The Most Impactful Deep Venous Trials to Date

A summary of pivotal and upcoming trials assessing the safety and efficacy of treatment of deep venous disease.

By Misaki Kiguchi, MD, MBA, FACS, and Kyle Reynolds, MD

Chronic venous disease affects approximately 25 million people in the United States alone, contributing to a high health care expenditure.[1] Deep venous disease of the lower extremities, such as acute deep vein thrombosis (DVT) and subsequent chronic venous hypertension, often causes leg heaviness, swelling, discoloration, and, in the severest form, venous ulcers. Rather than relying solely on conservative management, numerous advanced technologies have emerged in the past few decades to address this large unmet need to treat deep venous pathology, beyond anticoagulation and compression. By understanding the most impactful deep venous trials, we have a better understanding of current guidelines and where the future of deep venous technology lies.

ATTRACT TRIAL

Several randomized clinical trials have evaluated the ability for endovascular therapies such as catheter-directed thrombolysis (CDT) and pharmacomechanical CDT (PCDT) to decrease postthrombotic syndrome (PTS) incidence due to chronic venous hypertension from proximal DVT, compared with anticoagulation alone. Published in 2017, the largest trial, ATTRACT, failed to show a reduction in the occurrence of PTS with PCDT compared to anticoagulation alone.[2] However, multiple secondary analyses later demonstrated that for patients with acute iliofemoral DVT, treatment with PCDT decreased early leg symptoms (pain and swelling), PTS symptom severity, and thrombus burden as compared with anticoagulation alone.[3] However, major bleeding complications were noted to be higher in the PCDT group compared to anticoagulation alone. Major challenges to this trial, possibly affecting the conclusions, included an extensive exclusion criterion that limited patient selection, lack of imaging prior to and after intervention to determine residual disease, and not treating underlying pathologies, including venous stenting.

CAVENT TRIAL

At the time of the CAVENT trial, most studies had compared systemic thrombolysis to conventional treatment but not yet CDT. In this randomized controlled trial (RCT), 189 patients with acute iliofemoral DVTs were randomized to conventional anticoagulation alone or CDT with anticoagulation. Results showed no difference in incidence of PTS at 6 months between the two groups; however, the incidence of PTS at 2 years in the CDT plus anticoagulation group was reduced compared to the anticoagulation alone group (41.1% vs 55.6%; $P = .047$). Another important factor of this trial is the risk of bleeding. Although there was a higher bleeding risk in the CDT arm compared to anticoagulation alone in the CAVENT study, it was lower than the results seen in the systemic thrombolysis studies.[4]

CLOUT REGISTRY

Given the bleeding complications of CDT, mechanical thrombectomy (MT) devices have emerged as a favorable alternative to treatment of deep venous obstruction from thrombus. Newer large-bore MT devices have been designed to rapidly remove thrombus in a single session and completely avoid thrombolytics. The CLOUT registry is a prospective, multicenter, single-arm study (the largest of its kind) designed to evaluate real-world outcomes using the ClotTriever system (Inari Medical). Excellent short-term outcomes were report-

ed, with 95% normal flow on duplex and 90% freedom from moderate-severe PTS symptoms at 1 year.[5] Recently, the 2-year follow-up data were presented: Out of 228 patients, there was only a 7.3% incidence rate of moderate-severe PTS.[6] This is significantly lower than the results from the ATTRACT and CAVENT trials. Given that the ATTRACT trial was conducted prior to the newer MT devices, a propensity score–matched analysis was performed using CLOUT and ATTRACT data, allowing a comparison of matched patients with similar baseline characteristics. MT showed superior thrombus extraction and improved 30-day Villalta scores. Nearly twice as many CLOUT patients had complete thrombus removal, and approximately 13% fewer CLOUT patients had a Villalta score > 5 at 30 days.[7]

VENOUS STENTING INVESTIGATIONAL DEVICE EXEMPTION AND 3-YEAR OUTCOME TRIALS

The use of endovascular stent placement for chronic iliofemoral venous obstruction and stenosis has been widely practiced. However, it has become more in the forefront with the availability of FDA-approved, dedicated venous stents, which have higher flexibility and higher radial force compared to nondedicated venous stents. The initial four venous stents Venovo (BD Interventional), Vici (Boston Scientific Corporation), Zilver Vena (Cook Medical), and Abre (Medtronic) were FDA approved in the United States in 2019, following the results of their investigational device exemption (IDE) trials.

The trials (VIRTUS,[8] VERNACULAR,[9] VIVO,[10] and ABRE[11]) mainly focused on safety, efficacy, and short- and long-term stent patency for treating iliofemoral deep venous disease. All four trials showed high overall 12-month patency rates; all IDE trials showed similar 1-year patency rates that were greater in patients with nonthrombotic iliac vein lesions (NIVLs) compared to PTS patients.

All IDE trials have published or presented 3-year data[12-15] and have provided generalized robust data on the safety and efficacy of dedicated venous stents; however, the ABRE trial results have unique differences compared to the other venous stenting trials, reflecting some of the complexity inherent in venous pathology. When looking at the treated PTS cohort in the ABRE trial, patients had longer mean stent lengths (160 mm), longer lesion lengths (135 mm), and a higher number of common femoral vein stents placed (44%) compared to the other IDE trials, aligning closer to the complexity of real-world scenarios in PTS patients. Many of these patients with postthrombotic lesions after iliofemoral DVT have extensive disease from the common femoral vein to the IVC, a diseased segment often > 150 mm, thus the use of longer stents.[16]

Importantly, vital lessons can be gained from the stent failures, more than the successes. Stent occlusions in PTS patients from the ABRE IDE study highlighted reasons for stent failure, including missing disease, more inflow, technical errors, and need for anticoagulation to assist secondary patency. These important "lessons learned" bolstered the success of real-world clinical practice for providers and have promoted best practice guidelines in treating complicated venous pathology.[17]

These IDE trials on venous stenting are pivotal, but generalizations across all trials are difficult to assimilate due to the differences in inclusion criteria and lack of standardization in disease category definitions. This includes inconsistent use of intravascular ultrasound, criteria for adequate inflow and outflow, and imaging evaluation of patency on follow-up. In addition, the classifications of acute, subacute, and chronic thrombotic disease were varied across trials. The VIRTUS trial excluded acute DVT patients, while the VERNACULAR trial included acute DVT patients in the postthrombotic cohort. The ABRE trial included acute DVT patients but evaluated as a separate cohort, defined as patients with symptoms < 14 days. The VIVO trial included an acute DVT cohort for patients with symptoms < 30 days, while symptoms > 30 days were assigned to their chronic cohort.[10] This lack of standardization makes interpretation of results across trials difficult and guidance of clinical decision-making to treat venous disease even more difficult, demonstrating again that stenting for different disease pathologies affects clinical outcomes. For example, in the ABRE 3-year data, the subgroup analyses demonstrated a primary patency of 76.5% in the acute DVT group compared to 70.4% in the PTS group and 97.1% in the NIVL group.[18]

DEFIANCE TRIAL

With the increasing use of large-bore MT devices and data suggesting their benefits compared to CDT, the question remains if there is a significant benefit compared to anticoagulation alone. The DEFIANCE trial, which is actively enrolling, is the first prospective, multicenter, RCT addressing this important clinical question, looking at use of the ClotTriever versus conservative medical management alone. The study will enroll up to 300 patients with proximal DVT who have had symptoms for < 12 weeks and will follow them out to 6 months.[19] The primary endpoint is the severity of PTS at 6 months. Similar to the landmark trials comparing CDT to medical management, the DEFIANCE trial

will compare the clinical outcomes from MT compared to medical management alone and thus help direct decision-making in first-line treatment.

BOLT TRIAL

The BOLT trial is currently enrolling to demonstrate the safety and efficacy of the Indigo aspiration system (Penumbra, Inc.) as a MT technique in patients with acute (< 14 days of symptoms) unilateral iliac and/or common femoral DVT with 2-cm extension into the inferior vena cava. Primary outcome measures include a composite measure of device-related death, major bleeding, new symptomatic pulmonary embolism, rethrombosis of the treated vein, and change in Marder score. This multicenter, prospective trial aims to expand the technology landscape for percutaneous MT devices for patients with deep venous obstruction.[20]

SUMMARY AND FUTURE DIRECTION

Clinical trials are the backbone of assessing safety and efficacy of new technology, and with the exponential emergence to technology for treating venous disease, these trials are pivotal in guiding new and innovative techniques into everyday clinical practice, especially for patients who previously did not have option for treatment. These trials have generated a wealth of data to increase our understanding of successes and failures in treatment of deep venous disease. With appropriate standardization of procedures and enrollment of real-world pathology within more clinical trials, technology will continue to expand, with promise of longer patency rates and improvement of quality of life. ■

1. Kim Y, Png CYM, Sumpio BJ, et al. Defining the human and health care costs of chronic venous insufficiency. Semin Vasc Surg. 2021;34:59-64. doi: 10.1053/j.semvascsurg.2021.02.007
2. Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med. 2017;377:2240-2252. doi: 10.1056/NEJMoa1615066
3. Comerota AJ, Kearon C, Gu CS, et al; ATTRACT trial investigators. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis. Circulation. 2019;139:1162-1173. doi: 10.1161/CIRCULATIONAHA.118.037425
4. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet. 2012;379:31-38. doi: 10.1016/S0140-6736(11)61753-4
5. Bisharat MB, Ichinose EJ, Veerina K, et al. One-year clinical outcomes following mechanical thrombectomy for deep vein thrombosis: a CLOUT registry analysis. J Soc Cardiovasc Angiogr Interv. 2024;3:101307. https://doi.org/10.1016/j.jscai.2024.101307
6. Dexter D. Interim two-year outcomes following mechanical thrombectomy for deep vein thrombosis from the real-world CLOUT registry. J Vasc Surg Venous Lymphat Disord. 2024;12:101795. https://doi.org/10.1016/j.jvsv.2024.101795
7. Abramowitz S, Bunte MC, Maldonado TS, et al; CLOUT study collaborators. Mechanical thrombectomy vs. pharmacomechanical catheter directed thrombolysis for the treatment of iliofemoral deep vein thrombosis: a propensity score matched exploratory analysis of 12 month clinical outcomes. Eur J Vasc Endovasc Surg. 2024;67:644-652. doi: 10.1016/j.ejvs.2023.11.017
8. Razavi MK, Black S, Gagne P, et al; VIRTUS investigators. Pivotal study of endovenous stent placement for symptomatic iliofemoral venous obstruction. Circ Cardiovasc Interv. 2019;12:e008268. doi: 10.1161/CIRCINTERVENTIONS.119.008268
9. Robertson B, Neville E, Rucker L, et al. Initial experiences with Venovo dedicated venous stent: post market approval findings and results in a tertiary referral center [abstract]. J Vasc Surg Venous Lymphat Disord. 2021;9:554. https://doi.org/10.1016/j.jvsv.2020.12.048
10. Hofmann LR, Gagne P, Brown JA, et al; VIVO Study Investigators. Twelve-month end point results from the evaluation of the Zilver Vena venous stent in the treatment of symptomatic iliofemoral venous outflow obstruction (VIVO clinical study). J Vasc Surg Venous Lymphat Disord. 2023;11:532-541.e4. Published erratum appears in J Vasc Surg Venous Lymphat Disord. 2023;11:1292. doi: 10.1016/j.jvsv.2022.12.066
11. Murphy E, Gibson K, Sapoval M, et al. Pivotal study evaluating the safety and effectiveness of the Abre venous self-expanding stent system in patients with symptomatic iliofemoral venous outflow obstruction. Circ Cardiovasc Interv. 2022;15:e010960. doi: 10.1161/CIRCINTERVENTIONS.121.010960
12. Razavi MK, Gagne P, Black S, et al; VIRTUS investigators. Midterm and long-term outcomes following dedicated endovenous nitinol stent placement for symptomatic iliofemoral venous obstruction: three- to 5-year results of the VIRTUS study. J Vasc Interv Radiol. 2022;33:1485-1491.e1. doi: 10.1016/j.jvir.2022.08.028
13. Dake MD, O'Sullivan G, Shammas NW, et al; VERNACULAR trial investigators. Three-year results from the Venovo venous stent study for the treatment of iliac and femoral vein obstruction. Cardiovasc Intervent Radiol. 2021;44:1918-1929. Published erratum appears in Cardiovasc Intervent Radiol. 2021;44:2027. doi: 10.1007/s00270-021-02975-2
14. Comerota AJ, Gagne P, Brown JA, et al; VIVO clinical study investigators. Final 3-year study outcomes from the evaluation of the Zilver Vena venous stent for the treatment of symptomatic iliofemoral venous outflow obstruction (VIVO clinical study). J Vasc Interv Radiol. 2024:35:834-845. doi: 10.1016/j.jvir.2024.02.025
15. Black S, Sapoval M, Dexter DJ, et al; ABRE study investigators. Three-year outcomes of the Abre venous self-expanding stent system in patients with symptomatic iliofemoral venous outflow obstruction. J Vasc Interv Radiol. 2024;35:664-675.e5. doi: 10.1016/j.jvir.2024.01.030
16. Murphy EH. Venous stenting: a behind the scenes look at the trial data. Endovasc Today. 2022;21:37-42. https://evtoday.com/articles/2022-nov/venous-stenting-a-behind-the-scenes-look-at-the-trial-data
17. Pouncey AL, Kahn T, Morris RI, et al. Risk factors and classification of reintervention following deep venous stenting for acute iliofemoral deep vein thrombosis. J Vasc Surg Venous Lymphat Disord. 2022;10:1051-1058.e3. doi: 10.1016/j.jvsv.2022.03.006
18. Black S, Sapoval M, Dexter DJ, et al; ABRE study investigators. Three-year outcomes of the Abre venous self-expanding stent system in patients with symptomatic iliofemoral venous outflow obstruction. J Vasc Interv Radiol. 2024;35:664-675.e5. doi: 10.1016/j.jvir.2024.01.030
19. DEFIANCE: RCT of ClotTriever system versus anticoagulation in deep vein thrombosis (DEFIANCE). Clinicaltrials.gov website. Accessed June 3, 2024. https://clinicaltrials.gov/study/NCT05701917
20. BOLT: Study of Indigo® aspiration system when used in patients with deep vein thrombosis. Clinicaltrials.gov website. Accessed June 3, 2024. https://clinicaltrials.gov/study/NCT05003843

Misaki Kiguchi, MD, MBA, FACS
Vascular Surgeon, Associate Professor of Surgery
MedStar Georgetown University Hospital
Director, MedStar Health Vein Centers
MedStar Washington Hospital Center
Site Chief, MedStar Georgetown University Hospital
Washington, DC
misaki.m.kiguchi@medstar.net
Disclosures: Speaker's bureau for Medtronic and Boston Scientific Corporation.

Kyle Reynolds, MD
Vascular Surgeon, Assistant Professor of Surgery
MedStar Georgetown University Hospital
Site Chief, Medstar Montgomery Medical Center
Washington, DC
kyle.b.reynolds@medstar.net
Disclosures: Speaker's bureau for Boston Scientific Corporation, Shockwave Medical, and Cook Medical.