The case against catheter-directed thrombolysis in patients with proximal deep vein thrombosis

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This article has a companion Point by Chiasakul and Cuker.

Catheter-directed thrombolysis (CDT) is thought to reduce the risk of postthrombotic syndrome (PTS) in patients with proximal, iliofemoral deep venous thrombosis (IFDVT). However, the efficacy of CDT is controversial except in cases of critical limb ischemia. The costs and risks of CDT must be weighed against the benefits.

The risk of PTS is low with systemic anticoagulation alone

Severe PTS, as graded by the Villalta score, is rare: between 0.9% and 3% of patients will have persistent, severe PTS (total Villalta score ≥15) 2 years after the diagnosis of an acute IFDVT. In fact, in 1 study of 865 patients treated with systemic anticoagulation and compression stockings only, the mean Villalta symptom score was 2.43 (of a maximum 15) at the 24-month follow-up visit. Although patients with extensive IFDVT may be at somewhat higher risk of experiencing severe PTS, only 1 of 89 such patients who were managed with anticoagulation alone had severe PTS at the 5-year follow-up visit in the Catheter-Directed Thrombolysis for Deep Vein Thrombosis (CaVenT) trial.

Studies of VKA-based therapy may overestimate the risk of PTS

The majority of patients were treated with vitamin K antagonists (VKAs) in the trials on compression stockings and in the trials comparing CDT with systemic anticoagulation alone. Little is known about how consistently the patients in these studies were therapeutically anticoagulated. In the CaVenT study, therapeutic rates of warfarin were less than ideal: 61.1% of patients in the CDT group and 52.6% of the control group had international normalized ratios between 2 and 3 at the 6-month visit. Although the rates of PTS in patients on direct oral anticoagulants (DOACs) have not been reported, the risk of PTS associated with DOACs may be even lower than with VKA because, with DOACS, there is less interindividual dose-response variability and less potential for diet- or medication-related alteration of anticoagulant effect.

CDT does not improve quality of life

In 2 large randomized control trials of CDT vs systemic anticoagulation alone, there was no difference in the quality of life measurements. Although the CaVenT trial showed a reduced overall incidence of PTS following CDT (43% in CDT, 63% in control; P < .0001), there were numerically more patients with severe PTS at 5 years of follow-up in the CDT group (5% vs 1%, P = not significant). When patients with moderate or severe PTS were considered, CDT was associated with an absolute risk reduction of 6% in the CaVenT trial. Similarly, CDT effected a 6% absolute risk reduction in moderate or severe PTS in the US-based Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial. Taken together, these trials suggest that the most favorable conclusion one can draw about CDT is that 17 patients would need to receive CDT plus anticoagulation (rather than anticoagulation alone) to prevent 1 case of moderate to severe PTS. Unfortunately, neither trial used sham procedures for patients in the control arm, the potential for a placebo effect in the intervention arm of both studies raises the possibility that the observed, modest benefit of CDT may have been overestimated.

Negative results from the ATTRACT trial are strong evidence that CDT does not prevent PTS in a real-world setting

Compared with CaVenT, the ATTRACT trial enrolled more patients (692 vs 209) from more treatment centers (56 US centers vs 4 centralized Norwegian centers). The larger sample size increases the power of the negative results and strengthens the conclusion that CDT does not prevent PTS in a real-world setting.
of the study. The number of different study sites, along with a protocol that (in most cases) allowed the treating investigator to pick the catheter-based intervention that seemed most appropriate for an individual patient, means the results of ATTRACT can be generalized. The ATTRACT trial was powered to detect a small benefit from CDT, but, even when analyzed per protocol, there was no benefit of CDT on the rates of PTS, including within the a priori subgroup analyses.

Post hoc analyses of the ATTRACT results reportedly show that the composite end point of “moderate or severe” PTS was significantly less common in the subgroup of patients with iliofemoral DVT who received CDT. However, this difference should not drive clinical decision-making for several reasons. First, the composite end point was not a primary outcome; one must always interpret post hoc secondary outcome differences observed in a subgroup carefully when the primary outcome was not different in the overall trial. Second, the composite end point combines 2 outcomes (moderate and severe PTS) that result in very different morbidity for patients (for example, a patient could be asymptomatic, but categorized as moderate PTS based on clinical examination findings). Although the treatment effect of CDT on the composite of moderate or severe PTS was similar for patients with iliofemoral DVT in the ATTRACT and CAVENT studies (see the figure in the companion Point by Chiasakul and Cuker), the combined data must be viewed with caution because the assessments were made at different time points, the comparisons involve subgroups, and the final calculation mixes clinical events of very different significance into a single meta-analysis.

CDT increases major bleeding

In the ATTRACT trial, 1.7% of patients receiving CDT had major bleeding within the first 10 days compared with 0.3% of the control group. In the CaVenT study, there were 20 bleeds, including 3 major bleeding events and 5 clinically relevant nonmajor bleeding events related to CDT, and none in the control group (Table 1). Taken together, these results suggest that at least 1 excess major bleed will be caused for every 30 to 50 patients treated with CDT. Although there were no intracranial or fatal bleeding events among the CDT-treated patients in either trial, it seems likely that, if one treats enough patients with CDT, one can expect such a catastrophe to eventually occur. Importantly, the CaVenT study reported 4 nonbleeding complications in the CDT arm (2 transient neurological deficits in treatment limb, 1 infection at the catheter site, 1 episode of sepsis).

CDT is not cost-effective

Even if the evidence of a clinical benefit from CDT were more convincing, it would be difficult to make the case that this therapy is cost-effective for patients without limb-threatening vascular compromise. An analysis of the CaVenT trial suggesting that CDT is cost-effective was based on rates from the Norwegian health care system. In the United States, costs would be higher. One retrospective US study showed that patients who receive thrombolysis for proximal DVTs have longer hospitalizations (7.2 vs 5 days, \( P < .001 \)) and higher hospital charges ($85 094 vs $28 164). Assuming that >17 patients would need to undergo CDT to prevent a single case of moderate to severe PTS, the cost-effectiveness of this intervention would be marginal, even without considering the increased risk (and cost) associated with the inevitable excess bleeding events.

Table 1. Comparison of ATTRACT and CaVenT

<table>
<thead>
<tr>
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<th>ATTRACT</th>
<th>CaVenT*</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>336/355</td>
<td>87/89</td>
</tr>
<tr>
<td>Age, y‡</td>
<td>52/53</td>
<td>58/53</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>205 (61)/221 (62)</td>
<td>57 (66)/53 (60)</td>
</tr>
<tr>
<td>Major bleeds, n (%)§</td>
<td>19 (5.7)/13 (3.7)</td>
<td>3 (2.7)/0 (0)</td>
</tr>
<tr>
<td>Nonmajor bleeds, n (%)§</td>
<td>46 (14)/38 (11)</td>
<td>5 (4.6)/0 (0)</td>
</tr>
<tr>
<td>Final incidence of PTS, n (%)§</td>
<td>37 (42.5)/63 (70.8)</td>
<td>37 (42.5)/63 (70.8)</td>
</tr>
<tr>
<td>Severe PTS, n (%)§</td>
<td>3 (1)/1 (1)</td>
<td>3 (1)/1 (1)</td>
</tr>
<tr>
<td>Final mean Villalta§</td>
<td>3.40/4.56</td>
<td>NR/NR</td>
</tr>
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*5-year follow up from the CaVenT trial, which included fewer patients than the 2-year outcomes.
†Mean age was reported for CaVenT; median age was reported in ATTRACT.
‡Bleeding events: reported as all bleeding events from time of randomization to 1-year follow-up in the ATTRACT trial. The CaVenT trial reported bleeding events as bleeding events related to CDT over the course of 1 year following randomization. Nonmajor bleeds refers to clinically relevant nonmajor bleeding.
§Outcomes reported at the conclusion of each trial rather than the cumulative incidence (2-year visit for ATTRACT; 5-year visit for CaVenT). The ATTRACT trial also reported the mean Villalta scores of patients at the final 2-year study visit.

Moderate to severe PTS has been uncommon in patients with IFDVT who are treated with systemic anticoagulation alone, even in the era of warfarin. With the advent of DOACs, the rates of moderate to severe PTS among patients treated solely with anticoagulation may be lower. CDT does not provide a meaningful reduction in severe PTS or an improvement in quality of life, the 2 outcomes about which patients care the most. Additional investigation is needed on the use of CDT in other clinical situations, such as May-Thurner syndrome. In summary, the available evidence suggests that CDT will be beneficial for very few patients with IFDVT without critical limb ischemia. Unless additional analyses or future studies identify a subgroup of individuals for whom the clinical (and cost) tradeoffs are more favorable, CDT cannot be justified in this setting.

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Authorship

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