Clinical Trials on Acute DVT Intervention

An insight into current research on catheter-directed thrombolysis.

BY PROF. CEES H.A. WITTENS, MD, PhD, AND MAAIKE J. DE GEUS, MD

The standard method of care for patients with deep vein thrombosis (DVT) is a combination of anticoagulation and compression. This treatment has good short-term outcomes by reducing pain and swelling, as well as preventing pulmonary embolism and death. However, in the long term, a large quantity of patients develop leg complaints, such as cramps, pain, heaviness, paresthesia, pruritus, varicose veins, edema, and skin changes. A combination of these complaints after DVT is called *postthrombotic syndrome* (PTS). This can be as severe as the formation of a painful venous ulcer. PTS has a large influence on quality of life and has an incidence of 50% to 70% after an iliofemoral DVT.[1] PTS is thought to be the result of both residual obstruction and reflux caused by valve incompetence. We know that early clot lysis correlates with better patency and better valve preservation with less reflux.[1-3]

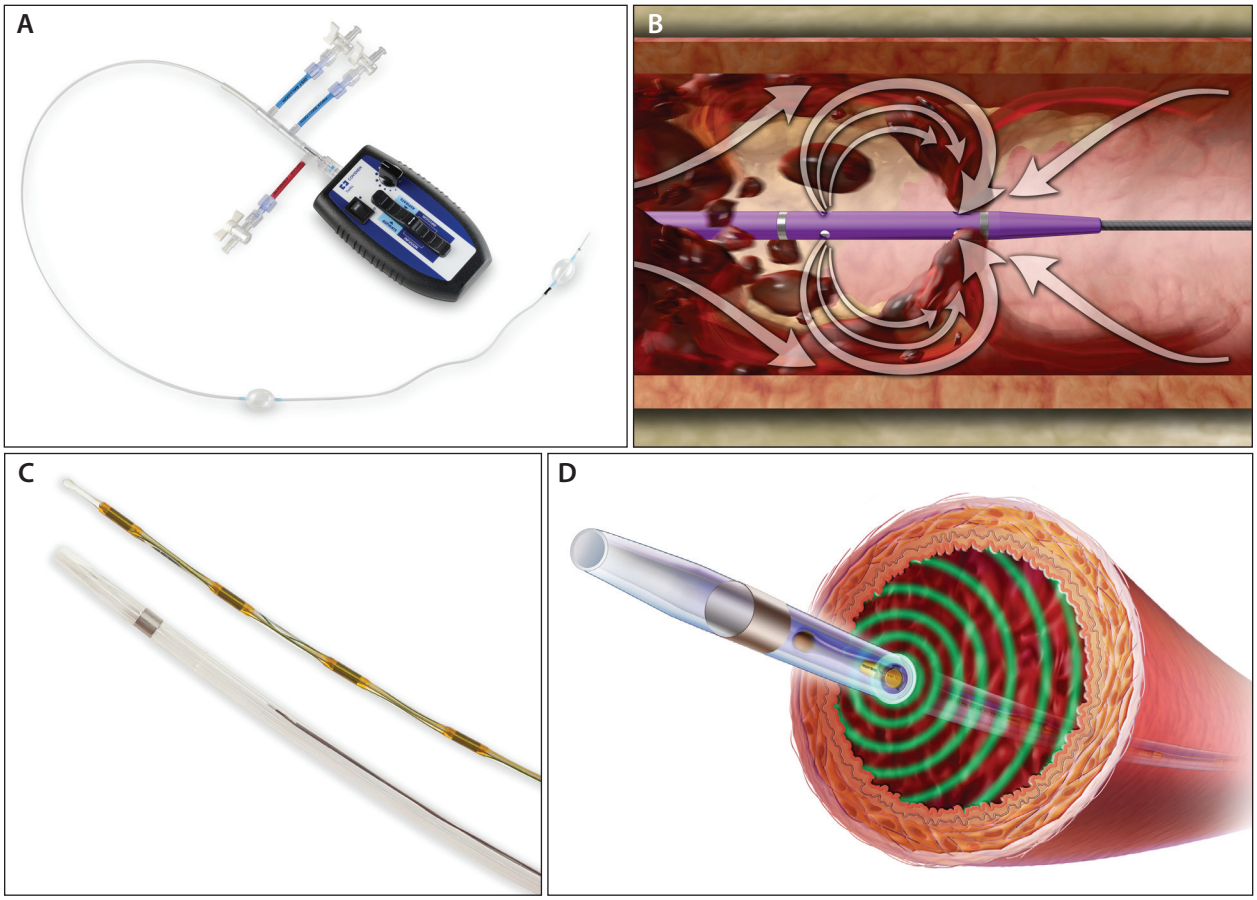
THROMBOLYSIS

The current information suggests that early clot lysis can prevent PTS and thereby improve health-related quality of life. A conventional method of clot removal is thrombolysis. However, systemically administered thrombolytic agents are associated with a high rate of bleeding complications and a low incidence of clot lysis. Therefore, the more sensible course of action is to administer the thrombolytic agent directly into the clot, which is known as *catheter-directed thrombolysis.* Case series have shown that it is a safe and effective method of clot removal,[4,5] and a retrospective study has demonstrated that after catheter-directed thrombolysis, patients have a higher health-related quality-of-life score compared to patients treated only with anticoagulation.[3] A randomized clinical trial that enrolled 35 patients with acute iliofemoral thrombosis showed better patency and valve competence in those treated with catheter-directed thrombolysis compared to those treated with anticoagulation alone.[6] Whether the results of catheter-directed thrombolysis reduce the incidence of PTS and thereby improve quality of life must be evaluated in more randomized clinical trials.

MAJOR CLINICAL TRIALS

To assess the benefits of catheter-directed thrombolysis, there are three major trials to review. All of these trials compare some kind of catheter-directed thrombolysis with a control group treated with anticoagulation and compression. The CAVENT (Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis) trial started in 2006 in Norway. It was a multicenter, randomized controlled trial that included 209 patients with first-time acute DVT involving the iliac, common femoral, and/or upper femoral vein. The investigators used regular perfusion catheters and alteplase as the lytic agent. All patients, both in the intervention and in the control group, received knee-high compression stockings for 24 months and anticoagulation therapy with low-molecular-weight heparin followed by oral warfarin for at least 6 months. The primary outcomes were patency rate at 6 months and PTS, as assessed by Villalta scores over 2 years of follow-up. Secondary outcomes included clinical bleeding, quality of life (measured with the EQ-5D and VEINES-QOL/Sym questionnaires), and PTS related to patency.[7-10] The results were published in *The Lancet* in 2012.[9]

The ATTRACT (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis) study is an ongoing multicenter, randomized, assessor-blinded clinical trial in the United States sponsored by the National Heart, Lung, and Blood Institute. The investigators included 692 patients with symptomatic proximal DVT, whom they will be following for 24 months after treatment. The method of catheter-directed thrombolysis differed slightly from the technique used



Images courtesy of Covidien, Boston Scientific Corporation, and Ekos Corporation.

Figure 1. The Trellis (A), AngioJet (B), and EkoSonic (C, D) devices.

in the CAVENT study. Whereas in the CAVENT study, regular perfusion catheters were used, in the ATTRACT study, pharmacomechanical catheter-directed thrombolysis is used. When there is good inflow to the popliteal vein on initial angiography, either isolated thrombolysis (thrombolysis with an oscillating wire within the catheter [Figure 1A; Trellis, Medtronic; note that this product is no longer commercially available as of April 2015]) or power-pulse thrombolysis (thrombolysis with a powerful pulse-spray catheter [AngioJet, Boston Scientific Corporation]) is performed (Figure 1B). When initial angiography shows poor inflow to the popliteal vein, infusion-first thrombolysis is performed. In this technique, the thrombolytic agent (alteplase) is infused through a multisidehole catheter. When there is any residual thrombus, additional methods of thrombus removal, such as balloon maceration and aspiration or mechanical thrombectomy, are performed. When there are any obstructive lesions, patients could be treated with balloon angioplasty or venous stenting. The primary outcome measure is PTS, as assessed by Villalta scores. Other outcomes are major bleeding, the presence of valvular reflux and/or obstruction at 1 year after treatment, and cost effectiveness.[11] Patient enrollment ended in December 2014, and after follow-up, results are expected in 2017.

The CAVA (Catheter Versus Anticoagulation) trial is the only trial that is still enrolling patients for inclusion. It is a multicenter, randomized controlled trial that is being executed in the Netherlands. The aim is to include 180 patients with recent (< 14 days existing) first-time iliofemoral DVT. These patients will be randomized between ultrasound-enhanced catheter-directed thrombolysis (EkoSonic, Ekos Corporation, a BTG international group) with regular care and a control group receiving regular care alone. For this technique, an EkoSonic device is inserted across the length of the blood clot (Figure 1C and 1D). The device uses miniscule high-frequency ultrasound transducers to achieve better penetration of the thrombolytic agent through the clot. The main outcome of the study is the presence of PTS, as assessed by Villalta scores, or the presence of a venous ulcer at 12 months after randomization. Secondary study outcomes include health-related quality of life (evaluated by the SF-36, EQ-5D, VEINES-QOL/Sym, and pain disability index ques-

tionnaires), recurrent venous thromboembolism during follow-up, clot lysis, patency after 12 months, and bleeding events during anticoagulation therapy. So far, about 110 patients are included in this study.

RESULTS

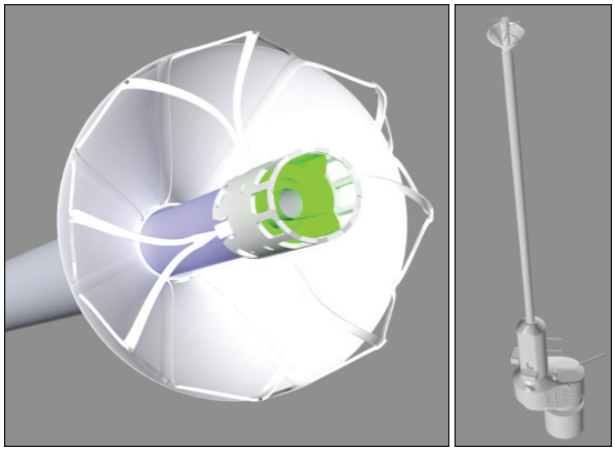
The CAVA and ATTRACT studies are still ongoing, and the results have not yet been published. Therefore, for now, the CAVENT study is the only trial that provides any answers. In this study, a total of 209 patients were included, of whom 101 patients were allocated into the intervention group. Of these patients who were treated with catheter-directed thrombolysis, 10 had unsuccessful lysis. Unsuccessful lysis was defined as < 50% lysis after ending the procedure, technical difficulties, or early ending of the procedure due to bleeding complications. One must note that 39 patients received adjunctive endovascular treatment. This included balloon angioplasty, venous stenting, and in one case, thrombus aspiration. During this study, 20 patients experienced bleeding complications, of which three were major, and five were clinically relevant. Short-term patency was evaluated by ultrasound in 118 patients 6 months after treatment, showing a rate of 64% in those treated with catheter-directed thrombolysis compared to 35.8% in those in the control group. This correlates with an absolute risk reduction of 28.2%.[8]

Long-term results were available for 189 patients and demonstrated an absolute risk reduction for PTS of 14.4% after 2 years. Patency at 6 months proved to be a good predictor of PTS occurrence after 2 years for both groups.[9] When assessing quality of life 2 years after treatment, there was no significant difference between patients allocated to the thrombolytic therapy and patients in the control group. However, those with high Villalta scores (positive for PTS) had a poorer quality of life.[10]

DISCUSSION

When these three randomized trials are finished, it is anticipated that patients who were successfully lysed, with stenting of an identified underlying cause, will do significantly better. Unfortunately, the trial results will be affected by the fact that the methods used are not dedicated devices to treat DVT. Rather, most of these devices were originally developed to treat arterial thrombosis. The clot burden in venous disease is significantly higher, necessitating dedicated devices.

Also, the inclusion of patients with only a femoral DVT who still have good outflow through the common femoral vein could influence the outcome negatively, as conservative treatment in these patients is not expected to perform poorly. The ATTRACT study has stratified the randomization by whether the common femoral iliac was involved, so the subgroup analyses should enable some insight into the differences between the risk-benefit ratio of lysing iliofemoral DVT versus femoral-only DVT. The development and analyses of the Lower Extremity Thrombosis score showed that there is a significant difference in quality-of-life outcome depending on the level of the DVT.[12,13] Thromboses at the calf, upper leg, or abdominal level are known to recanalize in approximately 95%, 85%, and < 50% of cases, respectively, influencing the quality-of-life outcome significantly.



Courtesy of AngioDynamics.

Figure 2. A new, experimental device by AngioDynamics that advances a basket from the popliteal fossa to the inferior vena cava to capture thrombus.

A third issue is that due to the use of lytic agents, patients with cancer or those who have had recent surgery are excluded from this therapy.

It is expected that if these trials show beneficial results after successful treatment, more manufacturers will work to develop an ideal device with which thrombectomy can be performed in an outpatient setting in 1 hour without lytics. Several companies are working on this but are still having difficulties retrieving large amounts of clot at the iliac level and leaving too much residual thrombus. As a consequence, many stent implantations are performed for residual stenosis, potentially related to residual clot, which may not be optimal for a patient's long-term health.

Ideally, a device should retrieve all clot in one run without damaging the valves or wall. Experiments performed with a new device by AngioDynamics (Figure 2) are promising; in these experiments, a basket is advanced from the popliteal fossa to the inferior vena cava, capturing all thrombus in veins that are 8 to 25 mm in diameter. Clinical trials are expected to begin soon. If all thrombus is successfully removed, only real residual

obstructions due to old intraluminal pathology or compression from outside need to be stented.

CONCLUSION

To draw a final conclusion about the effectiveness of early clot removal by pharmacomechanical catheter-directed thrombolysis, one must await the results of the CAVA and ATTRACT studies. However, if those trials show good results, new devices will emerge, and the indications will broaden due to devices obviating the need for thrombolytic drugs and procedures that can be performed on an outpatient basis. ■

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