

# Ultrasound-accelerated catheter-directed thrombolysis for the prevention of post-thrombotic syndrome

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A stylized tree with a thick, grey trunk and branches, topped with a splash of water. The trunk is a solid, vertical column that widens at the top. From the top of the trunk, two main branches extend outwards and upwards, each further dividing into smaller, more intricate branches. The top of the tree is a dense, chaotic splash of water, with many small droplets and bubbles. The text "Valorisation addendum" is centered over the upper part of the trunk.

Valorisation addendum



When a condition which affects 2,5-5,0% of the population can potentially be fatal and leads to detrimental long-term comorbidity in the majority of patients, any improvement in its treatment has the potential to benefit millions of people. Deep vein thrombosis is such condition. In the acute phase the development of pulmonary embolism, which is fatal in up to 10% of those affected, needs to be prevented. On the long-term 40-60% of patients will develop post-thrombotic syndrome, meaning the persistence or development of debilitating complaints in the post-thrombotic leg. This does not only result in limiting disabilities and a significantly reduced quality of life, it also puts a large strain on the health care system and increases health care costs. Currently, treatment of post-thrombotic syndrome is purely symptomatic since curative treatment options are lacking. Evidently, prevention is to be preferred.

This thesis contributes to the discussion regarding catheter-directed thrombolysis as a potentially preventive additional treatment for post-thrombotic syndrome in patients with acute iliofemoral deep-vein thrombosis. Prior to the randomized controlled CAVA-trial which is presented in this thesis, two major randomized controlled trials (the CaVenT-trial and ATTRACT-trial) had already addressed this question yet came to contradicting conclusions. The CaVenT-trial found an absolute risk reduction of 14,4% regarding the development of post-thrombotic syndrome after two years when treated with additional catheter-directed thrombolysis. After five years the risk reduction had even increased to 28%. Furthermore, as an additional treatment modality, catheter-directed thrombolysis appeared to be cost-effective and have a low risk of major bleeding.

However, the much larger ATTRACT-trial was not able to reproduce the preventive effect on the development of post-thrombotic syndrome. Neither in their total study population, nor in a selection of patients in which use of this additional treatment was expected to be most beneficial based on thrombus localisation. Although the results of the CAVA-trial were inconclusive, it did provide us with more insights regarding the potential of this treatment modality as well as suggestions for its optimization. Therefore, its results are being incorporated in international guidelines.

Nevertheless, further research regarding pre-procedural (e.g. accurate patient selection), per-procedural (e.g. improvement of current treatment protocols or the development of new techniques and devices), and post-procedural (e.g. formulation of evidence based guidelines for post-interventional anticoagulant therapy) factors is necessary.

Arrangements are being made for an individual patient data meta-analysis involving the three major trials (i.e. CaVenT, ATTRACT, and CAVA). This will, hopefully, provide us with the answers to the remaining questions and give an indication of the position of catheter-directed thrombolysis in the treatment of acute iliofemoral deep vein thrombosis. If additional catheter-directed thrombolysis indeed contributes to a beneficiary outcome regarding the development of post-thrombotic syndrome, symptoms of chronic venous pathology, and the experienced quality of life, these benefits should be balanced against the accompanying costs and health risks. Furthermore, options to optimize the post-thrombotic management as experienced by the patient (e.g. early diagnostics, adequate instruction and application of compression therapy, anticoagulant therapy using effective, safe, and patient-friendly regimens) should be considered and incorporated.

Furthermore, the results of this thesis should raise awareness in general practitioners and other physicians involved in the diagnostics and conservative treatment of deep vein thrombosis. Iliofemoral deep vein thrombosis should be considered as a separate disease entity compared to thrombi of the more caudal vein segments based on its pathophysiology, prognosis, as well as its treatment opportunities which go beyond standard treatment. Physicians performing these interventions (i.e. catheter-directed thrombolysis, venous stent placement) are offered insights in the thoughts and considerations that should be critically appraised when considering these treatment modalities for their individual patient. Treatment indications should be well formulated in order to optimize treatment outcomes and limit the risk of eventual complications. Improvement of current treatment protocols and the development of innovative techniques or devices should be encouraged in order to provide this specific group of patients with better treatment opportunities and a more positive outlook on their future.