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THE ATTRACT TRIAL: A STEP FORWARD FOR EVIDENCE-BASED DVT CARE

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Editorial

The ATTRACT Trial was a 56-center, randomized controlled trial (RCT) that evaluated pharmacomechanical catheter-directed thrombolysis (PCDT) for prevention of post-thrombotic syndrome (PTS) in patients with acute proximal deep vein thrombosis (DVT)[1]. The study found that PCDT: 1) did not prevent PTS through 2 years (primary outcome); 2) increased major bleeding; 3) did not influence health-related quality of life (QOL) or recurrent venous thromboembolism; 4) improved leg pain and swelling through 30 days; and 5) reduced the severity of PTS.

To understand these results, it is crucial to recall what question the study was designed to answer. In clinical practice, DVT patients are initially anticoagulated. Most patients improve, but some develop progressive symptoms, thrombus extension, and/or severe activity limitation, and may be referred for PCDT. Patients in this *highly selected sub-population* are more likely to: 1) be poor responders to initial anticoagulation; 2) have severe symptoms and extensive iliofemoral DVT, with or without an iliac vein stenosis; and 3) receive PCDT many days after symptom onset, when acute and subacute clot are present.

In contrast, in ATTRACT, PCDT was offered as *first-line treatment* for DVT along with anticoagulation. The severity of symptoms, initial response to anticoagulation, and thrombus burden were not used as study entry criteria. Hence, ATTRACT included many patients who are not typically referred for PCDT in clinical practice. Indeed, this was the whole point of the study: we were not seeking to validate the existing use of PCDT as "salvage" therapy; rather, ATTRACT was boldly intended to determine if PCDT should be extended as ***routine, first-line therapy*** to a much larger and broader cohort of DVT patients.

With this core understanding, the study's conduct and findings become clearer. Some physicians believe that iliac vein stenting was under-utilized. In fact, the protocol *encouraged*

stenting of iliac vein lesions causing ≥ 50% venous diameter narrowing, mean pressure gradient > 2 mmHg, or robust collateral filling; operators were required to show experience and comfort with iliac vein stenting; and many were actually early advocates of a highly pro-active posture towards stenting[2]. Rather, the utilization of stents in ATTRACT likely relates to the above-noted differences between the study population and our clinical practices. In ATTRACT, one would expect fewer patients to have iliac vein lesions needing stents because: 1) 43% had only femoral-popliteal DVT; 2) we did not restrict enrollment only to poor responders to anticoagulation (which may predict a lesion); and 3) we lysed patients at a median of 6 days after symptom onset, when very few patients would have lysis-resistant subacute thrombus.

In fact, the endovascular operators performed well. Safety (just 1.4% additional major bleeds) was better than previous CDT/PCDT studies, and clot removal (mean post-lysis modified Marder score 2.7 out of 24 maximum points) was comparable to previous studies[3,4]. We did not capture data on the intensity of anticoagulation delivered during PCDT, but the largely successful thrombus removal and low rate of early re-thrombosis suggest that it was adequate. We did not observe between-arm differences in use of anticoagulant therapy during follow-up.

PTS exhibits diverse clinical phenotypes and has no diagnostic gold standard, so we used a Villalta PTS Scale score ≥ 5 as our primary outcome measure, per international guidelines[5]. However, a major strength of the study was its use of *multiple* venous outcome measures. Even using the Venous Clinical Severity Scale, there was no significant difference in PTS rates (30% PCDT versus 36% Control). QOL assessment using two validated measures found no benefit with use of PCDT in the overall study population, consistent with a previous RCT[3].

Some ATTRACT findings hint at likely differences in PCDT effect between patients with iliofemoral DVT versus femoral-popliteal DVT – we continue to explore the magnitude,

statistical significance, and clinical importance of such subgroup effects. The inclusion of patients with femoral-popliteal DVT was well-justified because they are at high risk for PTS, because previous studies suggested that they may benefit from clot removal, and because some practitioners were exposing these patients to the risks of thrombolysis.

ATTRACT featured unprecedented precautions against bias: central randomization, stratification by thrombus extent, blinding of assessors and adjudicators, control of confounders, independent data management, and rigorous site monitoring and data verification against source documents. The study's size, diverse physician subspecialty involvement, and rigorous design should encourage strong physician confidence in relying on its results to guide clinical practice. To this physician-investigator, this means that most DVT patients do not need thrombolysis. Rather, consideration for PCDT should focus on patients who are highly symptomatic with acute iliofemoral DVT despite initial anticoagulant therapy, < 65 years of age, with low bleeding risk, who understand the risks and desire a more active treatment approach.

Physicians should be glad that patient complications and costs from unnecessary PCDT procedures will be reduced. Once the detailed subgroup analyses of PTS severity and QOL are completed, physicians will have a stronger foundation of high-quality evidence from which to judge which patients should, or should not, receive thrombolytic therapy – a major step forward in the treatment of DVT.

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