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EDITORIAL

# Continuing to Advance the Venous Agenda: Long-Term Insights From the CAVA Trial

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Recent pharmacologic and technologic advances have transformed the treatment paradigm for proximal deep vein thrombosis (DVT).[1] The mainstay of therapy involves anticoagulation, which decreases the risk of pulmonary embolization and allows endogenous fibrinolytic enzymes to break down the thrombus.[2] Over the past decade, direct oral anticoagulants have replaced heparins and vitamin K antagonists as the preferred anticoagulant therapy. These medications are highly effective at preventing mortality and recurrence. Despite these advances, significant challenges remain in preventing and treating 1 major sequela of DVT, post-thrombotic syndrome (PTS).

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One of every 2 or 3 patients with acute DVT will go on to develop long-term limb symptoms.[3] The pathophysiology related to development of PTS is hypothesized to be related to 2 processes that may exist concurrently or in isolation to cause venous hypertension. The first is obstruction of deep venous flow by persistent residual thrombus and the second is conversion of compliant vein with functional valves to a stiff fibrotic vessel with refluxing valves. The resulting clinical presentation ranges from asymptomatic venous reflux to limb edema, telangiectasias, skin hyperpigmentation, lipodermatosclerosis, and ulceration in response to very minor trauma. The diagnosis of PTS is based on typical signs and symptoms. It should not be made within the first 6 months of DVT diagnosis because of the acute limb swelling and pain that accompany the initial insult. Although the majority of patients who eventually develop PTS do so within the first 2 years following DVT diagnosis, a steady increase in incidence is seen over 10 to 20 years.[4] PTS costs on average $7000/patient per year for the remainder of his or her life.[5] The most severe manifestation of PTS, venous ulceration, results in 2 million work days lost per year.[3] There is no cure nor highly effective treatment once a patient has been diagnosed with PTS.

Over the past several decades, effort has been made to prevent PTS by removing the acute thrombus, with the assumption that prompt alleviation of the obstruction will prevent impaired venous return, valvular damage, and reflux, a theory coined "the open vein hypothesis."[6] It was observed that patients who had large residual thrombus burden compared with those without were more at risk of developing PTS.[7] Early randomized control trials evaluating open venous thrombectomy and the catheter-directed alteplase therapy CAVENT (Catheter-directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis) trial suggested that there may be a benefit to restoring unimpeded venous flow by reducing PTS incidence by up to 28%, with the most compelling data emerging after 5 years of follow-up.[8,9] Advances in endovascular technology such as suction thrombectomy devices, large caliber nitinol stents designed specifically for the venous system, and catheters with ultrasonic cores

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have been singe designed to address the obstructive pathophysiology of PTS.

Patient selection for invasive treatment and optimal endovascular technique for clearing the acute proximal obstructive thrombus has been an evolving topic. In the contemporary era, both the ATTRACT (Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis) and CAVA (Ultrasound-accelerated Catheter-directed Thrombolysis versus Anticoagulation for the Prevention of Post-thrombotic Syndrome) trials attempt to address the utility of modern endovascular therapy as a method of PTS prevention. The widely publicized ATTRACT trial randomized patients to receive pharmacomechanical catheter-directed thrombolysis or standard of care anticoagulation. Data from the trial showed no protection from PTS development at 24 months but did find a decrease in PTS severity among patients with obstructive DVT in the iliofemoral segment.[10,11] The CAVA trial, in comparison, used acoustic pulse thrombolysis with the premise that this technique speeds dispersion of the thrombolytic agent throughout the thrombus and avoids injury to the vein that may occur with mechanical thrombectomy devices.[12,13]

The primary outcomes of the CAVA trial demonstrated no significant decline in PTS with the use of ultrasound-accelerated catheter-directed thrombolysis as compared with standard treatment (primarily anticoagulation) over a 12-month follow-up period.[14] However, many patients develop significant PTS-related symptoms beyond 1 year after acute DVT. Therefore, in this issue of the *Journal of the American Heart Association (JAHA)*, Dr. Notten and colleagues performed a prespecified analysis of the CAVA trial to examine the impact of ultrasound-accelerated catheter-directed thrombolysis on the incidence of PTS over more than 3 years of follow-up.[15] In this analysis, PTS is primarily defined as a Villalta score of ≥5 on 2 occasions at least 3 months apart or the presence of a venous ulceration. A secondary definition of PTS relied on the International Society on Thrombosis-consensus method, which included venous ulceration or a Villalta score ≥5 occurring ≥6 months after initial presentation.

In this analysis, 120 of the 152 (78.9%) patients included in the initial intention-to-treat analysis were followed for a median 39.0 months (interquartile range, 23.3–63.8). PTS, using the primary definition, occurred in 19 of 62 (30.6%) patients who received thrombolysis as compared with 26 of 58 (44.8%) patients who received standard therapies (odds ratio [OR], 0.54; 95% CI, 0.26–1.15; *P*=0.11). There were a small number of new PTS diagnoses made after the 12-month primary outcome results from the original CAVA publication. There was no difference in severity of PTS between the intervention and control groups in longer term follow-up.

When PTS was defined using the International Society on Thrombosis-consensus method, the proportion of patients who developed PTS was lower in the group randomized to thrombolysis therapy (29/62 [46.8%] versus 40/58 [69.0%]; OR, 0.40, 95% CI, 0.19–0.84; *P*=0.01). This difference was primarily concentrated among patients with mild PTS (12/62 [19.4%] versus 24/58 [41.4%], *P*=0.01).

Use of compression therapy declined during longer term follow-up. In the intervention group, the number of patients who refrained from compression therapy increased from 11 (17.7%) at 12 months to 34 (54.8%) at 39 months (*P*<0.001). A similar trend was seen in the control group (17.2%–43.1%, *P*=0.002) without a difference between the intervention and control groups.

These long-term results from the CAVA trial demonstrate 3 key points for clinicians and clinical researchers. First, they confirm the high morbidity associated with acute iliofemoral DVT. Depending on how PTS was defined, between one-third and one-half of patients developed PTS symptoms despite aggressive medical and interventional therapies. This provides important prognostic and natural history data for clinicians to share with patients. It also underlines the importance of continuing to develop and study therapies aimed at reducing morbidity associated with acute DVT. Finally, it exemplifies why prevention of DVT is critically important.

Second, disease state definitions can have important impact in how treatment effectiveness is interpreted. This is particularly important when a laboratory- or imaging-based test is not sufficient to define a disease. In particular, the study of PTS is difficult owing to lack of a widely validated, objective standard scoring system. Although the Villalta score is associated with ambulatory venous pressures, assesses severity of PTS, documents change in severity over time, and has good interobserver reliability, its use is limited by its subjective nature and diagnostic accuracy.[16,17] As clinical trialists increasingly incorporate patient-reported outcomes, using agreed-upon definitions and severity thresholds will be important for comparing outcomes across different trials.

Third, the open vein hypothesis remains just that, an unconfirmed hypothesis. The shortcomings of the CAVENT trial, with a likely underpowered cohort and overlappingCIs, have been highlighted by more recent, larger randomized trials. The CAVA trial, in addition to the CAVENT and ATTRACT trials have failed to uniformly confirm or refute the hypothesis that opening an obstructed vein will improve medium- and long-term morbidity for patients.[8,10,11,18] Subgroup analysis indicate that patient selection is likely paramount. Specifically, patients with more severe and more proximal presentation have an increased likelihood of experiencing benefit from aggressive therapies.[10] Ongoing

studies (eg, NCT00970619, NCT04411316) may offer additional insights into patient selection, specific interventional approaches, and key outcome measures associated with a reduction in PTS following acute DVT.

More than ever, these recent trials have highlighted our lack of full understanding of the pathophysiology of PTS. Numerous studies have documented that thrombus resolution and vein wall fibrotic response occur as independent processes.[19–21] Thus, rapidly resolving the thrombus alone may not lead to a clinically useful outcome if the vein wall and valves are damaged in the process. Vascular fibrosis depends upon interaction of local inflammatory factors and infiltrating immune cells.[22–25] In today's era of personalized medicine, rapid explosion of immune-based biologic therapies represent 6 of the 10 current bestselling pharmaceuticals and half of all ongoing clinical trials.[26] Yet, there are currently no Food and Drug Administration-approved agents that serve to reduce the risk of venous fibrosis. Availability of a safe agent that modulates the vein wall response to thrombosis with or without concurrent thrombus removal would represent a major advancement in PTS prevention.

For now, patient selection remains critically important for acute DVT management. Although the use of routine catheter-directed thrombolysis cannot be supported for all patients with acute DVT, there may be a role in select patients at low risk for bleeding who present with iliac veins thrombosis. In our own practice, those patients who are young, ambulatory, place a high value on avoidance of PTS with iliofemoral DVT, and fail to improve with a short trial of anticoagulation and compression are offered more invasive therapy.[27,28] The results from Dr. Notten and colleagues underscore the high morbidity burden and need to continue exploring both interventional and noninterventional strategies to improve patients' quality of life following acute proximal DVT.

## ARTICLE INFORMATION

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