COMMENTARY

Catheter-directed thrombolysis for deep venous thrombosis might be cost-effective, but for whom?

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Post-thrombotic syndrome (PTS) remains an important concern in patients who suffer from a deep venous thrombosis (DVT). Its frequency varies from 20 to 50% across series, due to differences in definition and time-frame; therefore comparing the effectiveness of preventive interventions is difficult. A fairly recent prospective study using the Villalta scoring system established that 30% of patients had mild, 10% had moderate and 3% had severe PTS 2 years after an acute DVT [1]. Predictors of more severe PTS were femoral or iliac vein thrombosis, previous DVT, high body mass index, older age and female gender. Adequate anticoagulation during the initial 3–6 months following DVT appears to be protective. In a recent analysis of the REVERSE study cohort, 34% of patients with suboptimal anticoagulation (INR below 2.0 more than 20% of the time) developed PTS compared with only 22% of those who were better treated [2]. Compression stockings are also effective, as demonstrated by several small randomized trials. A Cochrane Collaboration meta-analysis suggests a 69% reduction of PTS by compression stockings (odds ratio, 0.31; 95% CI, 0.20–0.48) and a similar 61% reduction in severe PTS [3]. However, adherence to that simple intervention is poor even using below-knee stockings and the still unpublished multicenter randomized SOX trial recently casted doubt on its efficacy [4]. Therefore, progress is certainly warranted to prevent PTS, especially in patients with iliofemoral DVT who are at higher risk; hence the recent interest in more invasive approaches aimed at restoring venous patency by mechanical means, such as stenting or catheter-directed thrombolysis.

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The Catheter-directed Venous Thrombolysis (CaVenT) study [5] from Norway is the only published randomized trial that assessed this technique with an adequate 24-month follow-up and it yielded positive results. However, the technique is invasive, resource-intensive, costly and increases the bleeding risk. An evaluation of its cost-effectiveness was definitely warranted. Such an analysis has been carried out by the investigators of the CaVenT study and is published in this issue of the *Journal of Thrombosis and Haemostasis* [6]. Cost-effectiveness analyses are models of reality and have their own set of potential biases [7], the main concern being the robustness and accuracy of the data on which the model is based. This warrants a closer look at the results of the CaVenT study because it provided several major figures included in the model. The study was a randomized open-label trial including 209 patients with a first episode of acute iliofemoral DVT treated either by catheter-directed thrombolysis with alteplase (CDT) or conventional treatment. Both groups received anticoagulant treatment and below-knee compression stockings. The two groups differed regarding prognostic factors such as better anticoagulant treatment and higher adherence to compression stockings in the CDT arm (63% vs. 51% still using them at 24 months), which might be explained by the open-label design. The main endpoint, the frequency of PTS as assessed by the Villalta score at 24 months, could be assessed in 189 patients. Surprisingly, while there was no difference at 6 months between the intervention and control groups in terms of frequency of PTS (30% vs. 32%) despite a significant difference in iliofemoral patency (66% vs. 47%), PTS was significantly less frequent in the CDT group at 24 months (41% vs. 56%, $P = 0.047$). There was only one case of severe PTS at 24 months in the control group. Bleeding risk was higher in the thrombolysis group (three major bleeds vs. none in the control group) [5].

To assess the cost-effectiveness of CDT, the authors designed a Markov model that adhered to adequate meth-

odological standards. They modeled a hypothetical cohort of 50-year-old patients with acute iliofemoral DVT. Overall frequency of PTS after 2 years and corresponding 95% confidence intervals were drawn from the CaVenT study [5]. Although higher than usually cited figures, this is acceptable considering that a higher risk of PTS is to be expected in the case of extensive proximal DVT. Figures for severe PTS were estimates because there were no severe cases in the CaVenT trial (2% in the CDT strategy vs. 6% with standard treatment). Bleeding risk deserves special consideration because using a technique that increases the risk of a disabling intracranial or fatal hemorrhage to prevent PTS, a most often not severely disabling and never fatal complication, is a major concern. The risk of a disabling intracranial or fatal bleed was extracted from an American registry of 473 patients with DVT who underwent catheter-directed thrombolysis with urokinase (mean dose 7.8 million IU) and was deemed to be 0.63% with an upper limit of the confidence interval of 2.4%.

In cost-effectiveness analysis, life expectancy is adjusted for quality of life by incorporating a utility factor between 0 and 1 (1 representing the ideal state of health and 0 associated with death). Utilities can be measured by interrogating patients with the state of health of interest using various techniques. This was done by the CaVenT investigators after 2 years of follow-up in patients with non-severe PTS (utility of 0.77; 95% CI; 0.73–0.82), severe PTS (0.67; 0.60–0.70) and without PTS (0.86; 0.82–0.90). Although in itself correct, one can be surprised that a year spent with non-severe PTS equals only 9.4 months (8.9–10.0), particularly given that the utility of non-severe PTS is very close to that of suffering a non-disabling intracranial bleed (utility 0.71). A distinct limitation of utility measurements is that they can usually not be performed in the same patients for different health outcomes (for instance a group of patients who have both severe PTS and suffered an intracranial bleed), questioning the comparability of the utility figures for different health-states incorporated into the model. Finally, costs were extracted from the CaVenT study (direct costs from a third-payer perspective). Costs of standard treatment appear overestimated ($9780) because those patients stayed for an average of 2.3 days in the hospital while the standard for treating DVT, including at the iliofemoral level, is outpatient treatment [8,9]. Additional CDT was 2.3 times more expensive, with an additional cost of $13 166.

What are the results? CDT added 0.63 quality-adjusted life years (QALYs) for an additional cost of $12 843 compared with standard treatment, yielding an additional cost per QALY gained of $20 429. This figure is usually referred to as the incremental cost-effectiveness ratio (ICER) and summarizes the result of a cost-effectiveness analysis. It is compared with the willingness-to-pay threshold (i.e. the ICER below which a health system is ready to consider an intervention as cost-effective). The willingness-to-pay threshold is of course arbitrary and varies from country to country. The National Institute for Health and Clinical Excellence (NICE) in the UK adopted the figure of $30 000–$45 000, a more conservative figure than the corresponding $50 000–$100 000 in the United States. However, the summative figure should not obscure its components [10] and it should be stressed that the additional QALYs provided by CDT are exclusively due to increased quality and not length of life. Sensitivity analyses are very important to test the robustness of the ICER and can be performed in two different ways. One consists of varying the value of each variable included in the model over a reasonable range (usually the corresponding 95% confidence interval) and checking whether this modifies the ICER. The ICER was sensitive to changes in the efficacy of CDT. If the absolute PTS risk difference decreased from the observed value in the CaVenT study (15%) to 5%, CDT would no longer be cost-effective at a $50 000 threshold. Bleeding complications could be increased significantly without affecting the result: assuming a 1.4% risk of a fatal bleed or 1.0% risk of a disabling intracranial bleed did not increase the ICER over a $40 000 threshold. However, those figures would still appear conservative in elderly patients. Indeed, all analyses were performed for a 50-year-old patient, which maximizes gains in life expectancy as the ICER is calculated over a lifetime. Finally, the model was sensitive to the utility of PTS and increasing the utility of PTS to 0.85, which already represents a 15% reduction in quality of life, would increase the ICER to $50 000, above the acceptable cost-effectiveness threshold. The other types of sensitivity analyses are probabilistic and consist of simulating random variations of all variables over the predetermined range of possible values simultaneously. The output is the probability that the ICER will consistently be below a specific cost-effectiveness ratio. In this analysis, the probability of the CDT strategy being cost-effective would be 82% using a $50 000 willingness-to-pay threshold, but only 60% adopting the more conservative $30 000 threshold set by the NICE Institute.

In summary, CDT might be cost-effective in a patient 50 years old or younger with extensive proximal DVT and a high risk of developing a severe post-thrombotic syndrome provided non-severe PTS be considered disabling enough to reduce quality-of-life by 23% and the bleeding risk is low. However, cost-effectiveness analyses are destined to inform choices by health-policy makers between new treatments and this would still result in spending around $20 000 per additional QALY that might be better invested in interventions that increase actual length and not only quality of life. Moreover, the estimates of the efficacy of CDT in preventing PTS and of the risks associated with the procedure are imprecise and the disutility associated with PTS appears exaggerated, casting doubt on the true ICER of CDT. Therefore,

it is improbable that the technique will be widely adopted, as reflected by the downgrading of the recommendation regarding CDT in the last edition of the American College of Chest Physicians (ACCP) guidelines from grade 2B to grade 2C and the clear recommendation in favor of anticoagulant treatment over CDT [11]. For centers performing the technique, the ACCP guidelines consider a suitable patient's preference as an important element in deciding between treatment options. However, to properly inform the patient, one should be able to determine just how severe a DVT should be to justify the added risks and costs of the technique. At present, the answer to that question is at best elusive.

Addendum

A. Perrier and H. Bounameaux analyzed the study commented on in this article and discussed the contents of this commentary. A. Perrier drafted the paper. H. Bounameaux revised it critically and both authors approved the final version of the manuscript.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interests.

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