

# The ATTRACT Trial

An update on the future of DVT therapy.

BY SURESH VEDANTHAM, MD

**T**he incidence of first-episode deep vein thrombosis (DVT) is estimated at 300,000 cases per year in the United States.<sup>1,2</sup> Anticoagulant drugs have been successful for primary prevention of DVT and pulmonary embolism (PE), prevention of PE in patients who are diagnosed with DVT, and secondary prevention of late recurrent venous thromboembolic events, and they may now be delivered to most patients in the outpatient setting.<sup>3</sup> However, the basic paradigm of DVT treatment has remained essentially static during the last 50 years, and it has not adapted to our contemporary understanding of the ways in which DVT actually impairs health. For instance, despite the routine use of anticoagulant therapy, postthrombotic syndrome (PTS) is known to develop in 25% to 50% of proximal DVT patients.<sup>4-6</sup> Patients with PTS experience leg pain, swelling, heaviness, and/or fatigue; severely affected patients develop lifestyle-limiting venous claudication, work disability, and/or venous ulcers. Randomized clinical trials (RCTs) show that DVT patients who wear elastic compression stockings daily after a proximal DVT episode develop PTS much less frequently than those who do not.<sup>5,6</sup> Yet, young physicians receive scant information about PTS, despite well-designed prospective studies showing that PTS is sometimes preventable and is a major cause of adverse quality of life (QOL) in DVT patients.<sup>7,8</sup>

In regard to endovascular methods of PTS prevention, research has clearly linked the development of PTS to the persistence of venous thrombus and venous valvular injury that stems from the inflammatory reaction to this thrombus.<sup>9,10</sup> Clinical research studies of thrombo-reductive strategies are largely concordant in suggesting dramatic reductions in PTS; however, they have significant methodological limitations.<sup>11-16</sup> Although these treatments also pose legitimate safety questions, the strong likelihood of a patient benefiting in terms of PTS prevention would seem to merit rigorous investigation in RCTs. It has become cliché in discussions of catheter-directed

thrombolysis (CDT) for DVT to add the caveat that an RCT is urgently needed before recommending its widespread use. In fact, several industry-sponsored attempts at such a trial were made during the last decade but were ultimately not completed.

The barriers to successful conduct of these studies, and to general progress in this area, were aptly outlined by the participants in a 2004 multidisciplinary research consensus panel convened by the Society of Interventional Radiology (SIR) Foundation. These barriers included: (1) the lack of consensus among gatekeeper DVT physicians regarding the importance of PTS prevention; (2) the lack of validated PTS measures that were widely accepted by the scientific community combined with the lengthy follow-up period needed to properly assess for PTS, which precluded committed industry sponsorship and follow-through; (3) the lack of standardization of endovascular treatment practices, the multimodality nature of the treatment, and the frequent need for monitoring in the intensive care unit rendered elusive a protocol that might be acceptable to the US Food and Drug Administration (FDA), medical physicians, and endovascular physicians; and (4) the lack of a multidisciplinary investigator network with sufficient expertise in endovascular intervention, PTS measurement, and clinical trial methodology.<sup>17</sup>

## DESIGNING THE ATTRACT TRIAL

Fortunately, the DVT landscape has undergone a veritable transformation during the last 5 years. In 2008, the National Heart, Lung, and Blood Institute (NHLBI) decided to commit \$10.2 million over 5 years to fund the ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis) trial. This phase III, open-label, assessor-blinded, multicenter RCT will evaluate the ability of pharmacomechanical CDT (PCDT) to prevent PTS in patients with proximal DVT. In understanding the rationale underlying this study's design, its potential impact on DVT care, and the NHLBI's decision to fund the study, it is useful to con-

sider how the previously mentioned barriers to such an RCT were ultimately overcome.

First, the importance of PTS to DVT patient health was highlighted in a number of important scientific venues between 2004 and 2008. At the October 2004 research consensus panel of the SIR Foundation in Bethesda, MD, representatives from the National Institutes of Health and FDA witnessed a multidisciplinary expert panel name an RCT to evaluate PCDT for PTS prevention as its top research priority.<sup>17</sup> In December 2004, the NHLBI issued a Request for Application for studies of PTS. In January 2006, the same study concept was highlighted as an important research priority at the Pacific Vascular Symposium.<sup>18</sup> In May 2006, the US Surgeon General and NHLBI hosted a workshop on DVT at which a number of attendees highlighted the importance of PTS and strongly urged the conduct of this type of study. Also, the combination of new PTS publications in widely read medical journals<sup>7,8</sup> and the adoption of a less restrictive stance toward CDT in the 2008 *American College of Chest Physicians Treatment Guidelines* now provide “cover” to medical physicians who refer patients for enrollment in ATTRACT, greatly enhancing its feasibility.<sup>3</sup>

Second, a number of clinical measures of PTS have undergone various degrees of validation during the last 10 years. The International Society of Thrombosis and Hemostasis has endorsed the use of the Villalta PTS scale for diagnosing PTS in DVT treatment trials.<sup>19,20</sup> On the other hand, the American Venous Forum has advocated use of the Venous Clinical Severity Score (VCSS) as a measure of outcome in studies on chronic venous disease.<sup>21</sup> To satisfy all physician communities that manage DVT patients, the Villalta scale, VCSS, and the clinical, etiologic, anatomic, pathophysiologic (CEAP) classification system will all be used.<sup>22</sup>

Third, the specific choice of endovascular method for use in the ATTRACT trial required a great deal of consideration. The use of CDT alone (with no mechanical component) was not favored due to resource utilization considerations and the fact that most practitioners use mechanical devices.<sup>23</sup> A strategy of mechanical thrombectomy alone was not favored because no device used without a thrombolytic drug has exhibited sufficient safety and efficacy to warrant routine stand-alone use for DVT. Recombinant tissue plasminogen activator (rt-PA) was chosen as the thrombolytic drug because of its widespread use, availability, and nonallergenicity. After candid conversations with a number of medical physicians, it was decided that the routine incorporation of an endovascular treatment into clinical DVT practice would be greatly aided were it to be efficiently delivered without the need for patient monitoring in an intensive care unit. Although

it is accepted that there is no conclusive evidence in favor of the superiority of any single technique, this judgment prompted a decision to rely on PCDT techniques that allow treatment to be completed in one procedure session. For most patients, physicians will use single-session PCDT; rt-PA is delivered by either the Trellis peripheral infusion system (Bacchus Vascular, Santa Clara, CA) or the AngioJet rheolytic thrombectomy device (Medrad Interventional/Possis, Indianola, PA), which are both FDA approved for the delivery of thrombolytic drugs to the peripheral vasculature.<sup>24-27</sup> For some patients who have poor popliteal vein inflow, an initial CDT infusion may be performed instead. After the initial approach, balloon maceration, aspiration thrombectomy, rheolytic thrombectomy, and/or stent placement may be used to restore flow, as is commonly done in clinical practice.

Finally, it is important to recognize ATTRACT not as an interventional study promoting a catheter-based intervention, but as a multidisciplinary collaboration of DVT research leaders seeking to solve an important public health problem. The development of the ATTRACT trial involved the close collaboration of investigators from interventional radiology, vascular surgery, cardiology, pulmonary medicine, epidemiology, hematology, economics, and biostatistics. The ATTRACT trial's Clinical Coordinating Center is based at the Mallinckrodt Institute of Radiology at Washington University School of Medicine. The Ontario Clinical Oncology Group at McMaster University, a renowned clearinghouse for DVT trials, serves as the ATTRACT trial's Data Coordinating Center and provides significant methodological and biostatistical expertise to the study. Core laboratories in vascular ultrasound (VasCore, at Massachusetts General Hospital [Boston, MA]) and health economics (at St. Luke's Mid America Heart Institute [Kansas City, MO]) play major roles in coordinating an ultrasound substudy and a cost comparison, respectively. Each of the 40 US clinical centers in the ATTRACT investigator network fields a multidisciplinary investigator team—which includes an endovascular physician, a medical physician, an emergency department physician, and the vascular ultrasound laboratory director at a minimum—yielding a network of over 200 investigators. The trial is actively supported by four industry partners: (1) BSN Medical Inc. (Charlotte, NC), which is donating compression stockings; (2) Bacchus Vascular, which is donating funds; (3) Genentech, Inc. (San Francisco, CA), which is donating rt-PA; and (4) Medrad Interventional/Possis, which is donating funds. Finally, in providing strong support letters to the NHLBI in favor of this trial, and in continuing to support its successful conduct, the SIR Foundation, the American Venous Forum, and the American College of

Phlebology are working together to ensure that the ATTRACT trial remains a community initiative.

## QUESTIONS ADDRESSED BY THE ATTRACT TRIAL

The ATTRACT trial will begin patient enrollment in July 2009 and will randomize 692 patients with symptomatic proximal acute DVT to receive either PCDT and standard DVT therapy or standard DVT therapy alone. Standard DVT therapy consists of initial anticoagulant therapy with unfractionated or low-molecular-weight heparin, long-term warfarin therapy, and elastic compression stockings. All study patients will have follow-up visits after 10 and 30 days and 6, 12, 18, and 24 months. The following important research questions will be addressed:

### Does the routine first-line use of adjunctive PCDT prevent PTS in proximal DVT patients?

The primary outcome measure will be the cumulative incidence of PTS over 2-year follow-up using the Villalta PTS scale. ATTRACT will test the hypothesis that adjunctive PCDT can reduce the occurrence of PTS by one-third (two-sided alpha 0.05, 80% power). PTS severity will be assessed by comparing scores on the Villalta, VCSS, and CEAP measures.

### Does PCDT better preserve QOL?

Patients in both study arms will have both general (SF-36 health survey) and venous disease-specific QOL assessed at all time points.<sup>28-30</sup>

### Does PCDT provide better relief of presenting DVT symptoms?

Patients in both study arms will assess their own leg pain (using a Likert scale) and have their calf circumferences measured at 10 and 30 days.

### Is PCDT safe and cost effective?

Rates of major bleeding, transfusion, intracranial bleeding, symptomatic PE, recurrent venous thromboembolism, and death will be described at 10 days and at 2 years. Patients will maintain a cost diary and have their hospital bills collected during follow-up. If PCDT prevents PTS but is more costly than standard DVT therapy alone, a cost-effectiveness analysis will be conducted to estimate the incremental cost per quality-adjusted life-year gained with use of PCDT.

### Do successful clot removal and absence of valvular reflux predict lower PTS risk?

Valvular reflux and residual thrombus will be rigorously

assessed via duplex ultrasound in a 142-patient subgroup in seven clinical centers at 1-year follow-up.

## THE IMPACT OF THE ATTRACT TRIAL

If the trial results are positive, this will fundamentally change clinical DVT practice and improve health by enabling prevention of PTS—a common, morbid, and expensive condition—in thousands of patients. If PCDT does not prevent PTS or if its risk-benefit ratio proves unfavorable, this finding will also improve health by eliminating the routine use of a costly and somewhat invasive therapy. Therefore, either study outcome will decrease morbidity from DVT and thereby improve public health. Furthermore, positive findings will validate the open vein hypothesis, catalyze a fundamental change in the current paradigm of initial DVT treatment, and provide a critical driving force toward early referral of DVT patients for PCDT, extension of PCDT to other DVT subgroups (eg, recurrent DVT or upper extremity DVT), and increased investment in novel and potentially safer clot removal technologies, with the extension of endovascular thrombolysis to additional patient subgroups.

## CONCLUSION

On September 15, 2008, the US Surgeon General issued a national Call to Action on DVT and PE. In this call to action, the impact of DVT, PE, and PTS on public health was highlighted, and the need for new research and multidisciplinary partnerships to address these challenges were emphasized. Specifically, the potential for endovascular clot-removal treatments to improve patient outcomes via PTS prevention is listed as an important research priority.<sup>1</sup> By addressing this important research question with the unprecedented degree of interdisciplinary collaboration outlined above, the ATTRACT trial represents an important part of the answer to this important Call to Action. As the study begins enrolling patients, it will hopefully continue to receive outstanding support from the community of DVT physicians. ■

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