

The ATTRACT Trial: Understanding the Results.

Interview by Lauren LeBano

The recent publication of the landmark ATTRACT trial has offered important data on the treatment of acute deep vein thrombosis (DVT). Anthony Comerota, MD, is one of the authors of the paper, and he joined us to explain the findings of the trial and takeaways for clinical practice. Dr Comerota is a vascular surgeon who is on the Steering Committee of the ATTRACT and resides in Perrysburg, Ohio. He spoke about the ATTRACT trial at the 2018 International Symposium on Endovascular Therapy in Hollywood, Florida.



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VDM: Tell me about what the ATTRACT trial was designed to study.

Dr Comerota: The ATTRACT trial focused on acute deep venous thrombosis. We know that more than 600,000 patients per year develop deep vein thrombosis (DVT) in the United States, making it a major problem. The magnitude of the problem of venous thrombosis and pulmonary embolism (PE) in the United States led to a Surgeon General Call to Action report on thromboembolic disease in 2008.

Despite the use of appropriate medications, about 40% of patients will go on to develop postthrombotic syndrome (PTS). PTS, which involves chronic pain and swelling, can have a major impact on patients' quality of life. Patients who are classified as having moderate-to-severe PTS experience major disabilities, including venous claudication and venous ulcers. As many as 5% to 10% of patients can fall into this severe category in as short a time as 2 years.

Pharmacomechanical catheter-directed thrombolysis (PCDT) is a minimally invasive treatment that can remove blood clots in a couple of ways. One method is by delivering clot-busting drugs such as rt-PA, along with catheter-based devices that mechanically break up the clot. Prior to the ATTRACT trial, the benefits and risks of PCDT had not been studied in a rigorous fashion.

ATTRACT was a multicenter randomized controlled trial that compared PCDT with standard anticoagulation in 692 patients with acute DVT located above the knee. The landmark study was performed in 56 hospitals in the United States, and the study was led by principal investigator Dr. Suresh Vedantham, along with an outstanding team of researchers.

On December 7, 2017, the final results of the ATTRACT trial were published in the *New England Journal of Medicine*. The trial was sponsored by the National Heart, Lung, and Blood Institute, and it is unquestionably the most rigorous study performed to date of catheter-based treatment of patients with acute DVT.

VDM: What did ATTRACT find?

Dr Comerota: We found that 48% of our patients developed PTS by 2 years, and 24% of the patients developed moderate-to-severe PTS. However, the results indicated that in most patients with acute DVT, the additional PCDT did not reduce the overall occurrence of PTS. PCDT is an invasive form of treatment and involves a sliding risk gradient compared with anticoagulation, so it is important to note that PCDT should not be used routinely in acute DVT. However, PCDT did reduce the severity of PTS and provided better relief of DVT-related pain and swelling in patients randomized to PCDT. Further analysis will reveal which DVT patients are likely to experience these benefits.

Prior to randomization, the ATTRACT trial stratified patients with femoropopliteal DVT and iliofemoral DVT. That means that the randomization of femoropopliteal DVT patients did not influence the randomization of the iliofemoral DVT patients, and the randomization of the iliofemoral DVT patients did not influence randomization of the femoropopliteal DVT patients.

Additional analyses are being planned for these two important groups of patients, femoropopliteal DVT and iliofemoral DVT. I think these analyses will provide important insights on improving treatment for these patients in the future.

I believe that ATTRACT has advanced patient care by providing high-quality evidence that enables most patients with DVT to avoid an unnecessary procedure. It also suggests that patient comfort during DVT care may be improved and that long-term DVT disability may be reduced through a more targeted use of PCDT to specific patients. The data that were generated by ATTRACT on the benefits and risks of this approach to treatment of DVT will unquestionably enable patients to make better choices for their own care, and we all hope the trial will catalyze additional research in this area.

VDM: Do you anticipate any immediate changes to clinical practice?

Dr Comerota: I believe that many physicians who are frequently using catheter-directed thrombolysis will re-evaluate their approach. I also believe that the documented high incidence

of PTS following acute DVT will bring attention to the benefits of PCDT in patients with the most severe acute DVT.

VDM: Did patients experience any adverse effects or complications?

Dr Comerota: Bleeding is the most frequent complication of PCDT, and no patients experienced an intracranial bleed. There was a difference in major bleeding complications that was significant though. Major bleeds occurred in .3% of patients receiving anticoagulation versus 1.7% of patients receiving catheter-directed thrombolysis. This is one of the lowest levels of major bleeding for catheter-directed thrombolysis published to date. It was nevertheless significantly greater than in patients receiving anticoagulation alone.

VDM: Can you tell me something notable about the data?

Dr Comerota: There was a significantly lower severity of PTS with patients who were randomized to PCDT, so that implies benefit. Whether the benefit is judged to be clinically meaningful is an open question. In other words, PCDT didn't change the class of PTS across the board in the patients during follow-up, but it did change the severity of the PTS numerically on the basis of the Villalta score. Additionally, the primary outcome was PTS at 2 years, and a 2-year endpoint is a substantial follow-up.

Lastly, ATTRACT was notable as a randomized controlled trial that provided Level 1 data. It was a very large trial and is likely generalizable to the population at risk. I believe it will have a major impact on future guidelines.

VDM: Did the trial reveal anything surprising?

Dr Comerota: It's difficult to say at this point because we don't yet have the analysis of the femoropopliteal DVT patients versus the iliofemoral DVT patients. I think it's fair to say that most clinicians in the United States offer catheter-based techniques to eliminate the clot in patients with iliofemoral DVT, so that analysis is anxiously awaited. The reason why that is an important subgroup is that all the venous drainage returns through the common channel of the common femoral vein and the external iliac vein. These patients develop particularly severe symptoms with their acute DVT, and particularly severe PTS, when those veins are thrombosed and patients are treated with anticoagulation alone, which permits the thrombus to evolve to collagenous postthrombotic obstruction. Many physicians have chosen to treat these patients with PCDT because nonrandomized data show benefit, and because smaller studies have shown benefits in the

patients with iliofemoral DVT.

VDM: Did the trial confirm anything that you were expecting to see?

Dr Comerota: The trial did confirm that moderate-to-severe PTS was significantly reduced in those patients receiving PCDT. That observation was gratifying.

VDM: Is there any other research in this area that you are awaiting?

Dr Comerota: There is a randomized trial underway in the Netherlands called CATHeter Versus Anticoagulation Alone for Acute Primary (Ilio)Femoral DVT (CAVA). It's a small trial compared to ATTRACT, but we are certainly looking forward to their outcomes and data.

VDM: Do you have any other comments on the ATTRACT trial?

Dr Comerota: From a personal perspective, I think we would choose a different primary endpoint if we were constructing the protocol today. When we were designing the protocol 12 years ago, we chose PTS as a "yes" or "no" endpoint. That includes patients with a mild PTS defined as a Villalta score of more than 4. Many patients can have very mild symptoms and be classified as having PTS. What we as clinicians are most concerned about are patients with moderate-to-severe postthrombotic symptoms, which cause pain, discomfort, diminished quality of life, disabilities, and incapacities. We want to help patients avoid this degree of postthrombotic morbidity. ATTRACT showed that moderate-to-severe PTS was reduced with PCDT. However, that is unfortunately considered a secondary endpoint. I'm not criticizing the trial design but merely stating an observation. We simply know much more about PTS now than we did 12 years ago.

It has been a privilege to be involved with the ATTRACT trial. We have had exceptional guidance by the principal investigator, Dr Vedantham, and the overall research team was of the highest caliber. ■

Editor's Note: Anthony Comerota, MD, has disclosed the following: Consultant, Tactile Inc; Grant/Research Support, National Institutes of Health; Speakers' Bureau, Bristol Myers Squibb and Pfizer.