ATTRACT 2-Year Data and Commentary

Two-year ATTRACT data show that anticoagulation alone is best for most deep vein thrombosis; pharmacomechanical catheter-directed thrombolysis benefits seen in certain iliofemoral patients.

The much-anticipated 2-year results from the ATTRACT study were presented by Suresh Vedantham, MD, FSIR, on behalf of the trial's investigators, at the 2017 Society of Interventional Radiology (SIR) Annual Scientific Meeting. The multicenter randomized trial evaluated two therapeutic strategies for treating deep vein thrombosis (DVT): pharmacomechanical catheter-directed thrombolysis (PCDT) plus standard therapy (including anticoagulation and compression) versus standard therapy alone (no-PCDT).

ATTRACT was primarily funded with the support of the National Institutes of Health (NIH), with additional support from the SIR Foundation, Boston Scientific, BSN Medical, Covidien/Medtronic, and Genentech. However, the companies did not play a role in designing or executing the trial or analyzing its data. A total of 692 patients were enrolled at 56 clinics, with 337 randomized to PCDT and 355 to no-PCDT. Overall, the 2-year data supported the use of standard therapy/anticoagulation alone in most DVT patients. PCDT was not shown to prevent postthrombotic syndrome (PTS) and was associated with increased bleeding. However, PCDT was shown to reduce early DVT symptoms as well as PTS severity. Based on these findings, Dr. Vedantham said the "open vein hypothesis" is likely relevant to PTS progression.

ATTRACT enrolled patients with either iliofemoral or femoropopliteal DVT. Those with iliofemoral DVT, who are more likely to develop PTS, appeared most likely to benefit from PCDT. However, although trends between the two subgroups can be observed and analyzed, when evaluated separately, they were not sufficiently powered to show statistically significant differences. The primary outcome assessed in the trial was the cumulative occurrence of PTS between 6 and 24 months using the Villalta Scale (total Villalta score > 5 or presence of ulcer). Secondary outcomes including PTS severity, quality of life (QOL), symptom severity, and safety outcomes were also assessed. Ultrasound and economic substudies were conducted but not included in the presentation at SIR.

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Dr. Vedantham, of the Mallinckrodt Institute of Radiology in Clayton, Missouri, detailed the ways in which systematic efforts to minimize bias were undertaken and noted that the assessors and adjudicators were blinded. The ATTRACT population's key demographics included: 62% male; median age, 53 years; 25% previous venous thromboembolism; and 57% iliofemoral DVT. Dr. Vedantham described baseline medical factors, anticoagulation, compression, and antiplatelet therapy administration as being similar between the two arms, and PCDT performance as consistent with past studies. The rate of mean thrombus removal was 74%. Further details on treatment methods and adjunctive procedures can be found in the forthcoming full publication of the findings, which has been submitted. Subsequent publications providing additional analysis are also planned.

The PCDT arm saw a statistically significant higher rate of major bleeding within 10 days (1.7% vs 0.3%; $P = .049$), which was anticipated based on previous experience, noted Dr. Vedantham. There was also a higher rate of any bleeding within 10 days (4.5% vs 1.7%; $P = .034$). Leg pain and

leg swelling were significantly improved in patients who received PCDT versus no-PCDT: (leg pain, 10 days: -1.62 vs -1.29; *P* = .019; 30 days: -2.17 vs -1.83; *P* = .026) (leg swelling, 10 days: -0.26 vs +0.27; *P* = .024; 30 days: -0.74 vs -0.28; *P* = .051). There were no fatal or intracranial bleeds in either arm within 10 days.

In the long-term outcomes, the rate of any PTS was approximately the same between the two groups (46.7% vs 48.2% for PCDT and no-PCDT, respectively; *P* = .56). There was a slight trend toward more recurrent VTE in the PCDT arm (12.5% vs 8.5%; *P* = .09) and little difference noted between the generic and venous-specific QOL between the two arms.

Dr. Vedantham noted that interesting findings were seen in the severity of PTS, with approximately 25% fewer patients in the PCDT arm experiencing moderate or severe PTS compared to the no-PCDT arm (17.9% vs 23.7%; *P* = .035). In patients with femoropopliteal DVT, there was little difference between severity of PTS (17.1% vs 18.1% moderate to severe); the difference in PTS severity was almost entirely seen in the iliofemoral DVT patients, with moderate/severe PTS seen in 18.4% of PCDT patients versus 28.2% in the no-PCDT group. PCDT was observed to be less effective in patients ≥ 65 years of age. Dr. Vedantham also provided substantial detail as to PCDT efficacy by PTS severity class and clot extent.

Limitations of the study as cited by Dr. Vedantham included losses to follow-up; its sample size (medium); and that it included multiple PCDT methods but was not designed to evaluate them individually.

Dr. Vedantham concluded that according to the experience observed in ATTRACT, PCDT does not prevent the occurrence of PTS, and there is a slight increase in bleeding with the procedure. "Based on this, most DVT patients can avoid having an uncomfortable procedure," he said, noting the importance of learning more about PTS. "However, PCDT does reduce early DVT symptoms and the severity of PTS."

Although the trial did not show statistically significant differences between the subgroups, Dr. Vedantham said that if operators elect to use lytic therapy for the purpose of reducing PTS severity, "The patients that may be most likely to benefit are those with iliofemoral DVT. It's hard to see a justification for treating those with isolated femoropopliteal DVT."

PANEL INSIGHTS

Michael R. Jaff, DO, of Newton-Wellesley Hospital in Boston, Massachusetts, joined Dr. Vedantham in moderating a series of multidisciplinary expert panel and asked for their assessments. Timothy P. Murphy, MD, FSIR, of Lifespan/Alpert Medical School at Brown University in Providence, Rhode Island, stated that although ATTRACT could be viewed as a negative study because it did not meet its primary endpoint, he feels it confirms the findings of the iliofemoral CAVENT study, which had a comparable 25% treatment effect. However, it also suggests that femoropopliteal patients should not be treated. "For most of us who have been treating patients based on CAVENT up to this point, it really doesn't change the treatment algorithm in my mind very much at all," said Dr. Murphy.

Clive Kearon, MD, PhD, of the McMaster University in Hamilton and an author of the American College of Chest Physicians (ACCP) guidelines, addressed the question as to whether the ATTRACT data will affect the guidelines. "The most recent ACCP guidelines made a weak or conditional recommendation against using catheter-directed thrombolysis or PCDT, but we also [aim] to identify the patients it will benefit," said Dr. Kearon. "And those were patients with more severe disease, iliofemoral disease, a low risk of bleeding, and a good functional status." Dr. Kearon felt that overall, the results of the study were disappointing and would probably have a negative influence on the guidelines. However, he did feel there is a role for PDCT in those with iliofemoral disease at the more severe end of the spectrum.

The stratification of patients with iliofemoral and femoropoplteal DVT was one of the strengths of the trial,

Key ATTRACT Data

- 692 patients (337 PCDT; 355 no-PCDT)
- 56 clinics
- 62% men; 38% women
- Median age: 53 years
- Mean thrombus removal: 74%

SHORT-TERM OUTCOMES

PCDT vs no-PCDT, within 10 days:

- Major bleeding: 1.7% vs 0.3%; *P* = .049
- Any bleeding: 4.5% vs 1.7%; *P* = .034
- Leg pain: -1.62 vs -1.29; *P* = .019
  - At 30 days: -2.17 vs -1.83; *P* = .026
- Leg swelling: -0.26 vs +0.27; *P* = .024
  - At 30 days: -0.74 vs -0.28; *P* = 0.51

0 fatal or intracranial bleeds in either arm

LONG-TERM OUTCOMES

PCDT vs no-PCDT

- Postthrombotic syndrome: 46.7% vs 48.2%; *P* = .56
- Recurrent venous thromboembolism: 12.5% vs 8.5%; *P* = .09

said Anthony J. Comerota, MD, of the Jobst Vascular Center in Toledo, Ohio, who feels the independent analysis of those groups was valid. He also noted that iliofemoral DVT has been viewed as a particularly morbid problem for decades. Further analysis of the data may show even more benefit in avoiding moderate and severe PTS in PCDT-treated patients, he noted.

Susan R. Kahn, MD, of Jewish General Hospital in Montreal, expressed that the ATTRACT trial provided very valuable contemporary data on the actual frequency of PTS, which is very high in this population. She agreed that the study provides confidence in not offering PCDT to most patients. However, should operators decide to offer this modality, the relatively low bleeding risk associated was encouraging. More research should now be directed toward PTS prevention and effective means of treating existing PTS, noted Dr. Kahn. Citing the results of the CAVENT trial out to 5 years, Dr. Comerota wondered if it would be possible to follow ATTRACT patients out to a similar time point, a notion that Dr. Murphy emphatically encouraged. Dr. Vedantham did not dismiss the idea, but noted the difficulties posed by the aforementioned study limitations in rendering a significant result at 5 years.

A key question posed by Dr. Jaff was why iliofemoral patients alone were not enrolled in the study. One reason cited by Dr. Vedantham was the established challenge of enrolling an iliofemoral-only trial, and also the fact that answers as to the outcomes in femoropopliteal patients were also of interest in order to make the study as generalizable as possible.

Additional research questions and future directions were discussed in another panel and will be addressed in future *Endovascular Today* coverage.

COMMENTARY

Regarding the ATTRACT data, SIR's 2016-2017 President Charles E. Ray Jr, MD, FSIR, provided the following statement:

"SIR Leadership was interested to learn that the ATTRACT Trials found PCDT helps a small population of patients with DVT reduce their risk of moderate-to-severe PTS. That said, SIR Leadership believes that work put into the study and its results demonstrate the important role that interventional radiology plays in providing clinicians with evidence that helps deliver the right care to the right patient. This information allows health care professionals to make better decisions as to who may benefit from PCDT, ensuring that each patient receives the best care for them and possibly reducing harm from unnecessary treatments. It was good to hear that the PCDT provided the overall study population with greater relief of leg pain and swelling during."

Mahmood K. Razavi, MD, FSIR, FSVM, was also a panelist in the session. In comments to *Endovascular Today* afterward, he emphasized that there is still much to be learned from ATTRACT and future studies. "The overall results of ATTRACT presented at SIR are only the beginning," said Dr. Razavi. "Secondary analyses may be quite informative as to who is more likely to benefit from catheter-based clot removal in DVT patients. This will likely ignite more interest in follow-up studies focused on iliofemoral DVT. Another important issue is to analyze the outcome of the patients who actually had complete clot clearance. The results of the latter group will shine some light on the open vein hypothesis of the ATTRACT trial.

"We also need to consider if the endpoint of 'any degree of PTS (Villalta score of 5 or greater)' is the right clinical endpoint," continued Dr. Razavi. "We have known for a long time that recanalization of postthrombotic iliac venous occlusions does not constitute a 'cure' in patients with advanced venous insufficiency, but rather it will reduce the magnitude of their symptoms. This is a similar situation in which the magnitude of symptoms is the more clinically relevant issue."

Among the interventional experts in the standing room only crowd for the ATTRACT data presentation were Robert Lookstein, MD, from Mount Sinai in New York, and John H. Rundback, MD, of Holy Name Medical Center in Teaneck, New Jersey. After the session, they provided their impressions of the data in comments to *Endovascular Today*.

"I think that the trial clearly shows us that the patient population that should be offered endovascular therapy are patients younger than 65 years of age, with low bleeding risk and acutely symptomatic iliofemoral DVT, who have demonstrated significant symptoms at presentation and appear to not be responding to traditional medical therapy," observed Dr. Lookstein.

Dr. Rundback agreed, noting that further analyses are necessary. "As Dr. Jaff pointed out, looking at the continuous data with regard to thrombus clearance and clinical outcomes will be relevant because it may well be that the strategies used were not adequate for thrombus clearance." Dr. Rundback further suggested that future studies should focus on devices and/or strategies that provide better acute results. Citing the overall numbers of DVTs that likely presented to the enrolling centers and the relatively low numbers randomized into the trial, he also wondered as to the screen failure rate.

"Lastly, particularly with regard to the femoropopliteal population, we now recognize—and did not recognize at the outset of ATTRACT—that there is a relatively high prevalence of venous compression syndromes, not just the typical May-Thurner, but also atypical forms of compression, which can very dramatically

affect subjective patient-reported outcomes, as well as objective Villalta scores and leg swelling," commented Dr. Rundback. "It would be interesting to look at the venograms in the femoropopliteal group to see how many of those patients actually had evidence of pelvic venous compression, but even that would be unreliable, as this phenomenon is often seen by intravascular ultrasound alone. But, certainly, the results in the femoropopliteal population need to be evaluated with some caution in light of this recognition."

Speaking with *Endovascular Today* after the session, Dr. Jaff pointed to the extent of postthrombotic venous insufficiency in the entire cohort when asked if any of the findings were particularly surprising to him. "It's really high," he indicated. "As Dr. Kahn said [during the panel], that has to force the question of how we can do more to prevent this. It's almost a 50/50 shot based on the ATTRACT data."

A WORD OF CAUTION IN INTERPRETATION

Importantly, Dr. Jaff cautioned that judgments based on the ATTRACT data should be reserved until after its full publication. "I wouldn't change anything until you read what the manuscript says, but the major message for me is to choose your patients wisely," he said. "Until then, if a DVT patient with a low bleeding risk has involvement of the iliac or common femoral vein and they're very symptomatic, I think this is a population that, in a skilled interventionist's hands, might benefit from a catheter-based intervention," further noting that this already largely represents his practice and referral patterns.

A PATIENT'S PERSPECTIVE

Before the data were presented and the panels commenced, Charles Lange, a patient with a history of multiple DVTs recounted his experience in seeking relief from his symptoms, which severely limited his mobility. He detailed his trips to the emergency room, orders to stay off his feet, and limited forward progress of any kind, prompting him to finally ask asked what else could be done, though did not feel he received a response that immediately addressed his concerns. Finally, a general practitioner arranged an appointment with an interventional radiologist, but it was set for 6 weeks later. "There was no sense of urgency," Mr. Lange noted. He sought out care on his own and was eventually successfully treated. The improvement after his procedure was almost instantaneous.

Mr. Lange expressed frustration at the inefficient way information was conveyed in his initial visits, and he emphasized the need to improve "the trickle of information" from the larger centers to the smaller hospitals and the doctors' offices he visited.

"Please continue to get the word out to all these smaller hospitals," he urged. "At least if they have the knowledge, they can diagnose it even if they can't treat it."

Dr. Vedantham then segued the session into a panel discussion that included Randy Fenninger, JD, of the National Blood Clot Alliance, and Gregory Piazza of the North American Thrombosis Forum. The discussion highlighted that this patient experience is not uncommon, and these two organizations exist to provide information and communications networks to patients with DVT.

"We have an obligation to develop a much more consistent approach to this disease across the entire United States and around the world," said Dr. Jaff, agreeing with Mr. Lange's assessment that improved understanding among health care providers at every level is needed, regardless of whether they offer the ideal therapy or refer to another center that does. ■

Dr. Vedantham disclosed research grant receipt from Cook Medical, BSN Medical, and Therakos. Dr. Jaff disclosed that he is a noncompensated advisor to Abbott Vascular, Boston Scientific, Cordis, and Medtronic; an equity investor in Embolitech, Venarum; and a compensated board member (Former) for VIVA Physicians, a not-for-profit education and research organization. Mr. Fenninger disclosed that he is CEO of the National Blood Clot Alliance. Mr. Piazza disclosed research grant receipt from Daiichi Sankyo, Janssen, BMS, BTG/Ekos, eXithera. Dr. Kearon disclosed that he is a consultant and research grant recipient with Bayer. Dr. Murphy stated that he had no relevant conflicts within the past 12 months. Dr. Razavi disclosed that he has served as an advisor and/or received honorarium from Abbott Vascular, Boston Scientific, Bard, Medtronic, Mecator, Gettinge, and Veniti in the past 12 months. Dr. Lookstein disclosed that he is a consultant for Boston Scientific and Medtronic. Dr. Rundback stated that he has no conflicts related to this discussion. Disclosure information was not available for Dr. Comerota or Dr. Kahn at press time.

HAVE QUESTIONS ABOUT ATTRACT?
ASK THE INVESTIGATORS

As a reminder, we are soliciting questions for the ATTRACT investigators. We will work to have as many as possible addressed in a future *Endovascular Today* feature.

Please send questions to:
askATTRACT@bmctoday.com