg/hr; (II) no more than 30 hours infusion; (III) no more than 25 mg in any one procedure session; and (IV) no more than 35 mg total.

In case of residual thrombus, balloon maceration, catheter aspiration, thrombectomy, percutaneous transluminal balloon venoplasty, stent placement (iliac or common femoral vein), or a combination of procedures were employed to clear residual thrombosis and treat persistent venous obstruction lesions. Stenting was performed in case of 50% or greater narrowing of vein diameter, robust collateral filling, or mean pressure gradient greater than 2 mmHg.

The primary efficacy outcome was PTS as defined by a Villalta score of 5 or higher or an ulcer in the leg at 6- and 24-month follow-up visit. The trial data showed that PTS developed in 46.7% of patients randomized to adjunctive PCDT, compared with 48.2% receiving anticoagulation alone at 2 years (P=0.56).

Short-term follow-up showed that PCDT was associated with higher major bleeds (1.7%) than anticoagulation alone (0.3%; P=0.049). Any bleeding was also more frequent with adjunctive PCDT (4.5%) than control (1.7%; P=0.049). No fatal or intracranial bleeds were recorded in either arm of the trial, suggesting a low risk of such complications with thrombolytics. PCDT was less effective in patients over 65 years (P=0.038).

Patients in the ATTRACT study were stratified by DVT extent (iliac-femoral versus femoral-popliteal) prior to randomization and the paper by Comerota *et al*. reports a post-hoc analysis of 391 patients who presented with acute iliac-femoral DVT (21), which is associated with lower recanalization rates when treated with anticoagulation alone (22).

The initial rt-PA delivery method in PCDT arm patients was the "infusion first" method in 52%, the AngioJet method in 24%, and the Trellis method in 19%. Endovascular methods were used in 91% of patients after initial rt-PA infusion. Standard anticoagulation was conducted mainly with warfarin with a limited number of subjects on DOACs.

The study's primary outcome measure, that is PTS, assessed by the Villalta scale, was observed in 96 of 196 (49%) PCDT arm patients and in 100 of 195 (51%) standard anticoagulation alone arm patients (RR: 0.95; 95% CI: 0.78–1.15; P=0.59) during 24 months follow-up (intention-to-treat analysis), with similar findings in the per protocol analysis in all subgroups evaluated. Moderate-or-severe PTS, as evaluated by a Villalta scale score ≥10 or ulceration, developed in 36 (18%) patients treated with PCDT and in 55 (28%) patients assigned to standard anticoagulation alone (RR: 0.65; 95% CI: 0.45–0.94; P=0.021). Patients <65 versus ≥65 years old and those with versus without a major reversible DVT risk factor at diagnosis appeared less likely to develop moderate-or-severe PTS with use of PCDT.

PCDT produced a significant improvement in DVT symptoms such as leg pain and swelling (P<0.01 for comparisons at 10 and 30 days) and in venous disease specific quality of life (QOL) scales (VEINES-QOL unit difference 5.6 through 24 months, P=0.029), but no difference in generic QOL (comparisons of SF-36 mental and physical component summary scores) over 24 months.

The data from this analysis may suggest that PCDT improves short-term recovery from DVT and reduces long-term progression of PTS severity in patients with iliac-femoral DVT.

However, a major limitation of this analysis was the high number of patients lost to follow-up that was unbalanced between the treatment groups as only 69% (135/195) patients completed the 24-month follow-up for PTS assessment (with 38 patients lost to follow-up) in the standard anticoagulation arm *vs*. 73% (145/196) patients in the PCDT arm (with 37 patients lost to follow-up). Such high proportions of losses to follow-up are a significant limitation of treatment effect estimates. In addition, the ATTRACT trial enrolled only 57% patients with iliac-femoral DVT, thus reducing the power to detect differences in outcomes.

These findings show that the evidence regarding the efficacy and safety of adjunctive early thrombus removal in the acute phase of iliac-femoral DVT to prevent PTS is still quite weak and limited. This approach cannot be universally recommended over standard anticoagulation alone as it also requires additional and specialized resources. It could be still be considered for some patients with severe symptoms (including those with phlegmasia cerulea dolens) and low bleeding risk (23), but only in specialized centres.

Further, some unsolved issues deserve to be mentioned. The mechanical therapies such as rheolytic thrombectomy, angioplasty, and stenting for venous valves employed in ATTRACT trial are quite aggressive and they can further damage venous valves, thus limiting the potential advantages of early thrombus removal for PTS development. The focus of future PTS studies should not be only vein patency, but

also the preservation of venous valve function (23).

In addition, there is uncertainty regarding optimal type and duration of post procedure systemic anticoagulation in the context of adjunctive pharmaco-mechanical techniques with relevant heterogeneity among the trials, with the decision about type and duration of antithrombotic treatment left to the attending investigator (24). Studies aimed at defining the optimal type, dosage, or duration of antithrombotic therapy after endovascular DVT treatment could be warranted.

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Footnote

Conflicts of Interest: Dr. Cosmi received speakers' bureau fees from Daiichi Sankyo and Sanofi in the lats two years. Dr. Palareti has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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