What if the ATTRACT Trial Had Been Positive?

Reflections on what is lost and gained when a well-designed trial produces unexpected results.

By Suresh Vedantham, MD

Would the venous world be different if the primary outcome of the ATTRACT trial had been "positive"?[1] The trial's development was an incredible collaborative accomplishment among physicians of different specialties, world-class trial methodology experts, government, industry, and patient advocates. Its success required group learning on a large scale, bringing new insights into the conduct of randomized controlled trials (RCTs) in the endovascular field. The energy created by ATTRACT and other deep vein thrombosis (DVT) initiatives of the time was enormous and continues to this day, more than a decade after the last study patient was enrolled.

Like many endovascular treatment advocates, I was surprised by the results but was fortunate to be positioned to view not just the selected published outcomes, but many additional data tables (including the full statistical report before its public release). A key takeaway for me was that in most ways that symptom outcomes were measured, endovascular therapy led to positive shifts. But equally unmistakable was the unimpressive magnitude of these effects—not nearly enough to validate the idea that restoring an "open vein" should be a dominant consideration in initial DVT care for most patients. Weak treatment effects were also seen in other quality trials.[2-4]

EFFECTS ON CLINICAL PRACTICE AND INNOVATION

Nevertheless, I was disappointed. Had the trial's primary outcome been positive, physicians could have treated many more acute DVT patients with pharmacomechanical catheter-directed thrombolysis (PCDT), reducing the severity of postthrombotic syndrome (PTS) in some of them.[1,5] There might have been a qualitatively different nature and scale of innovation in the field, given that the business case for larger investments in science and technology around DVT would have been stronger. Could the trend toward "large clot sucker" and "hard vein scraper" tools have yielded to more elegant methods that applied new biological principles to achieve "low-touch" clot disappearance? Perceptions of endovascular DVT therapy among medical physicians might be different. For example, although venous collaborations are stronger today than previous, the American College of Chest Physicians (CHEST) DVT treatment guidelines still do not include a voting panel member who performs endovascular DVT procedures; thus, medical physicians continue to be poorly informed about venous symptoms, PTS, and catheter-based interventions.

It would have been exciting to see more practitioners doing these procedures, although this might have been a double-edged sword. For example, large-scale use of dedicated venous stents and thrombectomy devices, spurred by regulatory approvals and an aggressive commercial push, has not always led to optimal patient selection, device safety, venous patency, or freedom from PTS. Decision-making for venous interventions presents hazards to inexperienced operators, and PCDT has a tight therapeutic index.[6] Complication rates with thrombolysis tend to be higher in real-world registries than in RCTs with carefully screened patients and vetted operators. Based on real-world data, if use of PCDT increased to 100,000 patients per year after a positive ATTRACT trial, it may have resulted in around 10,000 blood transfusions and 1,000 intracranial bleeds per year.[7] Locally, we may see a severe bleed once every 3 to 5 years that prompts hospital safety committee review. If a positive ATTRACT study prompted many more PCDT procedures, would we be discussing major safety events on a monthly basis? Could a therapy that involved intensive care unit (ICU) bed use for 1 to 2 days, complications, and high costs survive? Can we imagine the COVID-19 pandemic with DVT patients taking up ICU beds?

THE VALUE OF ASKING THE HARD QUESTIONS

Sometimes things work out for the best, even when not apparent initially. Large-scale PCDT would have been difficult to sustain in prime time; in fact, a backlash was likely. So, in recalling some of the tough decisions that were made up front, I don't have regrets.

Why was the binary occurrence of PTS rather than continuous PTS severity chosen as the study's primary outcome? Well, the study was specifically asking if PCDT should be used as routine, first-line therapy for acute proximal DVT—if its use should be extended to thousands of patients who were not being regularly referred. There was consensus that given the risks of catastrophic bleeding with recombinant tissue plasminogen activator administration, such widespread use could only be justified if PCDT led to a large benefit in preventing PTS entirely and improved quality of life (QOL). Whereas data on the binary occurrence of PTS (ability to prevent PTS cases) had already influenced CHEST recommendations on use of elastic compression stockings, it was entirely unclear how a guidelines panel or individual practitioner would interpret differences in continuous PTS severity scores (which could be of any magnitude), if present. As it turned out, in the overall proximal DVT cohort, PCDT produced a meager 1-point mean PTS score reduction on a 33-point scale, increased major bleeding, and no benefit in PTS occurrence or QOL.[1] Based on the data, one would need to lyse 17 patients to prevent one moderate-or-severe PTS case. It was a tough pill to swallow, but use of the binary PTS assessment proved to be foresighted, enabling many patients to avoid risky treatment that had only a very small chance of conferring a meaningful benefit.

Why were patients with isolated femoropopliteal DVT included? Although it may be forgotten or denied now, many of these patients were receiving PCDT at the time, so it was important to know if this practice was reasonable. By stratifying the randomization by thrombus extent, the study took full advantage of the opportunity to address the iliofemoral and femoropopliteal subgroups to the degree feasible, yielding more clinical and biological insights.[8] PCDT did not reduce PTS occurrence in either subgroup, so the inclusion of femoropopliteal DVT patients did not sway the study's primary outcome. But, thanks to this study design, updated societal guidelines finally recognize these two subgroups as distinct entities that merit different treatment recommendations to some extent, and most express comfort with use of CDT/PCDT as evidence-based treatment aimed at reducing PTS severity and initially presenting DVT symptoms for selected patients with acute iliofemoral DVT.[6,9,10] Researchers are actively studying inflammation and other PTS development mechanisms rather than putting all their proverbial eggs in the "open vein" basket. Physicians know more about who to treat, who to leave alone, and how to focus future research.

I believe ATTRACT's usefulness will only grow as more physicians apply an objective mentality in taking stock of its findings and the meticulous care with which it was conducted. In doing so, they will be well-served to rely on the published papers and involved investigators rather than hearsay. Perhaps most importantly, the study graphed the natural history of time-dependent recovery after acute proximal DVT for intervened and nonintervened patients, providing powerful insight that I share with my clinic patients every week to help them understand their condition, its prognosis, and options for management—this is truly "bench-to-bedside" translation in action.[8]

A positive primary outcome in ATTRACT might have increased comfort among endovascular physicians in relying on RCT data—a bit paradoxical (must trial data match the pretrial conceptions of an intervention's proponents, or should providers await quality evidence before advocating for it?), but such is the nature of human beings and confirmation bias. However, on the plus side, ATTRACT has served as a central developmental platform for additional National Institutes of Health–sponsored trials that are boldly seeking answers to questions about the treatment of PTS and pulmonary embolism (PE) that would not otherwise be addressed and can continue to do so. Such investigator-initiated studies are so important in ensuring that the rights and welfare of DVT patients are prioritized. Among many examples, one that has been on my mind is the rapid adoption of thrombectomy for DVT treatment. There seems to be a "blissful ignorance" at play in some corners: Recovering DVT patients are routinely offered thrombectomy despite a lack of data showing an added benefit, with little attention to the long-term status of the treated veins and with seeming unawareness of the fact (known to medical physicians and proven again in ATTRACT) that most DVT patients show gradual QOL improvement even without intervention.[8] Maybe this is beneficial, but given the risks and costs for patients, this theory needs to be tested in well-designed trials with objective clinical and imaging assessments. As we found with PCDT before ATTRACT, relying on industry to produce such rigor does not seem to be working.

EDUCATING VENOUS CLINICIANS AND RESEARCHERS

A continuing critical issue is education. Before ATTRACT was completed, an ambitious effort to provide

unbiased education and awareness about DVT, PTS, and endovascular procedures to providers and the public was being planned. That need is even more urgent now: We want providers to march forward in adopting new treatments when they are better, but we need them to actively apply the knowledge already gained about the disease, treatment outcomes, and trial design to ask the right questions and ensure delivery of excellent patient care. Endovascular proceduralists must master the natural history of DVT and the effects of conservative treatments, key domains where the ATTRACT results have advanced insight. Even nonresearcher clinicians should gain a basic understanding of trial design and sources of bias to properly interpret study results and limitations and to push industry sponsors to design clinical studies to minimize bias in assessing venous outcomes. Perhaps most importantly, clinical judgment is still needed to determine when endovascular DVT therapy should be delivered. For PE, we have PE response teams that operate locally, within a supportive national environment. Shouldn't we have something similar to ensure that DVT patients obtain the best multispecialty expertise to decide on use of advanced therapies and optimize holistic DVT care?

Finally, endovascular researcher preparation must improve, both in formal training programs and via additional approaches. For example, perhaps a multispecialty investigator mentorship model, such as what prepared me to lead ATTRACT, can be extended to other endovascular researchers to help them lead the rigorous investigator-initiated DVT studies of the future. I hope so—as I learned, such studies can deliver surprises, but they ultimately enable the truth to be discovered and provide essential directional guidance for patient care and research. I am so glad ATTRACT turned out the way it did! ■

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