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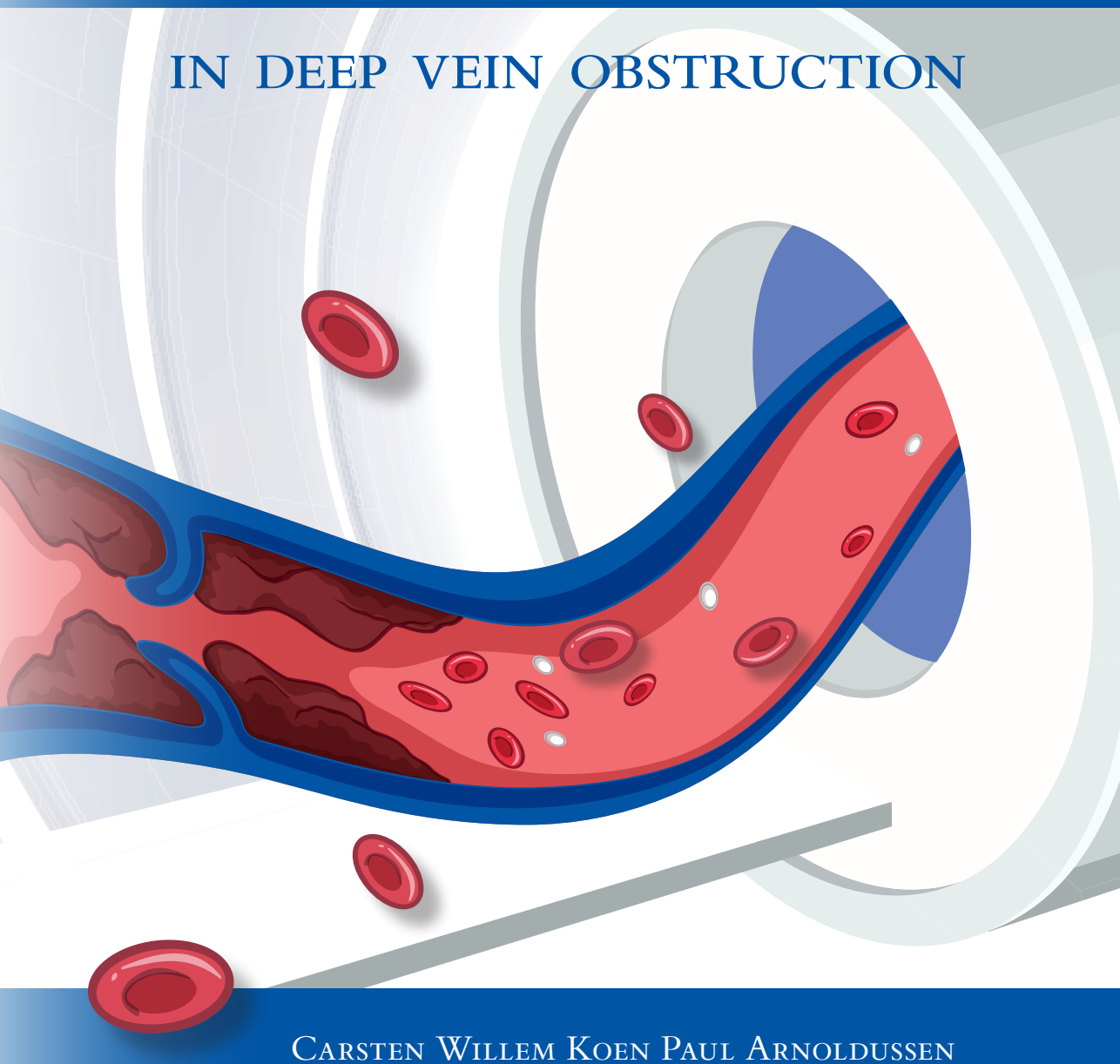

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Utilization of MR-Venography in deep vein obstruction

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Deep vein thrombosis and post-thrombotic syndrome

Deep vein thrombosis (DVT) occurs at an annual incidence of about 1 per 1000 adults. The incidence rises exponentially with age, from fewer than 5 cases per 100,000 persons younger than age 15 years to approximately 500 cases per 100,000 persons older than age 80 years.[1] Thus a large proportion of the general population will be affected by deep vein thrombosis over the course of their life time. Deep vein thrombosis is considered a major health problem that affects all ages with considerable morbidity and mortality. [2,3]

Causes of thrombosis are referred to as the 'Virchow's triad' and include vessel wall damage, stasis or low flow, and hypercoagulability.[4] These factors favor clot formation by disrupting the balance of the opposing coagulative and fibrinolytic systems. If resulting thrombi are untreated and persist, they can disrupt vascular integrity of the lower limb.[5] In approximately one-third of deep vein thrombosis patients, quality of life (QOL) does not return to baseline during the first 4 months after diagnosis, and QOL closely correlates with the development of post-thrombotic syndrome (PTS).[6] Typical symptoms associated with PTS are limb heaviness/fatigue, swelling, pain, and, in some cases, venous claudication. Eventually, skin changes associated with PTS can progress to stasis dermatitis and/or skin ulceration.[7]

Diagnosis and Imaging of DVT and PTS

The symptoms and signs of venous thrombosis are caused by obstruction to venous outflow, vascular inflammation, or pulmonary embolization. Physicians cannot rely solely on clinical signs and symptoms to establish diagnosis and extent of deep vein thrombosis, and must therefore depend on imaging studies to guide treatment.[8] In 60% to 80% of patients referred for clinically suspected venous thrombosis, however, diagnosis will not be confirmed by objective testing, stressing the clinical complexity of diagnosing deep vein thrombosis.

Duplex ultrasound (DUS) is the noninvasive diagnostic modality most often used for diagnosis of deep vein thrombosis, with a reported sensitivity and specificity of approximately 97%.[9] Other procedures that are currently used to diagnose deep vein thrombosis include computed tomography, and magnetic resonance imaging.[10,11]

It is essential to accurately diagnose deep vein thrombosis and to start treatment early. Early treatment of deep vein thrombosis with anticoagulants has been demonstrated to reduce the incidence of pulmonary embolism and associated mortality. [12] Furthermore, early treatment prevents extension of deep vein thrombosis from distal veins to more proximal veins and relieves acute symptoms in the leg.[13,14] Rapid achievement of therapeutic anticoagulation and adequate treatment duration prevent early recurrence of deep vein thrombosis and may also decrease the incidence of postthrombotic syndrome.[14]

DUS is well established as the imaging modality of choice for the assessment of deep vein thrombosis.[15] Examinations are non-invasive, rapidly obtained, and can be performed serially.

In symptomatic patients, venous DUS is sensitive and specific for lower extremity deep vein thrombosis; however, DUS is less sensitive for calf vein thrombosis, pelvic (ilio-caval) thrombosis and regarding asymptomatic DVT occurring after surgery.[16,17] Also, patients with symptoms of recurrent DVT are a difficult diagnostic challenge.[8] Only about 20% to 30% of these individuals actually do have recurrent venous thromboembolism (VTE); the remainder has symptoms arising from chronic venous insufficiency or other causes.[19] After an acute episode, DUS shows abnormalities indistinguishable from the original findings of deep vein thrombosis for a duration of 6 months in up to 50% of patients.[18] Hence, there are a significant number of patients and clinical circumstances in which the diagnosis of deep vein thrombosis is difficult to establish. Acute occlusion of the pelvic veins and the inferior vena cava, often due to thrombus extension from the femoropopliteal system, represents a major risk for pulmonary embolism (PE) and forms yet another diagnostic challenge.[20] Colour flow Doppler imaging is often limited for the diagnosis of iliocaval thrombosis owing to obesity and bowel gas.

Both computed tomography (CT) and magnetic resonance imaging (MRI) can be used to accurately diagnose acute pelvic vein or inferior vena cava occlusion and are also helpful in diagnosing central chest vein occlusion.[21-23] Multidetector computed tomography angiography (CTA), combined with late venous-phase imaging (indirect computed tomography venography (CTV)), can be used to accurately diagnose a pelvic vein or inferior vena cava occlusion, sometimes the source of significant pulmonary emboli. On CTA/CTV thrombi appear as intravascular hypodense masses, sometimes encircled by a hyperdense rim of contrast medium. The reported specificity and sensitivity compared to DUS are approximately 93-100% and 97%, respectively.[21,22] Indirect CTV in addition to CT pulmonary angiography is a relatively accurate method for evaluation of femoropopliteal venous thrombosis in one examination without the need for a second contrast bolus.[23] But introducing CTV as an alternative to DUS is not ideal since it introduces risks associated with radiation and iodine contrast material. The use of MRI is more appealing in this regard, as MRI is noninvasive, does not require radiation or iodinated contrast material and can also be used in specific risk groups such as pregnant women.[24] MRI is superior in soft tissue contrast and offers several different scanning techniques. Two-dimensional time-of-flight venography (TOF-MRI) has the potential to perform a magnetic resonance venography (MRV) without contrast. Thrombotic material is depicted as a filling defect or, alternatively MRI can detect a thrombus directly (MR direct thrombus imaging or MR-DTI). This technique detects methemoglobin, enabling direct visualization of pulmonary emboli and leg vein thrombosis without the need for intravenous contrast. Compared to DUS and contrast venography this method has been reported to have a sensitivity of 98% and a specificity of 96%.[25] MRI accuracy can be further improved by adding gadolinium-based contrast agents (MR angiography in the venous or steady-state phase, referred to as MRV). In a study designed to evaluate the diagnostic value of MRV and DUS in the assessment of deep vein thrombosis compared with contrast-enhanced venography, MRV was 100% sensitive and 100% specific in diagnosing deep vein thrombosis above the knee.[26]

With MRV it is also possible to differentiate between acute occlusion and chronic thrombosis, and it has also shown to be more accurate than DUS in detecting extension of deep venous thrombosis.[11,27] MRV also correctly depicts venous anatomy and patency of the central veins. Therefore, MRV should be considered the modality of choice for the evaluation of venous occlusion of the large systemic veins (e.g., inferior vena cava, pelvic veins, superior vena cava, subclavian veins and/or other deep chest/abdominal veins).

As it stands, MRV has not been established as superior to DUS for diagnosis of deep vein thrombosis in the arms or legs by peer reviewed medical literature. MRV has not been shown to be superior to DUS for lower limb deep vein thrombosis, except for imaging the deep femoral and hypogastric vessels. [28-30] Currently, information about these vessels is not routinely used in therapeutic decisions, except in patients with pulmonary emboli where the source of the emboli could not be identified using DUS.[13] If MRV assessment of deep vein thrombosis could contribute accurately to the clinical management decisions this might change.[31]

Treatment of deep vein thrombosis and PTS

The guidelines for treatment of deep vein thrombosis of the lower extremity recommend anticoagulant therapy using direct oral anticoagulants (DOACs) for the prevention of thrombus extension, recurrence, pulmonary embolism and death.[32] Therapeutic elastic compression stockings (TEC) have been recommended by national and most international guidelines for the reduction of acute symptomatology and the prevention of post thrombotic syndrome (PTS) for the last two decades. However, the publication of the SOX trial in 2014 showing no benefit of compression therapy has led to controversy on the usefulness of TEC.[33,34] Based on pooled results of randomized trials on compression therapy for the prevention of PTS, the Dutch guidelines nevertheless recommend the use of TEC.[35,36] One out of 4 patients will develop PTS within 2 years after the thrombotic event, despite these precautions.[37-38] PTS can manifest with only mild symptoms or as debilitating disease affecting a patient's QOL. Hence there is a great need to improve the available therapy to ameliorate long-term functional outcome. A systematic review including 12 studies found that additional thrombolytic therapy for rapid dissolution of thrombotic material in acute deep vein thrombosis may offer advantages in terms of reducing PTS and maintaining venous patency.[39] However, systemic thrombolytic therapy is associated with an unacceptably high risk of bleeding and is not recommended for the treatment of acute deep vein thrombosis.[13,40] Alternatively, catheter-directed thrombolysis (CDT) offers local delivery of the thrombolytic agent, significantly reducing the total dose required for dissolution of a venous thrombus. A case series on CDT revealed a high rate of technically successful thrombolyses at the expense of only a small additional increase in bleeding complications.[41-44] Initially, only one very small randomized controlled trial with short-term follow-up was performed.[45] Based on this evidence the 2008 guidelines of the American College of Chest Physicians were modified to recommend CDT in selected patients (grade IIB recommendation).[13] However, properly designed multi-center randomized controlled

trials (RCT) adhering to recent reporting standards are required to enable an evidence-based practice for venous thrombolytic therapy.[46,47] The RCT's performed in the past decade are the CaVent-trial, the ATTRACT-trial and the CAVA-trial. The CaVent trial has shown the potential for CDT to reduce the incidence of PTS at 2 and 5 years. [48,49] On the other hand, the ATTRACT-trial found that in patients with acute proximal deep-vein thrombosis of the lower extremity, the addition of pharmacomechanical CDT to anticoagulation did not result in a lower risk of developing PTS.[50] The ATTRACT-trial also showed that, in patients with (proximal) lower extremity deep vein thrombosis, PCDT results in greater improvement of disease-specific QOL compared to no PCDT at 1 month and 6 months, but not later. In patients with iliofemoral deep vein thrombosis, PCDT led to greater improvement in disease specific QOL during 24 months.[51] The results of the CAVA-trial will be discussed in this thesis.[52]

Aims and outline of the thesis

The first part of this thesis focusses on deep vein thrombosis patient identification, classification and selection to improve on the contribution of imaging studies in daily practice for the treatment of deep vein thrombosis.

In chapter 2 we describe and propose a strategy to improve and ensure uniform reporting on deep vein thrombosis in patients. Furthermore, we discuss an approach to the use of available imaging modalities for assessing deep vein thrombosis and address specific points of interest to be evaluated with imaging in iliofemoral deep vein thrombosis. In chapter 3 we further elaborate on the topic of imaging assessment. The aim was to identify reproducible thrombus imaging characteristics. We investigated the available literature on thrombus imaging characteristics and combined this with our own experience, and consequently developed a scoring system for 'virtual thrombus evaluation'. An imaging evaluation experiment was conducted to assess the feasibility and reproducibility of this scoring system. In chapter 5 the initial findings of the application of the scoring system in clinical practice are discussed.
Steady-state magnetic resonance venography (MRV) was (and is) embedded in our imaging work up of patients with suspected iliofemoral deep vein thrombosis, PTS and pelvic venous disorders (PeVD). Our protocol required the use of a specific MRI contrast material, gadofosveset trisodium (Vasovist ©), which is a blood pool contrast agent that was withdrawn from use in 2017. This led to a need for a MRV protocol not requiring the use of this blood pool contrast agent. In chapter 4 we evaluate a protocol using the regular commercially available gadolinium-based contrast agent gadobutrol (Gadavist ©).

The second part of this thesis reports the outcomes of the CAVA-trial (CAtheter Versus Anticoagulation alone for Acute Primary (Ilio)Femoral deep vein thrombosis) and explores the role of imaging in success or failure of treatment.

Patients with iliofemoral deep vein thrombosis are considered a high-risk patient group for the development of PTS. Early thrombus removal might prevent post-thrombotic syndrome by preserving venous function and restoring flow. Previous trials comparing additional catheter-directed thrombolysis to standard treatment showed conflicting outcomes. In the CAVA-trial (chapter 6) we aimed to assess the benefit of additional ultrasound-accelerated catheter-directed thrombolysis for the prevention of post-thrombotic syndrome compared with standard therapy in patients with iliofemoral deep-vein thrombosis.

When performing interventional procedures, there are always certain degrees of technical success we strive to achieve. In chapter 7 we assessed whether the specific technical goal of successful UACDT (defined as restored patency $\geq$ 90%) reduced development of PTS. Finally, in chapter 8 we investigated the potential clinical impact of using a dedicated MRV scoring system to assess thrombus characteristics prior to endovascular intervention for iliofemoral deep vein thrombosis.

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Part I:

Patient identification, classification and selection

Chapter 2: An imaging approach to deep vein thrombosis and the lower extremity thrombosis classification

2

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Abstract
The purpose of this article is to discuss an approach to deep vein thrombosis (DVT) imaging and propose a systematic approach to DVT management based on the newly introduced lower extremity thrombosis (LET) classification.

Introduction

Acute deep vein thrombosis (DVT) of the lower extremity is a disease which has life-impairing consequences in the majority of those affected. It occurs in close to one person per 1000 population per year. Under the current standard treatment regimen (systemic anticoagulation), the outcome is far from optimal, with up to 30% recurrence rate of DVT within five years and a 40% risk of post-thrombotic syndrome (PTS) within two years.[1,2] This highlights the need for improvement of treatment outcomes, which can potentially be achieved with more invasive treatment modalities such as catheter-directed thrombolysis,[3–5] as has recently been confirmed by the CaVent trial.[6]

The traditional classification of DVT offers two options: distal or proximal. The threshold location is the popliteal vein. Numerous observational studies have reported on outcome after 'proximal' or 'distal' DVT. Reviewing these studies, listing DVT extent, therapy and outcome, showed that there is a wide variety and inconsistency on reporting DVT with regard to the location and extent of DVT. Therefore the published data are not adequately comparable and the current medical reporting will not allow stratification to different therapy options.

With the current diagnostic imaging tools, including a range of new and updated imaging techniques, not only has identification of DVT become more easy but also visualization of the entire deep venous system is possible, allowing routine identification of potential underlying causes and accurate assessment of the location and extent of the disease. A combination of expanding the yield from clinical diagnostic imaging combined with standardized reporting will allow for an adequate comparison of published data and stratification to different treatment regimens.

Imaging

The described imaging techniques in the paragraphs below are not a complete review, but a summary of the key points of commonly used techniques to image DVT and their application in daily practice.

Over the past decade a wide variety of new imaging techniques to visualize DVT have been developed. Conventional phlebography, which is officially the gold standard, still has its uses, but as a routine diagnostic tool to identify DVT it has been surpassed by less invasive imaging alternatives. It is still the best imaging modality to visualize the extent of reflux in the deep venous system. The last major change with regard to imaging of DVT was duplex ultrasound replacing conventional phlebography in the (routine) examination of patients suspected of DVT. The main reason for this is that the diagnostic question in the clinical setting is only

the presence or absence of DVT. Thus the examination is often limited to verifying the compressibility and flow in the common femoral vein, the femoral vein and the popliteal vein. This also explains why there is such a wide variety and inconsistency on reporting DVT. Diagnostic imaging information, related to the extent of DVT, is scarce. Furthermore, there are also limitations to ultrasound imaging of DVT. In (morbidly) obese patients compressibility and flow can be difficult to assess, making the examination either inconclusive or false-positive. The same applies in patients who present with recurrent DVT. Due to the changes in the vein wall (which becomes more rigid) ultrasound assessment of these veins becomes significantly less accurate. Additionally no diagnostic information is available about the extent of the DVT. Questions such as: is it limited to one vein or more, does it involve not only the popliteal and/or femoral veins but also the iliac veins and are there signs of an underlying disease such as May-Thurner, atresia of the inferior vena cava, anatomical variants or a mass compressing the veins, remain unanswered. In the hands of a dedicated radiologist or technician, with enough time, duplex ultrasound can actually provide a lot of this additional diagnostic information in many cases. However, as mentioned before, in extensive or recurrent DVT there are other techniques that should be considered. For example, with the current generation of computed tomography-scanners (CT-scanners), a contrast enhanced CT can visualize the abdominal and pelvic deep veins as well as the femoral and popliteal vein segments in great detail with a relatively low contrast and radiation dose.[7] Such a CT scan will provide an overview of the entire deep venous system from the inferior vena cava down to the groin or even the upper calf, depending on the extent of the scan. In acute DVT this examination will depict the location and extent of the thrombosis accurately.[7] Unfortunately a CT scan requires ionizing radiation (with the highest administered dose in the pelvic region) and in heavy and obese patients a significantly higher tubevoltage is generally required to acquire diagnostic images. There are no reports with regard to the accuracy of CT-venography in patients with recurrent or chronic DVT. Alternatively, there are a number of different magnetic resonance imaging (MRI) techniques available to image DVT, which can roughly be divided into two groups. The first group of techniques focuses on depicting the deep venous system and its attributes, in most cases with the use of an intravenous (IV) contrast agent. The second group focuses on depicting/detecting thrombi specifically. This second group uses the magnetic attributes of methaemoglobin in clot, allowing visualization of thrombus without using intravenous contrast.[8] This MR direct thrombus imaging technique (MRDTI) has shown promising results with regard to the visualization of thrombi, and thus is effective with regard to the clinical question of whether or not DVT is present. In addition to that, this technique is also capable of providing information with regard to the level and extent of thrombosis. However, it does not visualize the entire venous system and surrounding structures to identify underlying causes or identify anatomic variations. Furthermore, since this technique focuses on imaging new or recent thrombus (0–3 months), there is no or limited visualization of older thrombi or chronic (fibrotic) changes in the veins due to old DVT events. This brings us to the first group, in

which there are MR techniques that allow us to visualize the deep venous system completely. The aim of these contrast enhanced MR techniques is to accurately identify thrombosis, while providing a detailed anatomical overview of the veins, arteries and surrounding tissues. In addition to that they might have the potential to visualize late and/or chronic changes in these veins, which still has to be investigated. There are a few variations of this contrast enhanced MR technique, but in order to be able to visualize the entire deep venous system from the calf up to the inferior vena cava, there are a few prerequisites, at the moment limiting the suitable protocols. In order to be able to scan such a volume (3–5 stations) 15–30 minutes of contrast enhanced scan time is required. Keeping the injected contrast volume within reasonable limits, this requires the use of a specific contrast agent, a so-called bloodpool contrast agent. The advantage of the use of a bloodpool contrast agent is that this greatly improves the contrast enhanced phase duration and thus increases the effective scan time. With a conventional MR contrast agent the contrast enhanced phase lasts only 5–10 minutes effectively, whereas with a bloodpool agent the contrast enhanced phase can last up to at least 30 minutes, allowing the high resolution depiction of the entire venous system with the administration of a single dose of contrast. Furthermore, it requires dedicated equipment and technicians to be able to keep the scan times within a reasonable window (25–40 minutes).

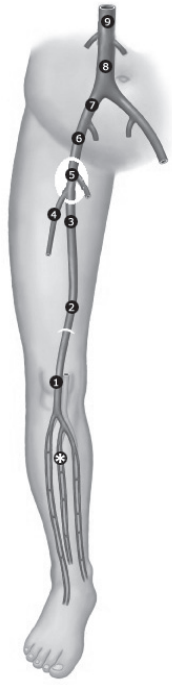
In conclusion, there are a few (good) options to complement duplex ultrasound in the diagnostic imaging of patients with DVT. Depending on local expertise, equipment and available examination time, dedicated CT or MRI protocols are both capable of creating a broad overview of the deep venous system.

Classification

As mentioned above, high-resolution imaging of the entire deep vein system is now feasible, allowing for accurate assessment of the location and extent of the DVT. This makes it possible to establish a standardized classification of DVT based on anatomical landmarks, avoiding the use of arbitrary definitions. The classification described below, the lower extremity thrombosis classification (LET) is designed upon the hemodynamic hypothesis that the severity of DVT, and the risk of developing PTS or recurrent DVT, is related to the extent of the outflow obstruction and residual thrombus in the deep venous system of the lower extremity.

Crucial are the involved vein segments (in particular at the level of the common femoral vein), that either make it possible for the main collateral pathways to 'take over' when the femoral vein(s) is/are obstructed, or the obstruction includes these collateral pathways impairing the outflow to a greater extent and limit the ability of the deep venous system to compensate for the occluded vein(s). The anatomical segmentation of the deep venous system we use in the LET classification is shown in Figure 1.

Figure 1 *Description of the venous segments used in the LET classification*



Segment 9: Inferior caval vein (suprarenal)
Segment 8: Inferior caval vein (infrarenal)
Segment 7: Common iliac vein
Segment 6: External iliac vein
Segment 5: Common femoral vein
Segment 4: Deep femoral vein
Segment 3: Proximal femoral vein
Segment 2: Distal femoral vein
Segment 1: Popliteal vein
Segment 0: Calf veins

LET: Lower Extremity Thrombosis classification

LET class I: calf vein thrombosis

Patients with an isolated calf vein thrombosis usually do not have an outflow limitation of the deep venous system of the lower leg. It is important to differentiate this subgroup of patients as it is known that calf vein thrombosis can potentially extend into the popliteal vein, evolving into a DVT which can obstruct the deep venous system and place the patient at higher risk of pulmonary embolism and more severe post-thrombotic morbidity. Furthermore, there is evidence that suggests that the identification of involvement of axial (para-arterial tibial) veins versus deep-muscle veins in the calf is of clinical significance with regard to the success of systemic anticoagulant therapy in these groups of patients,[9–12] although recent observations challenge prior concepts.[13]

LET class II: popliteal and femoral vein thrombosis

The second group is patients with thrombus in the popliteal and/or femoral vein. There is no occlusion of the common femoral vein. There can be impaired venous outflow due to an increased outflow resistance, but this is compensated for by increased venous return via superficial veins and a patent deep femoral vein system. This is the most likely explanation why the majority of these patients do not develop severe PTS following an episode of DVT.[14,15] Persistent deep venous incompetence in the femoral vein might influence outcome,[16] but in these cases, the collateral pathways (superficial and deep femoral veins) reduce outflow obstruction for the lower extremity. Systemic anticoagulation prevents progressive thrombosis and may allow adequate physiological lysis of the thrombus in this segment leaving minimal residual obstruction of the deep venous axis and a relative low risk for the development of PTS. There is no evidence suggesting that invasive therapeutic options such as CDT provide an outcome benefit over systemic anticoagulation and compression therapy.

LET class III: common femoral/iliac vein obstruction

The third group is patients whose thrombus occludes the common femoral vein and/or iliac veins, thus obstructing the outflow of the entire venous drainage of the lower extremity. This poses an increased risk for the development of PTS and/or recurrence of DVT.[9,14–16] Persistently impaired outflow produces severe venous hypertension, especially ambulatory venous hypertension. Valves in and distal to the thrombotic segments might develop valvular incompetence. Valvular incompetence is caused by the destruction of valves and secondary to the venous dilation due to persistent obstruction caused by persistent proximal obstruction. This results in impaired outflow and increased valve incompetence, increasing the chance of developing recurrent DVT and/or PTS. Based on available evidence, strategies of thrombus removal in patients with iliofemoral DVT offer patients an opportunity to restore patency, enjoy a better quality of life by avoiding PTS, and potentially reduce their risk of recurrence.

LET class IV: inferior vena cava

Thrombosis of the inferior vena cava (IVC) results in an outflow obstruction of the deep vein axis of both legs, which may or may not be associated with iliofemoral DVT of one or both legs. Similar to patients with iliofemoral DVT, restoring the outflow of the IVC to the heart can result in marked clinical improvement.

LET classification: imaging recommendations

Class I and Class II: Imaging can be limited to visualization of the popliteal and (common) femoral veins, crucial is the exclusion of involvement of the common femoral vein, reducing the probability of involvement of the inferior vena cava and/or iliac veins to less than 1%.

Class III and Class IV: Imaging should not only cover the popliteal and (common) femoral veins, but also the iliac veins and inferior vena cava. To effectively treat DVT involving the common

femoral vein (and above), unobstructed outflow to the IVC and/or heart needs to be documented. It is crucial to identify an underlying lesion which might have contributed to the initial venous thrombosis and may lead to recurrent thrombosis if left uncorrected (e.g. May-Thurner, IVC interruption or atresia). It is also essential to identify distal involved segments, because the total thrombus load influences outcome.[9,16] Table 2 is a comprehensive overview of the classification described above. Figure 2 shows how the thrombosed segments translate into a LET class.

Figure 2

	LET I	LET II				LET III			LET IV	
Rights	0	1	2	3	4	5	6	7	8	9
Left	0	1	2	3	4	5	6	7	8	9
	CALF	POPLITEAL / FEMORAL				COMMON FEMORAL / ILIAC			ICV	

Scoring the LET classification. Encircle the segments involved

Table 1 *Comprehensive overview of the LET classification*

LET class I

Isolated calf vein thrombosis

Extent of the disease is limited to segment 0

Segment 1 to 9 are not involved; there is no involvement of the popliteal-femoral axis

LET class II

Femoral-popliteal vein thrombosis

Deep vein thrombosis in the popliteal and/or femoral vein. The common femoral vein is not occluded. (Non-occlusive thrombus extending into the common femoral vein from the femoral vein will be graded as class II, as it does not obstruct outflow from the profunda femoris vein.)

Segments 1–4 can be involved, but there is no involvement (occlusion) of segment 5–9. Effectively there is an outflow obstruction of the drainage of the deep calf veins but no obstruction of the outflow of the profunda femoris veins at the level of the common femoral vein

LET class III

Common femoral and/or iliac vein trombosis

Deep vein thrombosis in the common femoral and/or iliac veins, obstructing the drainage of both the femoral and deep femoral vein. Segments 0–7 also can be involved, but the key to Class III is identifying involvement of segment 5 (common femoral vein) to segment 7 (iliac veins)

LET class IV

Inferior vena cava thrombosis

Deep vein thrombosis in the inferior vena cava. Segments 0–9 also can be involved, emphasis is on identifying the involvement of segment 8 and/or 9

Discussion

These new definitions will clarify the benefits of new modalities of patient care, especially those designed to mechanically or pharmacologically clear the venous system of clot. The LET classification organizes the clinical heterogeneity of patients with DVT of the lower extremities in sharply demarcated subgroups. This new nomenclature will be helpful when describing DVT of the lower extremities in both a research setting, in clinical practice and when stratifying risk of patients. Additionally, it will be helpful in the future when deciding on a more or less invasive treatment approach. We acknowledge that there is currently limited study data to support our proposed classification. However, in our opinion this only strengthens the need for a consensus with regard to describing the location and extent of DVT accurately. The reason that we want to introduce a classification, is that in regard of the current standards we are still treating very heterogeneous groups of DVT patients identically. Taking the results of recent DVT studies into consideration, it has been shown that there are significant subgroups within the 'proximal' and 'distal' standard groups. Not identifying these subgroups will hamper the outcomes of present and future studies. To make the next step in DVT research and future clinical treatment, it is needed that we enable ourselves to properly compare future study results as they apply to different anatomical distributions of DVT. These anatomical subgroups identify patients that might development PTS and recurrent DVT, and whether these post-thrombotic outcomes can be predicted and avoided.

Conclusion

In order to optimally treat DVT it is vital to accurately identify and describe the location and extent of the disease. Additionally in extensive iliofemoral DVT it is crucial to identify or exclude underlying disease. A multimodality imaging approach combined with standardized reporting (e.g. the LET classification) is a simple and potentially meaningful approach to manage DVT treatment. Identifying and reporting DVT more accurately allows for accurate stratification for initial patient care, future clinical trials, and appropriate descriptions for natural history studies.

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Chapter 3: Feasibility of identifying deep vein thrombosis characteristics with contrast enhanced MR-Venography

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Abstract

Purpose: To assess the feasibility of identifying deep vein thrombosis characteristics with contrast enhanced magnetic resonance venography.

Materials and Methods: A total of 53 cases of deep vein thrombosis extending in and/or above the common femoral vein were evaluated by 4 independent observers (2 expert, 2 novice) using pre-determined characteristics to determine the thrombosis present to be acute, sub-acute or old. If present, chronic remnants of a previous deep vein thrombosis were reported. Additionally these image qualifications were compared to the reported duration of complaints.

Results: In all cases all observers were able to qualify the thrombosis. The interobserver agreement between the experts was excellent (kappa 0.97) and good between expert and novice (kappa 0.82). Thrombosis identified as acute had an average duration of complaints of 6,5 (2–13) days, sub-acute 13 (8–18) days and old 22 (15–32) days.

Conclusion: Qualification of thrombosis as acute, sub-acute or old and identification of chronic remnants of DVT with CE-MRV using routinely identifiable characteristics is feasible and reproducible with good to excellent interobserver agreement.

Introduction

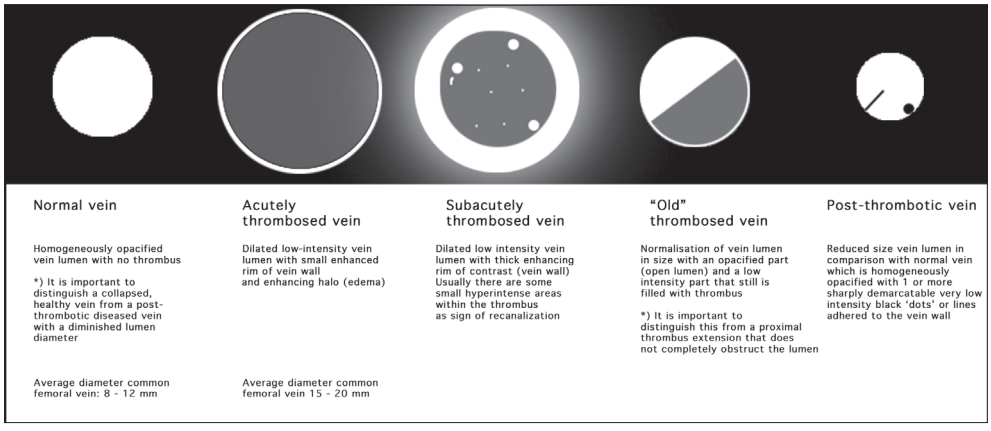
Deep vein thrombosis affects many patients every year. Despite best medical management with anticoagulation, there is a 30–50% risk to be subsequently affected by the post-thrombotic syndrome (PTS) resulting in long-term, mostly life-long persistent complaints of leg swelling, pain and potentially venous ulcerations.[1,2] For PTS there is no specific treatment for the underlying venous pathologies and treatment is mostly supportive. Much of the process of thrombus resolution in humans is still unclear but there is supportive evidence that early thrombus resolution reduces the chances of developing PTS, hence techniques such as catheter-directed thrombolysis (CDT) and pharmacomechanical thrombolysis (PMT) have gained more support. [3–5] In general, the use of these techniques is limited to patients with acute ilio-femoral deep vein thrombosis, defined by complaints 2 weeks and thrombus in the iliac and/or common femoral vein.[6–8] This period of 2 weeks is however arbitrary since we have to rely on duration of patient complaints to estimate this period and success with thrombolysis has been seen in patients with complaints for 3–4 weeks. There is currently no objective measurement to define the critical point beyond which thrombolysis is no longer feasible. The transitional process from acute deep vein thrombosis to "old" thrombus and eventually to chronic remnants in the vein and vein wall after DVT,[9–12] can take 6 months up to 1 year to stabilize but it has not been established at what point in time after the start of the event the disease is no longer susceptible to thrombolytic therapy. To be able to predict which patients can benefit from catheter-directed thrombolysis (CDT) versus those that are unlikely to benefit would be helpful in determining the preferred treatment plan and duration of anticoagulation. Additionally, it would be beneficial if patients unsuitable for CDT would be excluded prior to starting the thrombolysis and thus prevent exposure to the serious risks associated with

thrombolysis.[1] Ideally this measurement would not require any invasive procedure. Imaging with MRI would be a good option if interpretation is consistent and observer independent.

Concept

MRI as imaging modality for deep vein thrombosis has been investigated for many years.[13–16] A number of observations regarding thrombus characteristics identifiable with MRI have so far been described in the literature.[17] The first and most commonly acknowledged is that acute thrombus causes vein dilatation due to luminal filling with thrombus material. The second is the visibility of vein wall thickening and edema surrounding the thrombosed veins which has been associated with the inflammatory response to the thrombus.[18] The third is a hypothesis that the heterogeneity of the signal in the thrombus seen on some MRI sequences is a possible sign of recanalization within the thrombus (channel formation).[19] The blood within these channels has a different (higher) signal intensity in comparison to the remaining thrombus. The fourth is the visibility of post-thrombotic remnants in patients after an episode of deep vein thrombosis.[20] Different MRI sequences and protocols have been used in the individual studies describing these thrombosis-related findings. If we could identify all these findings with one MR protocol, routine evaluation to characterize the thrombosis might be feasible. If we link these observations with the in-situ process in thrombosed veins, we come to the following concept and interpretation of findings (see also Figure 1):

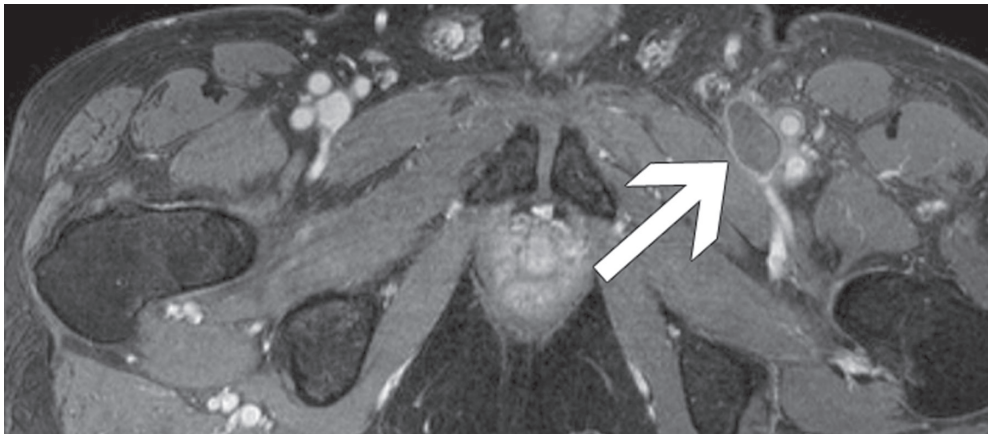
Figure 1



Concept of thrombosis characteristics as visualized with contrast enhanced MR-Venography.

1. Acute DVT is characterized by obstruction and dilatation of the involved vein(s). This can be identified on MRI as a dilated, homogeneously low-intensity vein lumen with a thin enhancing rim (vein wall).

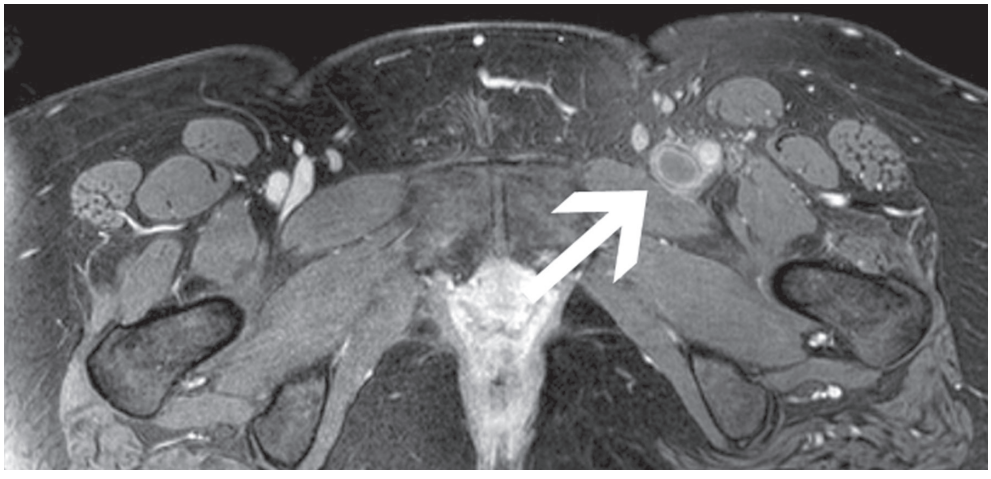
Figure 2



Acute deep vein thrombosis (left common femoral vein): An enlarged, dilated vein with homogenous low (hypo-intense) signal intensity surrounded by a thin enhancing rim of contrast (vein wall) can be seen (arrow).

2. In response to the presence of thrombus an inflammatory response takes place with contrast enhanced MRI increased vein wall enhancement and perivenous edema. Simultaneously recanalization takes place, which is visible on MRI as more heterogeneous signal intensity within the thrombus. Since this takes place in response to the acute event of thrombotic occlusion of the vein we define this as 'sub-acute.'

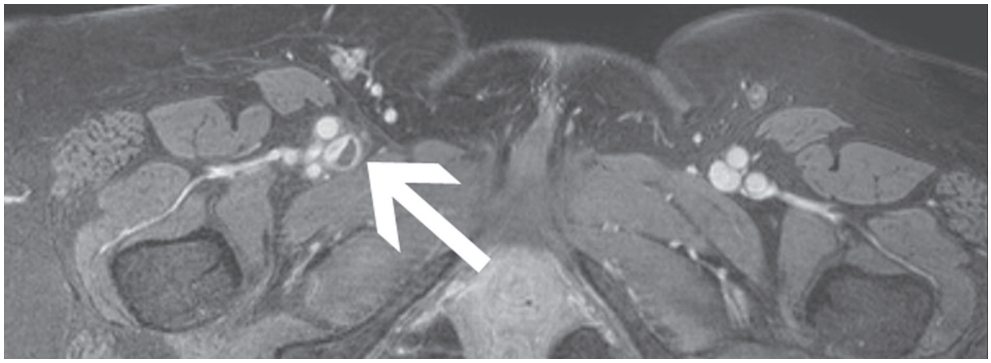
Figure 3



Sub-acute deep vein thrombosis (left common femoral vein): An enlarged dilated vein with a heterogeneous signal intensity surrounded by a thick enhancing rim of contrast (vein wall and surrounding edema) can be seen with some hetrogeneity within the thrombus as sign of recanalization (arrow).

3. Residual thrombus or transformed thrombus into more chronic material can remain in the vein(s) after the thrombus load has decreased and the inflammatory response has subdued with a normalization of the vein lumen size without evidently visible perivenous edema or vein wall thickening. The acute response of inflammation and lysis has seized and a more chronic process of (slow) residual recanalization takes place. For the purpose of this study we defined this as 'old'.

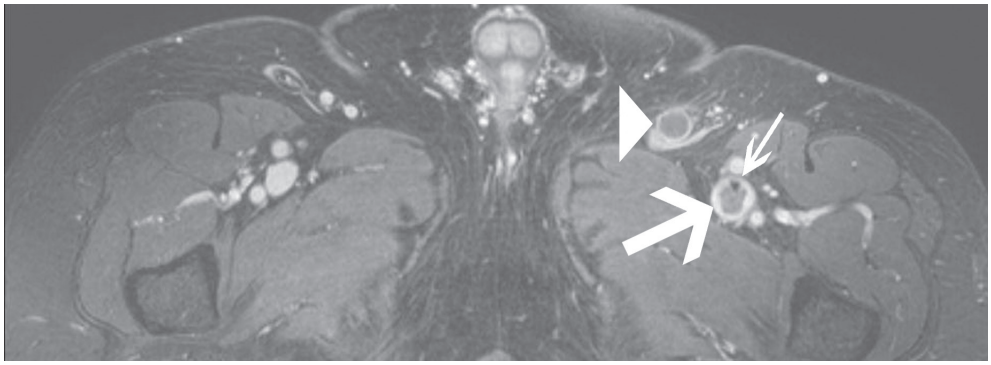
Figure 4



"Old" deep vein thrombosis (right common femoral vein): A normalized caliber vein with heterogeneous and/or hypo-intense material in the vein can be seen. There is no evident enhancing rim of contrast visible, there is no apparent edema (arrow).

4. Structural remnants (trabeculations/fibrotic strands) develop over time that can be identified as very low-intensity (black) strands on MRI. We define these as 'chronic'.

Figure 5



Acute on chronic (left common femoral vein): Adjacent to or in the vein wall, a dark, sharply demarcated dot or strand is visible (old- or post-thrombotic material) (thin arrow). The vein lumen is filled with homogenous low (hypo-intense) signal corresponding with the acute component (thick arrow). There is also an acute thrombosis of the great saphenous vein (arrow-head).

5. Additionally, these fibrotic stands can be identified as a separate entity next to acute thrombus in patients with recurrent deep vein thrombosis. The very low-intensity strands (chronic component) are visible separately from the (dilated) homogeneously low-intensity vein lumen filling (acute component). We defined this combination of image findings as 'acute-on-chronic'.

Materials & Methods

A retrospective analysis of 53 cases was performed with objectively verified iliofemoral DVT on routine ultrasound. 34 patients were male, mean age was 47 (range 17–77). All 53 had normal renal function and underwent CE-MRV.

CE-MRV protocol

All MR examinations were performed on a 1.5-T MRI system (Intera, Philips Medical Systems, Best, The Netherlands). For signal reception a dedicated 12-element phased-array peripheral vascular coil with a cranio-caudal coverage of 128 cm (Philips Medical Systems) was used. Patients were imaged in a supine position. A fixed dose of 10mL Gadofosveset Trisodium (Ablavar , Lantheus Medical Imaging, Billerica, MA, USA), a bloodpool contrast agent, was administered intravenously as a single dose at a speed of 1.0 mL/second in the median cubital vein, using a remote controlled injection system (Medrad Spectris, Indianola, PA, USA). Contrast injection was followed by 20mL saline flush injected at the same rate. A five-station three-dimensional ultrafast gradient echo (TFE) sequence with fat suppression (SPIR) was used for high-resolution steady-state imaging of the venous vasculature, ensuring coverage of at least the popliteal veins up to the entire IVC. Acquisition parameters were as follows: TR 7.8 ms, TE 3.8 ms, FOV 380 mm, matrix 400, 150 axial slices/station and voxel dimensions (reconstructed) were 0.95 0.95 1.50mm for all stations. Parallel imaging (sensitivity encoding, SENSE) was applied to reduce scan time (SENSE factor 2 in the anterior–posterior direction). For optimal signal intensity and reducing bowel and respiratory artifacts, a NSA of 2 was used. Total acquisition time for five stations was approximately 17 minutes.

Image assessment

Interpretation of studies was performed in 3 steps. Initially observer 1 (CA) interpreted all studies to evaluate if distinguishing the above-mentioned characteristics was feasible. The next step was instruction of observer 2 (RdG) by observer 1 with regard to image interpretation. Criteria on how to interpret the images including example images are shown in Figures 2 to 5. Both observers 1 and 2 had extensive experience with evaluating MR-Venography studies and vascular MR studies in general. The next step was instruction of observer 3 (DL) and 4 (ML) by observer 1. Observers 3 and 4 were inexperienced with evaluating MR-Venography studies and only had limited experience with vascular MR studies in general. All observers had access to all images in the study, which included axial and coronal reconstructions. Interpretation was done at the level of the common femoral vein. All 4 observers were blinded for the other results

and had no access to the patients' clinical history, duplex ultrasound findings or conventional venography studies performed. All observers characterized the common femoral vein on the thrombosed side as either acute, sub-acute or old thrombosis. Additionally, they were asked to identify any signs of acute-on-chronic thrombotic disease separately.

Comparison with clinical assessment

In addition to the comparison of the results of the 4 observers, the results of observer 1 were compared with the reported duration of complaints in the patient's clinical history.

Data analysis

The statistical analyses were performed using the statistical package SPSS version 18 (SPSS, Chicago, IL, USA). Interobserver agreement was calculated using the kappa statistic. For the purpose of evaluating the interobserver agreement observer 1 was used as reference to which all other observers were compared.

Results

All common femoral vein segments were visualized completely. All observers found all but one study to be conclusive. The findings for all 4 observers are presented in Table 1. The interobserver agreement between observer 1 and 2 (experts) was excellent with a kappa of 0.97 (Table 2). De interobserver agreement between observer 1 and 3 was good with a kappa of 0.82 and equal to observer 1 versus 4 (Table 3). In table 4 the comparison between image interpretation of observer 1 and reported clinical duration of complaints is listed.

Table 1. Findings of all 4 observers.

	Observer 1 (CA)	Observer 2 (RdG)	Observer 3 (DL)	Observer 4 (ML)
Inconclusive	1	1	1	1
Acute	14	15	19	17
Sub-acute	30	29	24	26
Old	9	9	10	10
Acute on chronic	2	2	2	2

(*) Patients with acute on chronic disease are listed twice, both as acute and acute on chronic

Table 2. Comparison of findings between observers 1 and 2.

Cross tabulation observer 1 and 2					
		RdG (2)			
		1.00	2.00	3.00	Total
CA (1)	1.00	14	0	0	14
	2.00	1	29	0	30
	3.00	0	0	9	9
Total		15	29	9	53

Symmetric Measures observer 1 vs 2					
Observer 1 vs Observer 2		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.969	.031	10.005	.000
N of Valid Cases		53			

[a]Not assuming the null hypothesis.
[b]Using the asymptotic standard error assuming the null hypothesis.

Table 3. Comparison of findings between observers 1, 3 and 4.

Symmetric Measures observer 1 vs 3					
Observer 1 vs Observer 3		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.824	.068	8.708	.000
N of Valid Cases		53			
Symmetric Measures observer 1 vs 4					
Observer 1 vs Observer 4		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.821	.070	8.578	.000
N of Valid Cases		53			

Table 4. Characterization of thrombus vs reported duration of complaints

MRI	Duration of complaints (days)	Average duration (days)	Known previous DVT ipsilateral leg (number of cases)
Acute	2-13	6,5	0
Sub-acute	8-18	13	0
Old	15-32	22	0
Acute on chronic	5-8	6,5	3

Discussion

Identifying thrombus characteristics as described in our study with contrast enhanced MR-Venography (CEMRV) is feasible and has a good to excellent interobserver agreement. Our data suggests that the degree of experience with vascular MR studies made no significant difference for accurate characterization, which makes routine evaluation by general radiologists feasible. There were however a few cases where the novice observers both experienced (and when asked described) issues with the interpretation. In 1 case the thrombus extension was only just into the common femoral vein from the femoral vein and the deep femoral vein was still patent. Distinguishing such an acute thrombus lip from an "old" thrombus can only be done by interpreting the total thrombus extension and surrounding (potentially patent) veins, which was not defined in the characterization protocol of this study. Most differences in interpretation between the expert and novice observers were between acute and sub-acute (Table 1).

This was mainly based on interpretation of the vein wall and surrounding edema as either already subtlety present according to the experts or not yet present according to the novices. When comparing the acute-on-chronic findings with the clinically reported previous DVT events on the ipsilateral side, one DVT was reported that was not seen on MRI in the common femoral vein (which was the evaluated segment in this study). Re-evaluating the case we found chronic changes in the femoral vein, but not in the common femoral vein. This particular patient had an acute DVT extending from the deep femoral vein into the common femoral vein and the external iliac vein. The femoral vein was post-thrombotic with a decreased (near pin-point) lumen and no current acute thrombosis.

Unfortunately we did not have the chance to correlate our CE-MRV findings with the actual thrombus present in these patients. Thus at the moment we have to accept the potential fact that the recognizable patterns on CE-MRV might not reflect actual critical points in the evolution of thrombosis over time but rather show signs of the local/systemic response to thrombus. Furthermore, assessment in this study was targeted at the common femoral vein in patients with iliofemoral vein thrombosis to ensure reproducibility.
Evaluation of larger veins (e.g. iliac or inferior vena cava) is not expected to be problematic, however smaller veins (e.g. distal femoral or popliteal vein) might be less reproducible, in particular in recurrent DVT with vein diameters approaching the scanned voxel size. Identification of chronic venous changes in these smaller veins is not a problem but identifying acute from 'sub-acute' or "old" might prove to be difficult.

Looking at the reported duration of complaints in comparison to the interpretation of the thrombosis characteristics it is interesting to see there is a relationship between duration and characteristics, but also quite an overlap in clinical duration between the different groups

defined by MRV. Obviously this raises the question whether interpretation of the MRV studies or reported clinical duration of complaints are inaccurate.
When asked in person most patients do not exactly recall when their complaints started unless the complaints are very severe or rapid in onset, which makes this particularly unreliable in those patients that have complaints for more than 2 weeks. This supports the fact that in the sub-acute and old groups patients might miss out on the opportunity of receiving CDT because of the duration of complaints or are mistakenly treated with CDT. This finding in particular requires more detailed investigation and correlation with CDT results.

Conclusion

CE-MR-Venography allows for identification of specific characteristics of the response on and evolution of deep vein thrombosis with good to excellent interobserver agreement. Correlation with thrombus specimens and consequences of these findings with regard to treatment choices need to be further investigated.

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Chapter 4: Gadobutrol versus gadofosveset-trisodium in MR-venography of the lower extremities

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Abstract

Objectives: MR venography (MRV) protocols have used bloodpool contrast agents and long scan sequences to identify patients suitable for treatment and preoperatively. However, variable availability of bloodpool contrast agents, high costs and a need to shorten acquisition times for routine MR protocols hamper everyday practice.

Materials: 20 patients (11 men; mean age 54 ± 11.8 years;body mass index 23.6 ± 2.5) were enrolled in this prospective study. An intra-individual comparison of image quality, interpretation and findings for two different contrast agents (regular gadolinium contrast agent gadobutrol vs. bloodpool contrast agent gadofosveset-trisodium) and two different scan protocols (long acquisition time protocol using a highresolution fast field echo (FFE) sequence vs. short acquisition time protocol using an ultra-fast gradient echo (GE) sequence) were performed.

Results: Image quality (average of 4.94 vs. 4.92 on a five-point scale), interpretation and contrast-to-noise ratio (44 vs. 45) were equal for both contrast agents. Image findings showed no statistical significant differences between the MR-protocols or contrast agents (overall $p = 0.328$).

Conclusions: For high-resolution MRV, it is possible to replace gadofosveset-trisodium with gadobutrol. Furthermore, an ultrafast GE sequence for MRV might considerably shorten acquisition time, without loss of image quality or diagnostic yield.

Introduction

With the introduction and success of minimally invasive treatment options for chronic venous obstructive disease, imaging of abdomino-pelvic and lower extremity veins is receiving increased attention.[1] Chronic venous obstructive disease is defined as post-thrombotic obstructive disease of the deep veins, in particular, at the level of the iliocaval confluence and or (proximal) femoral veins, which results in impaired deep vein outflow. An addition to the above definitionis the group of chronic venous obstructive lesions which are not related to deep vein thrombosis, called non-thrombotic iliac vein lesions (NIVLs).[2] Identification of such deep vein disease can be performed with duplex ultrasound, computed tomography venography (CTV) or magnetic resonance venography (MRV). In particular, above the groin, MRV is more suitable to accurately identify the location of deep vein obstruction and chronic sequela of previous deep vein thrombosis events as well as provide an anatomic overview in the pre-interventional work-up.[3-7]

Several studies have shown that the use of blood pool agents is favourable, due to the creation of a long steady state imaging window for the high-resolution acquisition of the entire deep venous system in the lower extremities, allowing for detailed depiction of the (intra)luminal changes.[8-11] However, in the clinical arena, we are currently facing a three-fold problem: First, blood pool contrast agents are expensive. Secondly, the most commonly used blood pool agent for vascular imaging, Ablavar, is no longer commercially available in Europe. Thirdly, the clinical acceptance of these MR protocols is limited due to the relatively long acquisition

time which easily exceeds 25 min.[6] An alternative technique to acquire large-volume, high resolution 3D images is a high-resolution 3D T1-weighted volume interpolated gradient echo (GE) sequence with fat suppression (ultrafast GE).[10,11] This sequence has the potential to greatly reduce acquisition time for the required (large) volume. Acquisition time of less than 20 min might form the basis for the broad use of conventional extracellular gadolinium contrast agents.[12-14] Our goal for this study was to provide a clinical alternative to gadofosveset-trisodium by using a globally available extracellular gadolinium-based contrast agent instead. Secondly, we optimized a shorter yet robust acquisition protocol for lower extremity MRV to be used in daily clinical practise.

Material and methods

Patients

During an 8-month period, 129 consecutive patients seen at our dedicated venous out-patient clinic with clinical signs of chronic deep vein obstruction were invited to participate in this prospective study. Clinical signs included a CEAP classification of 4 or more, a Villalta score of 15 or more, signs of venous claudication, recurrent upper leg and groin varicosities and/or venous ulcerations. Inclusion and exclusion criteria are listed in Table 1.

Table 1 *Inclusion and exclusion criteria for this study*

INCLUSION	EXCLUSION
Age between 18–65 years	Hemodynamic instability
Objectively documented CVD	Known allergy for gadolinium-based MRI contrast agents
Duplex ultra-sound suspected chronic deep vein obstruction (no DVT)	eGFR: < 30 mL/min 1.73 m2
Patient scheduled for CE-MRV	Claustrophobia
Patient able to undergo CE-MRV twice within 2 weeks	Pregnancy
Patient not scheduled to receive any treatment between CE-MRV examinations	

CVD: chronic venous disease. DVT: deep vein thrombosis. CE-MRV: contrast-enhanced magnetic resonance venography. MRI: magnetic reso- nance imaging. eGFR: estimated glomerular filtration rate.

The study protocol required patients to be scanned twice, within a 2-week interval. A minimum of 3 days between the two scans was required to ensure no residual enhancement of the previously administered contrast agent.[12,15] 21/129 individuals (16.3%) gave written informed consent; one patient did not undergo the entire protocol for logistical reasons. Hence, 20 patients (11 men, 9 women; mean age 54, SD 11.8 years; range 36–77 years, BMI 23.6+ 2.5) were enrolled. The study protocol was approved by the local ethics committee.

Magnetic resonance imaging (MRI) protocols

All MR examinations were performed on a 1.5-T MRI system (Intera, Philips Healthcare, Best, The Netherlands). For signal reception, a dedicated 12-element phased-array peripheral vascular coil with a cranio-caudal coverage of 128 cm (Philips) was used. Patients were imaged in a supine position. Prior to contrast delivery, all patients underwent a standard 2D non-contrast-enhanced balanced turbo field echo (BTFE) sequence to visualize the abdominal and pelvic veins. This was followed by contrast material injection which was administered intravenously at 1.0 mL/s in the median cubital vein followed by 20 mL of saline flush injected at the same flow rate, using a remote-controlled dual-head injector (Spectris; Bayer Medrad, Indianola, PA, USA). Acquisition of the first scan volume was started 30 seconds after contrast administration.

A 3D ultra-fast gradient echo sequence (Ultrafast GE, THRIVE, Philips Healthcare) with fat suppression (spectral pre-saturation with inversion recovery, SPIR) was used for high-resolution steady-state imaging of the venous vasculature, ensuring coverage of at least the popliteal veins up to the suprarenal inferior caval vein. Like the first examination, the second examination consisted of the sequences mentioned above with addition of the steady-state gradient echo sequence (HR-FFE) without fat suppression. For both examinations, the order of the scanned sequences is listed in Table 2.

Table 2 *Order of sequences for each examination*

EXAMINATION I	EXAMINATION II
BTFE sequence	BTFE sequence
Contrast administration (gadobutrol)	Contrast administration (gadofosveset-trisodium)
Ultrafast spoiled GE	Ultrafast spoiled GE
	HR-FFE

For the first examination, a standard extracellular gadolinium agent gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany, now: Gadavist, Bayer HealthCare, Berlin, Germany) was administered. To mimic the steady-state of the high-relaxivity agent gadofosveset-trisodium, we used a double dose (2x) of the regular gadolinium-based agent (0.2 mL per kg body weight, equals 0.2 mmol/kg).[13-16] For the second examination at 7 + 3 days, the bloodpool contrast agent gadofosveset-trisodium was used (Ablavar, Lantheus Medical Imaging, Billerica, MA, USA). All patients received a fixed dose of 10 mL of gadofosveset-trisodium (0.25mmol/mL). An overview of the detailed scan parameters is provided in Table 3.

Table 3 *Scan parameters of the sequences used*

	BTFE Abdomen / pelvis	**Ultrafast spoiled GE**	**HR FFE Legs**	**HR FFE abdomen / pelvis**
Scan mode	M2D	3D	3D	3D
Repetition time (TR) (ms)	3.8	7.8	12	12
Echo time (TE) (ms)	1.92	3.90	1.91	1.70
Flip angle (degrees)	65	10	20	20
Acquisition time (TA) (min) (for all stations)	6:40	14:52	13:37	7:48
Bandwidth (BW) (Hz)	595	181.8	159.4	186
Acquisition voxel (mm)	1.19 × 1.40 × 6.00	0.95 x 0.95 x 3.00	0.84 x 0.84 x 1.00	0.98 x 0.98 x 2.00
Reconstructed voxel (mm)	1.04 × 1.04 × 6.00	0.95 x 0.95 x 1.00	0.84 x 0.84 x 1.00	0.98 x 0.98 x 1.00
Number of slices	100	150 x 5 (750)	175 x 3 (525)	200 x 2 (400)
Acquisition matrix	336 × 228	380 x 266	560 x 392	560 x 392
FoV	400 × 319	400 x 280	470 x 329	470 x 329
Fat Supression	No	SPIR	No	No
Cardiac synchronisation (ECG)	Yes	No	No	No

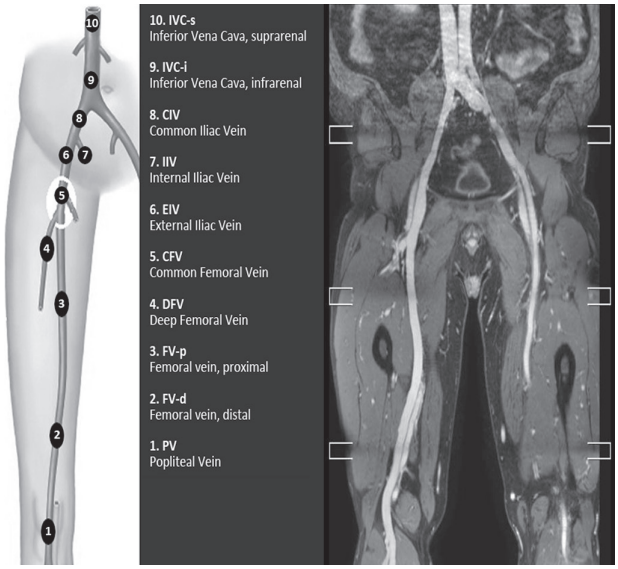
The BTFE sequence was acquired in two volumes to cover the abdomen and pelvis. The ultra-fast GE sequence was acquired using a coronal acquisition scheme in three volumes which were stitched and then reconstructed in the axial plane on the scanner. The HR-FFE was also acquired in three coronal volumes. Stitching is not available for this sequence, for each volume axial reconstructions were made on the scanner. The acquired volume for the 3D scans covered the deep vein system from the inferior vena cava (IVC) to the distal popliteal vein. The calf veins are not routinely included in our scan protocol for two reasons. First, inter-individual patient length varies (on average from 1.40 meters to 2.00 meters) which results in variable coverage of the calves. Second, findings in the (proximal) calf veins do not have consequences for treatment.

Evaluation of studies

All sequences were evaluated by two independent reviewers: 1 (CWKP) and 2 (NI), both blinded for the contrastmaterial used, individual scan dates and each other's results. Reviewer 1 had 5 years of experience with venous vascular MR studies specifically, and reviewer 2 had 1 year of experience. Each sequence was evaluated separately within different sessions. Both reviewers had access to the source images as well as common post-processing tools; multi-planar reconstruction (MPR)/curved planar reconstruction, maximum intensity projection (MIP). The reviewers were blinded for the clinical record of the patients. The following vessel segments were evaluated: 1: popliteal vein, 2: distal femoral vein, 3: proximal femoral vein, 4: profunda femoral vein, 5:commonfemoral vein, 6: external iliac vein, 7: internal iliac vein, 8: common iliac vein, 9: infrarenal inferior caval vein, 10: suprarenal inferior caval vein (Fig. 1).

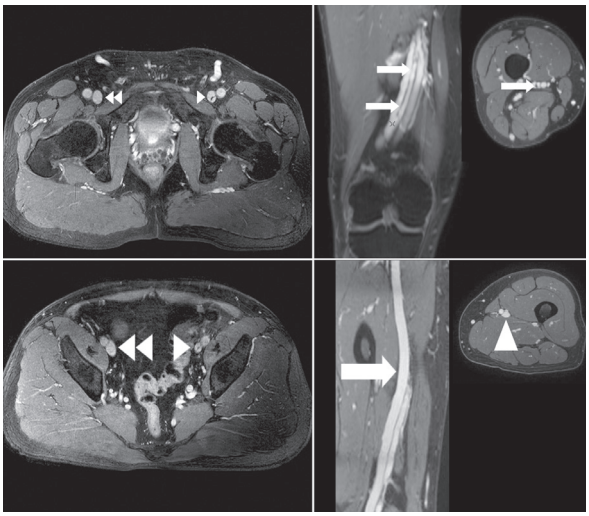
Figure 1

Schematic and MR-venography overview of the evaluated vein segments



In all patients, both legs were evaluated, allowing for evaluation of 360 vessel segments in total. The following items were subjectively scored: image quality, confidence of image interpretation and findings. Image quality was scored on a Likert-like scale from 1 to 5, with 1: not visualised, 2: poor, 3: fair, 4: good and 5: excellent. Image confidence was scored on a scale from 1 to 4, with 1: unsure, 2: mildly confident, 3: moderately confident and 4 very confident. Scoring systems used have been outlined before.[10,17,18] The image findings analysed were those associated with post-thrombotic obstructive disease: post-thrombotic scarring or trabeculations with or without severe luminal narrowing. On MRV, these scars or trabeculations are visible as hypo-intense dots or strands with or without a decreased size of the diseased vein (compared to, for example, a not diseased contralateral vein). Examples are shown in Fig. 2.

Figure 2



Example of post-thrombotic changes as visualised with MR venography. Top left: normal right common iliac vein (double arrowhead). Black strands in left common iliac vein (arrowhead) which are residual scarring/trabeculations after deep vein thrombosis. Bottom left: normal right external iliac vein. Similar scarring is seen in the left external iliac vein compared to the common femoral vein with the addition of >50% luminal narrowing compared to the right. Top right: coronal reconstruction showing scarring (arrows) of the femoral vein. Bottom right: coronal reconstruction showing a normal femoral vein without any (post-thrombotic) scarring (large arrow, large arrowhead)

If present, artefacts caused by parallel imaging reconstruction such as aliasing and ringing were registered. Confidence of image interpretation was scored on a scale from 1 to 4, with 1: unsure, 2: mildly confident, 3: moderately confident and 4: confident. Image findings were scored as either 0: no post-thrombotic changes or 1: post-thrombotic changes. Post-thrombotic changes were defined as visible post-thrombotic remnants such as vein scarring, lumen obstruction and/or collateral formation.[6] Left and right leg vessel segments were grouped for qualitative analysis. Finally, reviewer 1 measured vein and muscle signal intensity (S) for each vessel segment using the single acquisition technique for quantitative analysis described by Firbank et al.[19] Background noise was determined by placing a 500-pixel region of interest (ROI) in an artefact-free area of air. All measurements were performed at the level of the venous ROIs which were placed in the centre of the vessel segment. Noise values were corrected for magnitude effects by the Rayleigh factor of 0.665.[20] The signal-to-noise ratio (SNR) was calculated by $SNR = 0.655 \cdot S/\sigma$, with σ being the standard deviation of the signal in air. The CNR for the vessel segments was calculated as follows:

$$CNR_{vein} = (SNR_{vein} - SNR_{muscle})$$

Statistical analysis

To evaluate the degree of agreement among the two reviewers, the kappa value was calculated for image quality, image interpretation and image findings. Cohen's kappa coefficients of agreement between observers were determined for each feature. Agreement was based on the Fleiss classification: <0.40, poor; 0.40–0.59, moderate; 0.60–0.75, good; >0.75, excellent).[21] Generalized estimating equations (GEEs) were used to assess the effect of the imaging techniques and contrast

material on detection of intravenous disease changes, excellent image quality (score of 5) and very confident interpretation (score of 4). The reason to use GEEs with the logit link function was to correct for repeated measurements within the same patients (same patients and segments, different techniques). Additionally, we corrected for metallic implants. A p value < 0.05 was considered statistically significant. All calculations were performed using Microsoft Excel 2013 (Microsoft Office; Microsoft, Redmond, WA, USA) and IBM SPSS Statistics for Windows version 23.0 (IBM Corp. Armonk, NY, USA).

Results

Inter-observer agreement with regard to image quality was excellent between all three sequences with a kappa of 0.95. Inter-observer agreement with regard to confidence of image interpretation and image findings were excellent as well with a kappa of 0.85 and 0.84, respectively.

Image quality

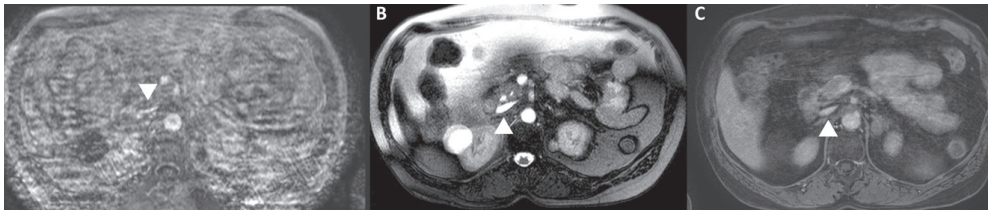
Comparison of image quality between both ultra-fast GE sequences and the HR-FFE sequence showed an overall high image quality for all sequences (91.5%, excellent score; Table 4).

Table 4 *Average scores of image quality per segment*

Vein segment	Sequence		
	Ultrafast GE (Gadobutrol)	Ultrafast GE (gadofosveset-trisodium	HR-FFE
Popliteal vein	3.75	3.8	3.8
Distal femoral vein	3.85	4	3.8
Proximal femoral vein	3.95	3.9	3.8
Profunda femoral vein	4	3.95	3.8
Common femoral vein	4	3.95	3.8
External iliac vein	3.9	3.85	3.9
Internal iliac vein	4	3.95	3.85
Common iliac vein	3.95	3.9	3.75
Inferior caval vein (infrarenal)	4	3.95	3.1
Inferior caval vein (suprarenal)	3.95	3.95	3
Average of all segments	3.94 (+0.35)	3.92 (+0.31)	3.7 (+0.82)

Overall, there was a significant difference between the three groups (p=0.045) in favour of the ultra-fast GE sequences. In particular, the image quality of the ultra-fast GE sequence with gadobutrol showed more often an excellent reported quality in comparison to the HR-FFE sequence (p = 0.013) (Fig. 3). There were no statistically significant differences (p = 0.578) in the reported image quality for the ultra-fast GE images from examination 1 (gadobutrol) compared to the ultrafast GE images from examination 2 (gadofosveset-trisodium).

Figure 3

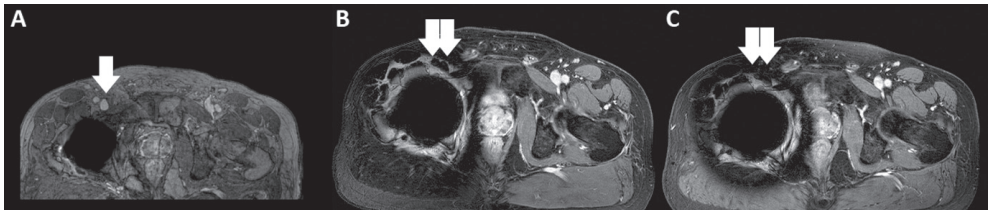


Example of inferior vena cava image quality. A) HR-FFE (gadofosveset-trisodium), B) BTFE (non-contrast-enhanced), C) Ultra- fast GE (gadofosveset-trisodium) sequence. All images show the inferior vena cava (supra-renal) at the same level in the same patient during the same examination (arrowhead). The apparent motion artifacts distort the image of the inferior vena cava only on the HR-FFE image

Image interpretation

The reported confidence of interpretation was high for all three imaging techniques (95.5%, very confident). Overall ($p = 0.139$), as well as between the techniques ($p = 0.295$) and the two contrast materials administrated ($p = 0.670$), there was no statistically significant difference in confidence of interpretation. In three patients, a lower confidence of interpretation was noted at the level of a metallic joint or spinal implant specifically on the ultra-fast GE sequences, which, in comparison, did not affect confidence of interpretation on the HR-FFE sequence (Fig. 4).

Figure 4

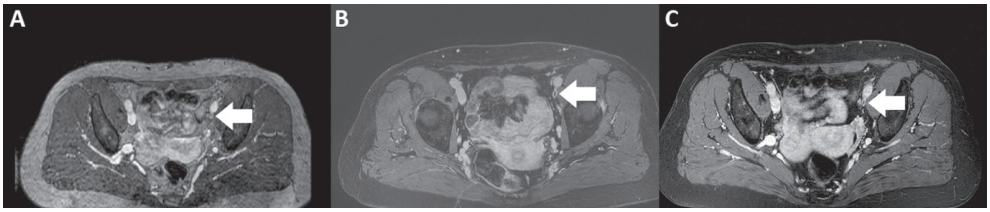


Metal artifacts caused by hip implant. A) HR-FFE sequence (gadofosveset-trisodium), limited artifacts with still a visible common femoral vein (arrow). B) Ultra-fast GE (gadofosveset-trisodium) sequence with severe artifacts (double arrow) and unsure interpretation of the vascular structures. C) Ultra-fast GE (gadobutrol) sequence with the same severe artifacts (double arrow) as in B)

Image findings

There was a high consistency with regard to image findings between the different scan sequences and contrast materials used. Examples are shown in Figs. 5 and 6. GEEs yielded no significant differences between all groups in regard to image findings ($p = 0.328$).More specifically, no significant differences were observed between HR-FFE gadofosvesettrisodium vs. ultra-fast GE gadobutrol ($p = 0.547$)and ultra-fast GE gadofosveset-trisodium vs. ultra-fast GE gadobutrol ($p = 0.527$).

Figure 5



Axial reconstructions in a patient with chronic obstruction of the external iliac vein. A) HR-FFE (gadofosveset-trisodium) sequence showing the typical appearance of an obstructed and shrivelled external iliac vein with trabeculae (arrow) as a sign of post-thrombotic changes. B) Appearance of the external iliac vein on the ultra-fast GE (gadofosveset- trisodium) sequence. C) Appearance of the external iliac vein on the ultra- fast GE (gadobutrol) sequence

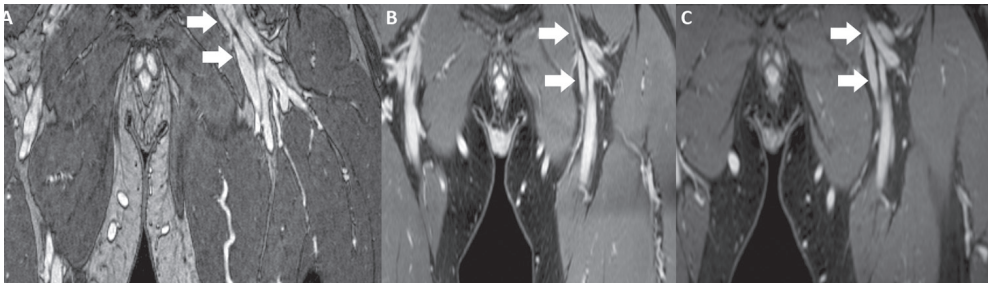
CNR

CNR ratios for the contrast-enhanced sequences were comparable for both contrast material and imaging techniques, as shown in Table 5.

Table 5 *Contrast-to-noise ratio measured for each vessel segment per sequence*

Vein segment	Sequence		
	Ultrafast GE (Gadobutrol)	Ultrafast GE (gadofosveset-trisodium	HR-FFE
Popliteal vein	52 (+15)	73 (+21)	29 (+24)
Distal femoral vein	44 (+22)	66 (+37)	47 (+28)
Proximal femoral vein	58 (+18)	50 (+8)	37 (+16)
Profunda femoral vein	42 (+18)	51 (+6)	37 (+22)
Common femoral vein	29 (+22)	24 (+6)	41 (+26)
External iliac vein	37 (+30)	34 (+16)	30 (+30)
Internal iliac vein	43 (+44)	36 (+30	55 (+20)
Common iliac vein	43 (+30)	41 (+42)	52 (+24)
Inferior caval vein (infrarenal)	34 (+24)	35 (+24)	40 (+38)
Inferior caval vein (suprarenal)	58 (+33)	43 (+35)	42 (+34)
Average of all segments	44 (+25)	45 (+23)	41 (+26)

Figure 6



Coronal reconstructions of an obstructed external iliac and common femoral vein. A) HR-FFE (gadofosveset-trisodium) sequence shows fibrotic strands in the external iliac and common femoral vein (arrows). B) Ultra-fast GE (gadofosveset-trisodium) sequence and C) Ultra-fast GE (gadobutrol) sequence of the same vein segments as A), showing the same post-thrombotic changes (arrows)

Discussion

Performing high-resolution MRV with a regular gadoliniumbased agent such as gadobutrol instead of a bloodpool contrast agent such as gadofosveset-trisodium is possible, allowing for high-quality MRV studies. Even though the two contrast agents used are different in terms of concentration and protein binding, we did not find any significant differences in reported image quality, confidence of interpretation or image findings.

In our daily practice, we used gadofosveset-trisodium as contrast material of choice for MRV. With regard to contrast clearance after injection, 94% of gadofosveset-trisodium is cleared after 72 hours compared to gadobutrol that is cleared 90% after 12 hours.[22-24] To prevent any interference related to the prolonged clearance time of the bloodpool agent, the initial scan of the study protocol was performed using gadobutrol and a safety margin of 3 days was used to allow for (near) complete clearance of the contrast administered. Since patients with chronic venous disease generally have stable disease no confounding factor was introduced by allowing 3 to a maximumof 14 days in between the two scans.[25]

Secondly, the reported findings with the ultra-fast GE sequence in comparison to the HR-FFE sequence are virtually equal. Additionally, we observed a slight increase in overall image quality using the ultra-fast GE sequence. This particularly holds true for the abdomino-pelvic segments, which are regarded as the most important segments in clinical practice.[6] The main reason for the acquisition of the non-contrast enhanced BTFE images in our study protocol were well known evaluation problems of the inferior vena cava on the HR-FFE sequence. In 6 out of 20 patients we observed image quality problems due to motion artefacts which hampered assessment on the HR-FFE sequence, that were not encountered on the ultra-fast GE sequence. This implies an additional benefit in terms of confidence and reduction in scan time (non-contrast enhanced acquisitions can be omitted) when implementing an ultra-fast GE sequence to the scan protocol. Using the ultra-fast GE-sequence instead of the HR-FFE +

BTFE sequences implies a nearly 50% reduction in acquisition time from 28 min to 15 minutes. There still are some patients that will benefit from HR-FFE scanning. In patients with metallic prosthesis of the hip, knee or spine the image quality of the ultra-fast GE sequence can be mediocre. In 3 segments we encountered more severe artefacts on the ultra-fast GE sequences in comparison to the HR-FFE sequence related to hip joint and spinal implants. This did affect confidence of interpretation but did not result in general impairment of the results reported for these MRV studies. In our practice we have not encountered MR acquisition issues with inferior vena cava filters, unfortunately none were present in the studied patients to compare image quality for these specific implants. With regard to the contrast material used we did not find any significant difference in reported image quality, confidence of interpretation or image findings. We have shown that performing MRV with a regular gadolinium based agent such as gadobutrol is feasible, allowing for high quality MRV studies all over the world. Interesting to note is that comparing gadobutrol to gadofosveset-trisodium the confidence interval shows gadobutrol being potentially slightly better for detection of disease.

Limitations of this study

Since there are no previous studies investigating the possibility of replacing a high relaxivity agent with a regular gadolinium based contrast agent for MRV specifically, we had to setup our protocol based on research for MR-angiography in other vascular territories. We had to assume that double dose of the regular gadolinium based contrast agent gadobutrol provided enough relaxivity to 'mimic' gadofosvesettrisodium even though the reported relaxivity for a single dose of gadobutrol is 5.5 compared to 19 for gadofosvesettrisodium. Fortunately, considering the current unavailability of a high relaxivity agent with a vascular indication in Europe, our study results show that a regular gadolinium-based agent can be an alternative for MRV. Furthermore we could not randomize the order of the administration of the contrast agents within our study design. To ensure no interference due to the prolonged clearance of gadofosveset-trisodium (more than 2 weeks) gadobutrol was always given first. However we acknowledge that a cross-over design would have been more ideal. The 20 patients included provided us with 3 x 18 measurements (= 54) per patient. The calculated intra-class correlation (ICC) for identification of a diseased segment was 0.325, which is relatively high. This means that the repeated measurements show some correlation. This implies that statistically we cannot interpret all measurements as completely independent. Considering the amount of measurements (20 x 54 = 1080) the study size is still adequate for our statistical analysis and the conclusions of our study.

Conclusions

For high-resolution MRV, it is possible to use a regular gadolinium-based agent (gadobutrol) instead of the bloodpool agent gadofosveset-trisodium. Furthermore, using an ultra-fast GE sequence for MRV can considerably shorten the scan time for the majority of patients without loss of image quality or diagnostic yield.

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Chapter 5: Thrombus age is ideally measured by history or MRV prior to thrombus removal

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Abstract

Many factors are known to be important in order to achieve optimal results after thrombus removal for iliofemoral DVT. Not much is published in the literature about timing the treatment, though many guidelines recommend treatment within 14 days. This time span lies within the phrase of acute DVTaccording to the definition given in many reporting standards. This article will highlight the value of information acquired from patients directly regarding onset of symptoms versus information acquired from imaging with the purpose of a more precise selection of patients for catheter-directed thrombolysis for iliofemoral DVT. What is the value of clinical information acquired from patients and does the information from imaging have additional value?

Introduction

Several international guidelines and recommendations suggest treatment with catheter-directed thrombolysis (CDT) or pharmaco-mechanical thrombolysis (PMT) in patients with iliofemoral deep venous thrombosis within 14 days of onset of symptoms.[1,2] Which clinical information and/or venous imaging would fulfill the optimal criteria for intervention before vein damage occurs? Is experience of symptoms from the patient identical with the formation of the thrombosis? Is the benefit of CDT determined by length of symptoms? The question is of course strongly connected to the problem: when will the thrombosis destroy the endothelium and thereby the valves? And what vein segment is not likely to recanalize?

The natural history of a thrombus

The resolution of a thrombus begins minutes after formation in a inflammatory response involving a lot of pathways including cytokines (for instance tumor necrosis factor-1 a, interleukin-6, macrophage and monocyte mediators). The fibrinolytic system acts additional to these inflammatory markers. Plasminogen and plasmin activators are seen in this process with vein wall re-modelling. The vein wall re-modelling during the time span from the initial attack of thrombosis to resolution is strongly connected to the thrombus load and location, including anatomic influence for instance the iliac compression syndrome with great impact on rates of recanalization.[3]

Animal experiments

Thrombus material contains biological active factors stimulating cellular and structural changes leading to postthrombotic abnormalities. Vein wall thickening with loss of compliance may impair valve leaflets and result in fibrosis with permanent dysfunction and reflux. In a large scale animal experimental research with rats it was demonstrated that thrombosis after permanent vein ligation peaked with cellular proliferation in the second week and recanalization in the third week contra normal vein wall appearance in the other group within 2 weeks after temporary vein ligation in 24 hours.4 It was concluded that thrombusinduced chronic wall

thickening may be an important factor in development of postthrombotic venous insufficiency. The results indicate a time span of rather few/some days before a thrombus has to be removed for avoidance of irreversible changes occurs. The final "time-proof" for the irriversible changes is still missing.

Clinical signs

Thrombosis of the iliofemoral segment will never be without symptoms and signs. The onset of symptoms will often be pain suddenly occurring in the groin and sometimes in the lower abdomen. Back pain is typical a sign of thrombosis in the inferior vena cava (IVC) or a patient with iliac thrombosis in connection with atresia of the IVC with thrombosis of the collateral veins. Often the pain will be observed even as a sudden snap. The pain is caused by dilatation of the vein and total lumen obstruction. The pain will persist and intensify along with inflammatory reaction during the following days accompanied by swelling from the ligament and with discoloration of the entire extremity. The ability to walk is reduced and a contraction in the hip joint is typical. It has to be stressed out that a complete swollen leg is a classical finding in patients with acute obstruction in the venous outflow tract meaning pelvic area and cranially. These overwhelming signs would not be forgotten or overlooked by any patient.

Findings with duplex scanning

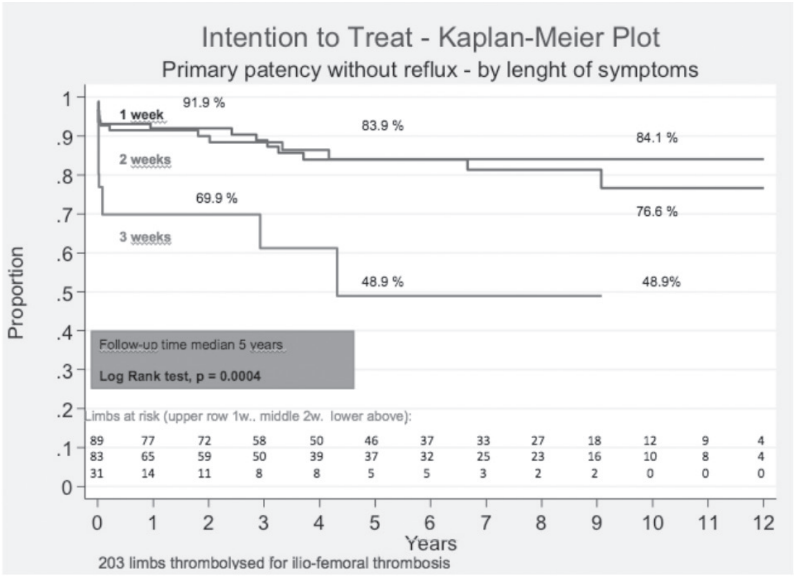
The next step is a duplex ultrasound examination. The veins will typical be dilated and not compressible. The thrombus appears with low echoes and will during few days be more echogenic. Trabeculation and recanalization can be seen within 14 days. After 3–4 weeks the thrombosis is considered chronic with thickening of the vein wall, reduced flow, collaterals and with increased reflectivity and reduced compressibility. Monocytes are particular important in thrombus recanalization. Recanalization is more frequent in older people, postoperative DVT and one segment DVT.5 A study including 73 lower limbs with DVT was investigated with duplex scanning 1, 4, 12 and 24 weeks after initial episode. At 1 week less than 10 % and after 4 weeks only 25 % of the thrombus load in the common femoral vein, femoral vein, popliteal vein and the calf veins showed sign of resolution.[6] After 6 months almost 80 % of the thrombus was resolved. Clot stabilization was seen in average after 11 days meaning lack of motion within the clot vein interface. This could be interpreted as a sign of irreversibility of damage on the vein wall. The calf veins are the level with highest rate of recanalization in another study.[7] The rate at the femoral level is 80 % and the left pelvic veins only 20 % over time.[8] The chance for developing reflux was significantly higher in patients with partial obstruction compared to those with complete recanalization.[9] PTS was found more frequently in patients with iliofemoral DVT than patients with either popliteal or below knee DVT.[10] No patients with DVT below the infraligament developed venous claudication, which on the contrary is a frequent symptom after iliofemoral DVT.[9] CTV and MRV The gold standard for identification of thrombus below the inguinal ligament is duplex ultrasound.[11] Above the

inguinal ligament duplex scanning is still valuable to identify thrombus and/or obstruction, if conclusive. Inconclusive cases that require additional imaging and more detailed information can be obtained with good results with either CTV or MRV.[12,13] CTV has been reported to be accurate in the identification of thrombus in the iliac veins as well as the inferior vena cava.[14] With regard to (chronic) inferior vena cava obstruction and iliac vein obstruction published data is limited even though promising new research is emerging.[15] MRV has been reported to be as sensitive as CTV and flebography in identifying thrombus in the IVC and iliac veins.[16] Additionally with the right protocol, detailed peri- and intra-venous changes can be identified allowing for detailed description of thrombus and lumen characteristics. As has been pointed out previously, one of the important signs to identify is a more chronic component of iliac obstruction that will not be susceptible to lysis and requires recanalization and stenting in order to restore the outflow from the leg to the IVC / heart.[17] Performing and/or extending thrombolytic therapy on such obstructions will only impose increased bleeding risks without therapeutic success. It is therefore vital in iliofemoral DVT to identify such lesions accurately. Second, it has been shown that identifying thrombus characteristics on MRV is feasible. These signs can aid us in identifying patients within or outside of the treatment window for catheter-directed thrombolysis.[18]

The Copenhagen experience

We have since 1999 in Copenhagen performed 205 CDT procedures in 195 patients with DVT involvement of the iliofemoral segment judged with duplex ultrasound. Our initial results are published earlier.[19] The inclusion criteria from the beginning concernig duration of symptoms were patients with symptoms up to 14 days. When we retrospectively went through the records for a later publication, we discovered 31 cases, in which this threshold was crossed. We tested this variable for the first 2 weeks and more than 2 weeks in a Cox regression hazard model indicating this parameter-among othersas an independent risk factor. Patients with symptoms with 1 week and 2 weeks had similar outcome shown in a Kaplan-Meier plot including patients to treat (Figure 1).

Figure 1



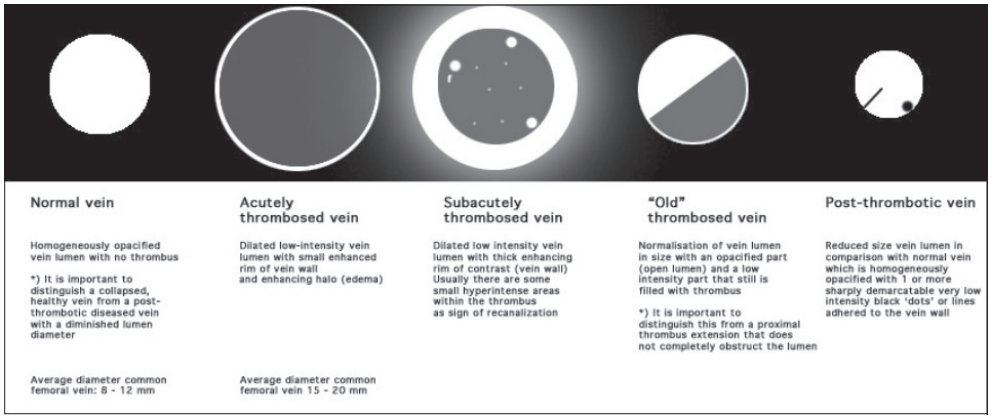
Kaplan-Meier plot illustrates the estimated percentage of patients with patent veins without reflux for patients with iliofemoral DVT allocated to different time spans of symptom duration.

Competent veins meaning patent vein without valve incompetence were achieved in 84 % after 5 years of the treated extremities with iliofemoral DVT. Patients with more than 2 weeks of symptom duration had significantly worse outcome with only 50 % of success (P.0.0004).20 These findings suggest that trusting the patients could guide to a simple stratification for choosing treatment in the right time-window.

The Maastricht experience

At the Maastricht University Medical Centre (MUMC) we have an outpatient clinic, which receives patients from all over the Netherlands for evaluation of treatment options for iliofemoral DVT. Transfer of patients from other hospitals to the MUMC is prompt, but the time between the initial visit to a physician and the referral to us varies. In order to identify patients (still) eligible for minimally invasive therapy we have a fixed routine of examinations performed prior to treatment. Upon admission to our hospital, in addition to venous questionaires and patient interviewing, we perform a duplex ultrasound to confirm iliofemoral involvement. Additionally we perform a magnetic resonance venography to get a complete overview of the thrombosed segments and identify chronic obstructive components such as pre-existing caval occlusion and/or iliac obstruction due to compression. The detail in the acquired MR images with a voxel size approaching 1 mm3 also allows for identification of subtle changes within the thrombus as well as in the veinwall and surrounding tissue (Figure 2).

Figure 2

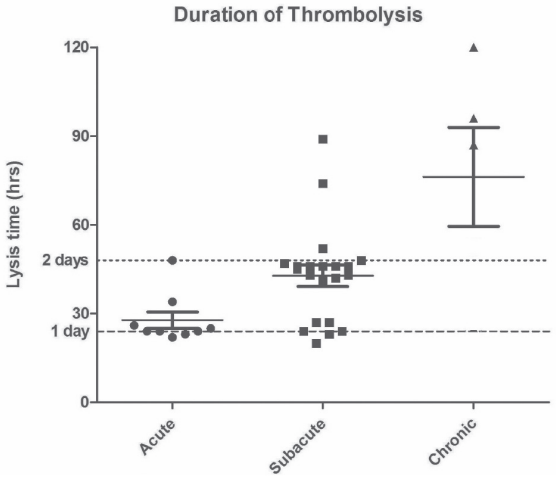


Thrombus characteristics as identifiable with Magnetic Resonance Venography.21

We use these to estimate the age of the thrombus and progression of the disease process. In some cases we have seen remarkable differences in the clinical appearance/information and MR images. The information acquired with MRV was new and in our multidisciplinary team discussion we initially only used thrombus location and extend combined with duration of complaints to select patients for CDT. Unfortunately, with the exception of a recently published article based on restrospective analysis of CT-Venography findings compared to conventional venography and our own publication investigating the feasibility of our MR-Venography image assessment, there is currently no published data to support our believes that imaging thrombus characteristics is not only feasible but also valuable for clinical practice. However, we would like to share some preliminary data that has shown us that the thrombus characteristics on MRV can predict duration and success of thrombolysis (Figure 3).

Figure 3

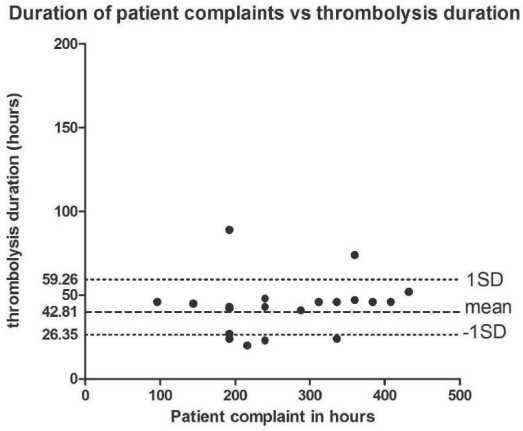
Duration of thrombolysis v.s. thrombus characteristics on MR-Venography (MRV). Y-axis shows lysis time for CDT in patients with iliofemoral DVT. X-axis shows thrombus characteristics interpreted with MRV as acute (within 14 days), subacute (15–28 days) or chronic DVT (more than 28 days) according to the definitions.22



Lysis time as reported is defined as the time between start of catheter-directed thrombolysis and the completion angiography or, in case of the more chronic cases when there was no evident progression of lysis for at least 24 hours.
Figure 3 shows the distribution between the groups identified as acute, subacute and chronic based on MRVenography characteristics. It is evident that thrombus appreciated as acute will lyse quickly, subacute will lyse within reasonable time and chronic (/old) will either lyse little or not at all, even in an extended time frame. Comparing the above findings with the information on the duration of complaints versus thrombolysis times shows the difference in value between clinical information and imaging findings (Figure 4).

Figure 4

Duration of patient complaints vs thrombolysis duration. On the Y-axis thrombolysis time in hours is listed. On the X-axis the time since onset of complaints is listed.



Both outliners with regard to duration of complaints and duration of thrombolysis can be seen in the chart that could not be distinguished based on clinical history.

Discussion

Taking into consideration the current consensus regarding valid indications for catheter-directed thrombolysis we would, without a doubt offer this treatment to patients with a symptom duration up to 14 days. The question is, are we to rigid or not rigid enough with the current criteria? Looking at our experience in Maastricht, if we would abide the 14 days symptoms rule, we would be excluding a significant number of patients we have treated, with symptoms longer than 14 days. This would imply we have to exclude patients in which we have seen technical success of catheter directed thrombolysis, despite them not meeting the 14 days criterium. Vice versa, we have selected patients for catheter directed thrombolysis that was not effective. Retrospectively we could identify the thrombus as old/chronic, even with symptom duration of <14 days. Old and/or more chronic thrombus is in our experience not susceptible to thrombolysis. These patients were and would be exposed to (prolonged) thrombolysis in an attempt to lyse the thrombus, exposing them to the associated risks without

reasonable added benefit. These results can help to pick up the relevant patients according to the above mentioned strategy. But these observations do not give any information concerning influence on long term results. The results from Copenhagen indicates firmly, that symptom duration reported from the patients themselves longer than 2 weeks in the long run is inferior compared to symptoms up to 2 weeks. Therefore we need to acquire prospective data regarding the influence of imaging on patient selection and long-term outcome benefits.

Conclusion

Selecting patients for CDT for iliofemoral DVT should be based on all information available, aiming for the best result for every individual patient. This information should include a precise history from the patient and a dedicated imaging protocol for iliofemoral DVT, which implies a combination of duplex ultrasound with (depending on availability) MRV or CTV. Multiple factors influence the outcome of catheter-directed thrombolysis, of which thrombus age is regarded as vital for both technical success of the procedure as well as long-term outcome. In particular the long term outcome benefits require more attention and we are waiting on the outcome from the large clinical trials to further strengthen the results. Current selection criteria are strict and they should be considering the risks, which strengthens our beliefs that these patients need an optimal pre-interventional work up. The time factor will always be very important, as prolonged thrombosis will increase the chance of PTS in iliofemoral DVT.

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Part II:

Selection-based outcomes

Chapter 6: Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial

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Summary

Background: Early thrombus removal might prevent post-thrombotic syndrome by preserving venous function and restoring flow. Previous trials comparing additional catheter-directed thrombolysis to standard treatment showed conflicting outcomes. We aimed to assess the benefit of additional ultrasound-accelerated catheter-directed thrombolysis for the prevention of post-thrombotic syndrome compared with standard therapy in patients with iliofemoral deep-vein thrombosis.

Methods: We did a multicentre, randomised, single-blind, allocation-concealed, parallel group, superiority trial in 15 hospitals in the Netherlands. Patients aged 18–85 years with a first-time acute iliofemoral deep-vein thrombosis and symptoms for no more than 14 days were randomly assigned (1:1) to either standard treatment with additional ultrasound-accelerated catheter-directed thrombolysis or standard treatment alone. Randomisation was done with a web-based automatic programme and a random varying block size (2–12), stratified by age and centre. Standard treatment included anticoagulant therapy, compression therapy (knee-high elastic compression stockings; 30–40 mmHg), and early ambulation. Additional ultrasound-accelerated catheter-directed thrombolysis was done with urokinase with a starting bolus of 250 000 international units (IU) in 10 mL NaCl followed by a continuous dose of 100 000 IU/h for a maximum of 96 h through the Ekos Endowave-system. Adjunctive percutaneous transluminal angioplasty, thrombosuction, or stenting was performed at the discretion of the physician who performed the intervention. The primary outcome was the proportion of patients with post-thrombotic syndrome at 12 months diagnosed according to the original Villalta criteria—a Villalta-score of at least 5 on two consecutive occasions at least 3 months apart or the occurrence of venous ulceration—and was assessed in a modified intention-to-treat population of all randomly assigned patients who passed screening and started treatment. The safety analysis was assessed in the same modified intention-to-treat population. This study is complete and is registered at ClinicalTrials.gov, NCT00970619.

Findings: Between May 28, 2010, and Sept 18, 2017, 184 patients were randomly assigned to either additional ultrasound-accelerated catheter-directed thrombolysis (n=91) or standard treatment alone (n=93). Exclusion because of screening failure or early withdrawal of informed consent resulted in 77 patients in the intervention group and 75 in the standard treatment group starting allocated treatment. Median follow-up was 12.0 months (IQR 6.0–12.0). 12-month post-thrombotic syndrome occurred in 22 (29%) patients allocated to additional treatment versus 26 (35%) patients receiving standard treatment alone (odds ratio 0·75 [95% CI 0.38 to 1.50]; p=0.42). Major bleeding occurred in four (5%) patients in the intervention group, with associated neuropraxia or the peroneal nerve in one patient, and no events in the standard treatment group. No serious adverse events occurred. None of the four deaths (one (1%) in the intervention group vs three (4%) in the standard treatment group) were treatment related.

Interpretation: This study showed that additional ultrasound-accelerated catheter-directed thrombolysis does not change the risk of post-thrombotic syndrome 1 year after acute

iliofemoral deep-vein thrombosis compared with standard therapy alone. Although this trial is inconclusive, the outcome suggests the possibility of a moderate beneficial effect with additional ultrasound-accelerated catheter-directed thrombolysis. Further research is therefore warranted to better understand this outcome in the context of previous trials, preferably by combining the available evidence in an individual patient data meta-analysis.

Introduction

Deep-vein thrombosis is a serious condition with a lifetime incidence of 2.5–5.0%,[1,2] with persistence of long-term complications known as post-thrombotic syndrome in 40–60% of those affected.[3,4] Post-thrombotic syndrome negatively impacts quality of life[5] and is associated with substantial costs.[6] Standard treatment of deep-vein thrombosis includes immediate anticoagulant therapy to prevent thrombus growth and embolisation, as well as early mobilisation and compression therapy with the potential to reduce residual thrombus burden and the onset of post-thrombotic syndrome.[7–9] Although effective in most patients, this treatment is not sufficient for those at the highest risk of post-thrombotic syndrome,[9] in particular those with iliofemoral thrombosis.[3,10,11] Early removal of the thrombus might improve long-term outcomes in these patients by restoring patency and preserving function of the affected vein segments.[12,13] Previous trials comparing additional catheter-directed thrombolysis to standard treatment showed conflicting outcomes.[14–16] Although the CaVenT trial[14,15] found an absolute risk reduction of 14.4% (95% CI 0.2–27.9) for the development of post-thrombotic syndrome with additional catheter-directed thrombolysis after iliofemoral deep-vein thrombosis, no difference in risk was observed for the incidence of post-thrombotic syndrome with additional pharmacomechanical thrombolytic treatment in the larger ATTRACT trial.[16] However, a subanalysis of the ATTRACT trial including patients with moderate-to-severe post-thrombotic syndrome did indicate a risk reduction with additional catheter-directed thrombolysis.[17] Because spontaneous resolution of iliofemoral thrombosis is rare, enhancing this natural process through ultrasound-accelerated catheter-directed thrombolysis might be most beneficial in these patients. Here, we present the ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation (CAVA) trial, in which we aimed to assess the efficacy and safety of additional ultrasound-accelerated catheter-directed thrombolysis for the prevention of post-thrombotic syndrome in patients with iliofemoral deep-vein thrombosis.

Methods

Study design and participants

The CAVA trial was a multicentre, randomised, single-blind, allocation-concealed, parallel group, superioritytrial done in 15 hospitals throughout the Netherlands (appendix p 2). Six centres were interventional centres thereby responsible for doing the thrombolysis and eventual adjunctive interventions. Details on the trial design are provided in the protocol (appendix (pp 23–89).

Eligible patients aged 18–85 years had an objectively documented first-time iliofemoral deep-vein thrombosis (ie, complete or partial thrombosis of the common femoral vein or more cranial vein segments) with acute symptoms for no longer than 14 days, a life expectancy of more than 6 months, and no previous thrombus in the affected limb. Exclusion criteria were pre-existent signs of venous insufficiency (CEAP classification C3 or higher);[18] history of gastrointestinal bleeding, cerebrovascular accident, or CNS disease within 1 year; severe hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg); active malignancy (metastatic, progressive, or treated within the previous 6 months); increased alanine transaminase levels (more than three times the upper limit of normal (34 international units (IU)/L for women and 45 IU/L for men); renal failure (estimated glomerular filtration rate <30 mL/min); major surgery within 6 weeks; pregnancy; or impaired mobility.[18]
This trial was approved by the review boards of all participating centres. Patients were recruited at the emergency room or outpatient clinic of the participating centres and written informed consent was obtained before randomisation.

Randomisation and masking

Before study participation, diagnosis of acute iliofemoral deep-vein thrombosis was done in all participating centres by compression ultrasound. After obtaining informed consent, individual patients were randomly allocated in a 1:1 ratio to the intervention group receiving additional ultrasound-accelerated catheter-directed thrombolysis (including standard treatment and adjunctive procedures) or to the standard treatment group. The study coordinator at Maastricht University Medical Centre conducted the randomisation procedure. A web-based randomisation programme (TENALEA, ALEA version release 2.2) was used with a random variable block size (2–12), and randomisation was stratified for participating centre and age in three strata (18–50 years, 51–70 years, and 71–85 years). The allocated treatment was communicated to the patient by the central study coordinator performing the randomisation. Patients received standard treatment for deep-vein thrombosis at their local hospital and were asked not to disclose their allocation during visits with their treating physician or (local) study personnel. Treating physicians were informed of the patient's participation in the study, but not on the treatment allocation.
The coordinating researcher at Maastricht University Medical Centre responsible for collecting, maintaining, and analysing the data was masked to assignment.

Procedures

Patients in both treatment groups received initial and long-term anticoagulation therapy according to international guidelines,7 with vitamin K antagonists (acenocoumarol or phenprocoumon), direct oral anticoagulants (rivaroxaban, apixaban, and dabigatran), or low-molecular-weight heparin.
Custom-fitted knee-high elastic compression stockings (30–40 mmHg pressure) initiated

within 24h after deep-vein thrombosis diagnosis with replacement every 6 months were prescribed to all patients. Patients were instructed to use compression stockings during waking hours of every day for a minimum of 24 months after the deep-vein thrombosis.

Thrombolytic intervention had to be started no later than 21 days after the onset of symptoms at one of the six intervention centres. The interventions were performed using urokinase (Medacinase, Lamepro, Netherlands) in combination with the Ekos Endowave-system (EKOS Corporation, Bothell, WA, USA). This system consists of an intelligent drug delivery catheter with a microsonic core containing multiple high-frequency (2 MHz) ultrasound transducers. A detailed description of the thrombolysis protocol is provided in the appendix (pp 7–9). A total bolus dose of 250.000 IU urokinase in 10 mL NaCl was administered directly after placement of the thrombolysis catheter followed by a total of 100.000 IU/h through continuous infusion during the intervention. Simultaneously, a therapeutic dose of heparin (a total of 1000 IU/h) was administered through the sheath to prevent new thrombus formation. During thrombolysis, which had a maximum duration of 96h, the patient was confined to bed. During the intervention, standard anticoagulation treatment would be stopped and patients would receive therapeutic doses of low-molecular-weight heparin to prevent further thrombosis. When the intervention was stopped, patients would be restarted on their regular anticoagulant drugs 1h after removal of the sheath. Coagulation status was assessed every 6h to inform decisions on dose adjustment, dose interruption, or treatment termination. Daily venography was performed to assess progress of thrombolysis. Interventions were terminated in the following cases: successful treatment (defined as a regained patency of ≥90%); no change in patency after 48h; persisting activated partial thromboplastin time longer than 80 s; fibrinogen less than 8 mm in FIBTEM (appendix p9); plasma fibrinogen less than 1.8 g/L; or when the maximum duration of thrombolytic treatment was reached. Adjunctive procedures (e.g., thrombosuction, percutaneous transluminal angioplasty, stenting, endophlebectomy, or creating an arteriovenous fistula, or any combination of these) were at the discretion of the physician performing the intervention; however, they were advocated in the case of compression syndromes or a persistent venous lumen reduction of more than 50%. Stenting, which was done in the intervention group only, was done using dedicated venous stents.

In the case of bilateral deep-vein thrombosis, the leg with the most cranial localisation was considered to be the index leg. In patients with bilateral thrombosis, additional ultrasound-accelerated catheter-directed thrombolysis was performed in both legs.

A detailed overview of study assessments and study visits is provided in the appendix (pp 4–5). Assessment of trial outcomes was stipulated in the outpatient clinic at 3, 6, and 12 months. If venous stenting was done, additional study visits to the intervention centre were planned 2 weeks and 6 weeks after the intervention, solely to assess stent patency. The follow-up visit at baseline and the 12-month follow-up visit were done at one of the six intervention centres nearest to the patients' home to collect additional imaging data (magnetic resonance venography, extended duplex ultrasound, and air plethysmography if available). The lower

extremity thrombosis (LET) classification was used to classify the extent of the thrombosis (LET class I defined as isolated calf vein thrombosis; LET class II as femoropopliteal thrombosis; LET class III as common femoral vein or iliac vein thrombosis, or both; and LET class IV as inferior cava vein thrombosis).[11]

The 3-month and 6-month study visits did not require any advanced imaging assessments or interventions. Therefore, at these visits, assessment of the Villalta score,[19] severity of complaints, the adherence to compression and anticoagulation therapy, and administration of quality-of-life questionnaires could be done at all participating centres.

Textual and full-colour visual aids for standardised scoring of the objective Villalta items were provided to all participating centres.[20] The different Villalta items were scored on a 4-point scale (0–3) with a total item score of 33. With higher scores indicating a higher severity of post-thrombotic morbidity, ranging from mild (5–9), moderate (10–14), to severe (≥15 or venous ulceration).[19,20] The severity of post-thrombotic syndrome was also quantified using the venous clinical severity score (0–30),[21] which was assessed at baseline and 12-month follow-up.

Adherence to compression therapy was based on patient-reported estimates of the number of days per week that compression stockings were used; this information was translated into percentage of adherence.

The occurrence of adverse events (ie, major bleeding, recurrent [non-stent] deep-vein thrombosis, in-stent thrombosis, pulmonary embolism, or death) was recorded when encountered. Serious adverse events, defined as any untoward medical event resulting in death, life-threatening events, (prolonged) hospitalisation, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or any unforeseen adverse outcomes, were also registered and reported to the adjudication committee (appendix p43).

Quality of life was assessed based on scoring from the general health-related quality of life short form-36 (SF36; version 2),[22] and EuroQol5D (EQ5D)[23] questionnaires, the venous disease-specific VEINES-QOL instrument[24–26] (original relative summary score [T score] and intrinsic score; appendix (pp 10–11), and the pain disability index (PDI).[27] More details on how quality of life was scored are in the appendix (pp 10–11).

Outcomes

The primary outcome was the proportion of patients with post-thrombotic syndrome at 12 months after the acute event (a Villalta-score of ≥5 on two occasions at least 3 months apart with the first assessment at least 3 months after the event or the presence of venous ulceration; appendix p 10).[19]

We also assessed the proportion of patients with post-thrombotic syndrome according to the International Society of Thrombosis and Haemostasis (ISTH) consensus scoring method (a Villalta score ≥5 or venous ulceration at the 6-month visit or later) was assessed.[20] Compared with this method, the original scoring method used for the primary outcome is more conservative in diagnosing post-thrombotic syndrome.

The main safety outcome was major bleeding (appendix p11), which was defined as a bleeding associated with a fall in haemoglobin of at least 2 g/dL (about 1.24 mmol/L), a need for transfusion of two or more units of packed red blood cells or whole blood, symptomatic in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular), or contributing to the death of the patient.[28]

Secondary outcomes of recurrent venous thromboembolism (objectified deep-vein thrombosis involving a new venous segment or a previously involved venous segment for which symptomatic and imaging improvement had been obtained in a patient with at least one previous episode of deep-vein thrombosis); pulmonary embolism (spiral CT showing an intravascular migration of a venous thrombus to the pulmonary arterial circulation); in-stent thrombosis (objectified deep-vein thrombosis involving stented vein segments); and death during follow-up were all assessed by an independent adjudication committee. Health-related quality of life was also a secondary outcome.

Data on the proportion of post-thrombotic syndrome during follow-up later than 12 months, data on clot lysis, patency, and valve function, and measurements of markers of coagulation and inflammation will be published in separate manuscripts.

Statistical analysis

The study was designed to show that additional ultrasound-accelerated catheter-directed thrombolysis was superior to standard therapy alone for the prevention of the post-thrombotic syndrome. Given the invasiveness of the procedure and the associated bleeding risks, we postulated that an outcome reduction of 17% (equivalent to an odds ratio [OR] of 0.26) resulting in a risk of 8% for the incidence of post-thrombotic syndrome in patients receiving additional ultrasound-accelerated catheter-directed thrombolysis instead of the previously reported 25%,[29,30] would be worth the risk posed by the intervention. 170 patients (85 per treatment group) were required for the trial to have 80% power at a two-sided type 1 error rate of 5%. To compensate for a 5% loss of patients during follow-up, 180 patients were to be included.

A prespecified interim analysis by the data safety monitoring board was planned to consider early termination of the trial for safety reasons at 6 months after the start of the study to compare the occurrence of major bleeding events between the two groups (appendix p44).

The primary outcome analysis was a modified intention-to-treat analysis including all patients who were randomly assigned, except those who did not pass screening and patients who immediately withdrew consent before start of allocated treatment (appendix p12). Additionally, a per-protocol analysis was done analysing data of all patients that completed the treatment and follow-up as assigned. For the primary outcome, the proportions of patients with post-thrombotic were compared with ^{2} analysis, and associated ORs and corresponding 95% CIs were calculated using StatPages and Open Source Epidemiologic Statistics for Public Health (OpenEpi). Additionally, we used the Kaplan-Meier method to calculate the cumulative

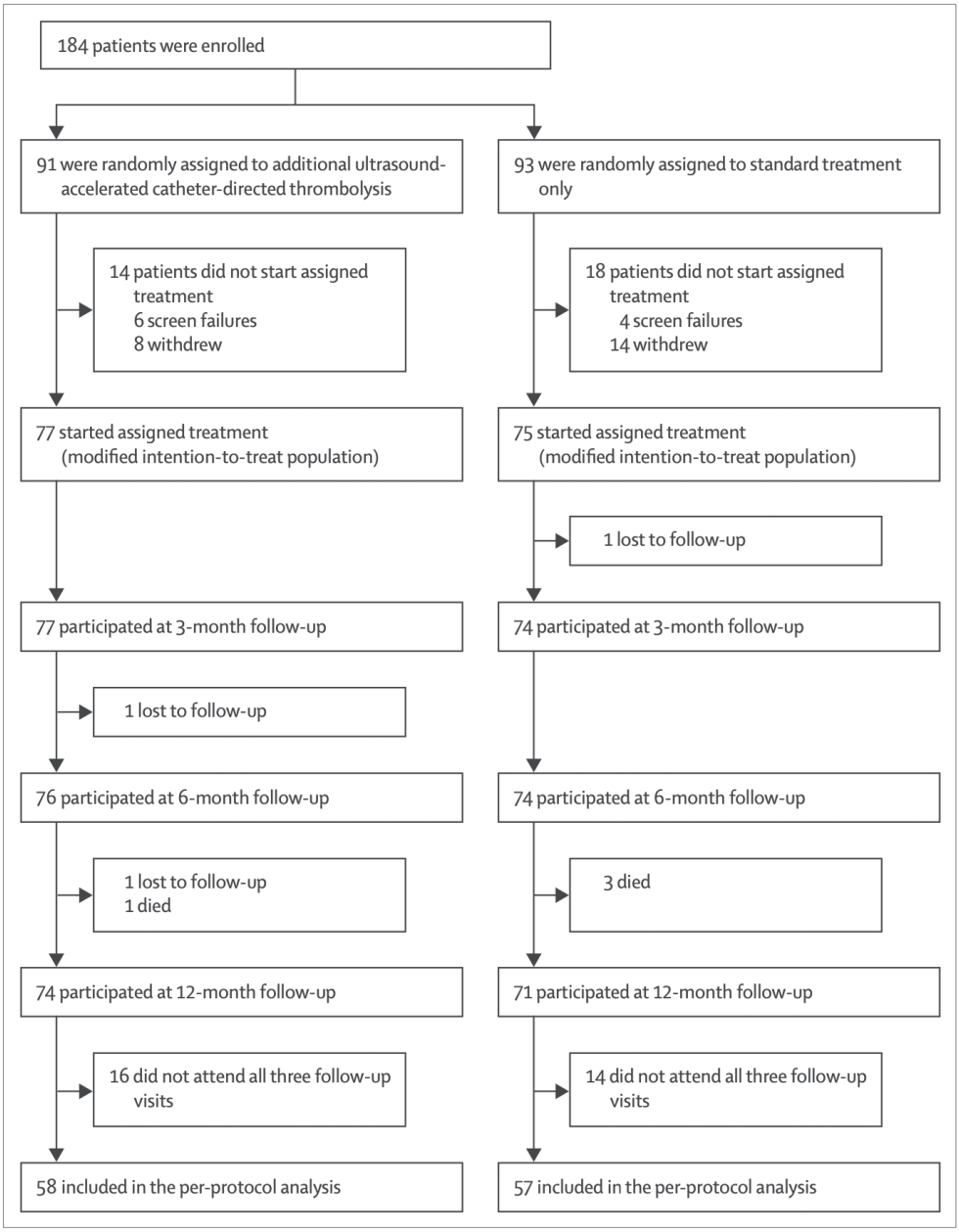
incidence of post-thrombotic syndrome at 12 months adjusted for centre to compare incidences between the two treatment groups. Loss to follow-up, withdrawals, and deaths were censored at the last available date. Hazard ratios (HRs) and their corresponding 95% CIs were calculated using Cox proportional hazard models, stratified for centre and adjusted for age, sex, clinical presentation of the thrombotic event (idiopathic or provoked), and extent of the index thrombosis at ultrasound using the LET classification.[11,31] Descriptive analyses were used to assess patient characteristics, risk factors for venous thromboembolism, the severity of post-thrombotic syndrome, adherence to therapy, treatment characteristics, the proportion of recurrent venous thromboembolism (deep-vein thrombosis of the leg and pulmonary embolism), in-stent-thrombosis, the proportion of major bleeding, and death. The safety analysis accounted for repeated events but not for differential follow-up. Safety was assessed in the modified intention-to-treat population of all patients who started the intervention. We applied a mixed-design analysis of variance to test for differences between the two treatment groups and to assess changes over time by comparing repeated outcome measures for quality of life scores at different timepoints during follow-up. A significance level of 0.05 (two-sided) or less was considered significant, in the case of multiple testing, adjusted significance levels based on the Bonferroni's correction were used. If 5% or more of data were missing, imputation would be performed.

All analyses were done using SPSS, version 24. The study is registered at ClinicalTrials.gov (NCT00970619).

Results

Based on the results of the 6-month interim analysis on Nov 1, 2010, the data safety monitoring board recommended that patient recruitment should continue to complete the originally planned sample size of 180 patients. Between May 28, 2010, and Sept 18, 2017, 184 patients were randomly assigned to standard treatment with additional ultrasound-accelerated catheter-directed thrombolysis (91 patients), or standard treatment only (93 patients; figure 1).

Figure 1 Trial profile



Eight of the screening failures were due to an incorrectly established location of the index thrombus on the diagnostic compression ultrasound. In all analyses, loss to follow-up or deaths were censored when encountered.

Before start of assigned treatment, ten patients were excluded because they did not meet inclusion criteria (ie, they were misclassified during screening; six in the intervention group and four in the standard treatment group) and 22 patients withdrew informed consent (18 at the day of randomisation, six patients from the intervention group vs 12 from the standard treatment group, and two from each treatment group within 2 days of randomisation; appendix p 12). Despite providing careful and thorough information before inclusion, various reasons led to withdrawal of informed consent directly after randomisation. Ten of the withdrawals in the standard treatment group were because of unwillingness of the patient to participate in additional study assessments while being allocated standard care. Withdrawal of informed consent led to termination of further follow-up. Specification of reasons for exclusion and withdrawal before start of allocated treatment are in the appendix (p12). The modified intention-to-treat analysis comprised 152 patients. Treatment groups were similar regarding observed baseline characteristics and anticoagulant treatment (table 1).

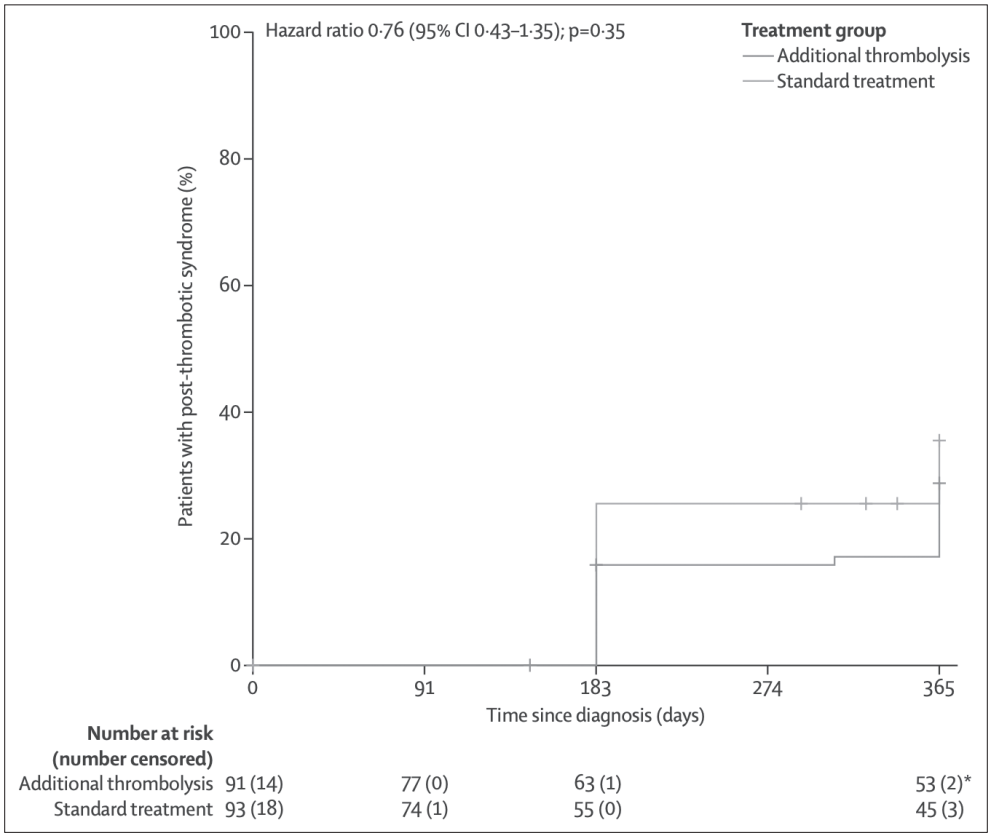
Table 1: *Baseline characteristics of the modified intention-to-treat population*

	Additional thrombolysis group (n=77)	Standard treatment group (n=75)
Age		
Median, years	49·0 (37·5–67·0)	52·0 (38·0–65·0)
<40 years	23 (30%)	20 (27%)
40–65 years	33 (43%)	38 (51%)
>65 years	21 (27%)	17 (23%)
Sex		
Female	38 (49%)	37 (49%)
Male	39 (51%)	38 (51%)
Body-mass index		
Mean, kg/m²	28·0 (5·6)	27·4 (4·1)
<25·0 kg/m²	24 (31%)	22 (29%)
25·0–30·0 kg/m²	31 (40%)	33 (44%)
≥30·0 kg/m²	19 (25%)	15 (20%)
Unknown	3 (4%)	5 (7%)
Provoked deep venous thrombosis*	40 (52%)	32 (43%)
Risk factors		
One	32 (42%)	22 (29%)
More than one	8 (10%)	10 (13%)
Surgery in the previous 2 months	9 (12%)	10 (13%)
Trauma in the previous 2 months	4 (5%)	4 (5%)
Pregnancy or childbirth in the previous 3 months	9 (12%)	5 (7%)
Hormone replacement therapy	2 (3%)	0
Oral contraceptives	9 (12%)	13 (17%)
Previous contralateral deep vein thrombosis	9 (12%)	5 (7%)
Previous pulmonary embolism	3 (4%)	5 (7%)
Active malignancy†	4 (5%)	1 (1%)
Thrombus location		
Left	54 (70%)	55 (73%)
Right	21 (27%)	17 (23%)
Bilateral	2 (3%)	3 (4%)
Duration of symptoms at inclusion, days	6·0 (3·0–11·0)	7·0 (3·0–10·0)
Anticoagulant therapy at inclusion		
Vitamin K antagonists	62 (81%)	63 (84%)
Direct oral anticoagulants	12 (16%)	6 (8%)
Low-molecular-weight heparin	1 (1%)	0
Unknown	2 (3%)	6 (8%)

Data are n (%), mean (SD), or median (IQR). *Acute deep-vein thrombosis is considered idiopathic or unprovoked in the absence of the following risk factors: surgery in the previous 2 months, trauma in the previous 2 months, pregnancy or childbirth in the previous 3 months, use of hormone replacement therapy, use of oral contraceptives, and active malignancy. †Active malignancy is defined as a current metastatic or progressive cancer diagnosis or having received cancer treatment within the previous 6 months.

Table 1: **Baseline characteristics of the modified intention-to-treat population**

Figure 2 *Cumulative incidence of post-thrombotic syndrome*



Tick marks show censored patients. ⋆*One censored patient (death) had already developed post-thrombotic syndrome and was registered as such.*

Median age was 52.0 years (IQR 38.0–66.5) with equal representation of both sexes (77 [51%] men and 75 [49%] women) and median symptom duration at inclusion was 6·0 days (3.0–10.3). The prevalence of risk factors was similar between groups.

Median follow-up was 12·0 months (IQR 6.0–12.0). At 12 months, the primary modified intention-to-treat analysis showed that post-thrombotic syndrome occurred in 22 (29%) of 77 patients who received additional ultrasound-accelerated catheter-directed thrombolysis and in 26 (35%) of 75 patients receiving standard treatment (OR 0.75 [95% CI 0.38 to 1.50], p=0.42; table 2)

Table 2 *Efficacy outcomes*

	Additional thrombolysis group (n=77)	Standard treatment group (n=75)	Difference between treatment groups (95% CI)	Odds ratio (95%CI)
Primary outcome*				
Post-thrombotic syndrome 12 months after deep-vein thrombosis assessed by Villalta's criteria	22 (29%)	26 (35%)	−6·1% (−21·6 to 9·8)	0·75 (0·38 to 1·50)
None (<5)	55 (71%)	49 (65%)	6·0% (−9·8 to 21·6)	1·33 (0·67 to 2·63)
Mild (5–9)	10 (13%)	10 (13%)	−0·3% (−10·8 to 11·5)	0·97 (0·38 to 2·49)
Moderate (10–14)	11 (14%)	12 (16%)	−1·7% (−13·5 to 10·4)	0·88 (0·36 to 2·13)
Severe (≥15)	1 (1%)	4 (5%)	−4·0% (−6·5 to 2·5)	0·23 (0·03 to 2·14)
Additional outcomes*				
Mean Villalta score at 12 months[19]	4·0 (3·2)	4·9 (4·2)	−0·8 (−2·1 to 0·4)	..
Post-thrombotic syndrome according to the ISTH Villalta scoring 12 months after deep-vein thrombosis[20]	32 (42%)	33 (44%)	−2·4% (−14·4 to 19·2)	0·91 (0·48 to 1·72)
None (<5)	45 (58%)	42 (56%)	2·4% (−14·4 to 19·2)	1·11 (0·58 to 2·10)
Mild (5–9)	20 (26%)	14 (19%)	7·3% (−20·6 to 7·1)	1·53 (0·71 to 3·31)
Moderate (10–14)	11 (14%)	15 (20%)	−5·7% (−7·3 to 17·6)	0·67 (0·28 to 1·56)
Severe (≥15)	1 (1%)	4 (5%)	−4·0% (−2·5 to 6·5)	0·23 (0·03 to 2·14)
Mean venous clinical severity score at 12 months[21]	4·2 (2·5)	4·8 (2·7)	−0·7 (−1·6 to 0·2)	..
Ulceration at any follow-up assessment	0	4 (5%)	−5·4% (−1·9 to 7·9)	0·10 (0·01 to 1·94)

Data are n (%) or mean (SD). None of the comparisons in this table showed a statistically significant difference between groups. ISTH=International Society of Thrombosis and Haemostasis. *In the case of bilateral deep-vein thrombosis, the least favourable Villalta scores were used.

The absolute difference was –6.1% (95% CI –21.6 to 9.8). The severity of post-thrombotic syndrome in the intervention group compared with the standard treatment group was mild (Villalta score 5–9; ten [13%] in the intervention group vs ten [13%] in the standard treatment group, p=0.95), moderate (Villalta score 10–14; 11 [14%] vs 12 [16%], p=0.77), or severe (Villalta score ≥15 or venous ulceration; one [1%] vs four [5%], p=0.21) and did not differ significantly between treatment groups (table 2). The cumulative incidence of post-thrombotic syndrome at 12 months was 22 (29%) of 77 for additional ultrasound-accelerated catheter-directed thrombolysis and 26 (35%) of 75 for the standard treatment group (hazard ratio [HR] adjusted for centre 0.76 [95% CI 0.43 to 1.35]). Post-thrombotic syndrome was diagnosed at 6 months in 13 (17%) patients in the intervention group and 19 (25%) in the standard treatment group, with another nine (12%) and seven (9%) patients diagnosed at 12-month follow-up. The HRs and 95% CIs stratified for centre and adjusted for age, sex, clinical presentation of the acute thrombosis, and extent of the thrombus for the intervention group versus the standard treatment group were 0.80 (0.44–1.45) with the original Villalta scoring and 0.93 (0.55–1.56) with the ISTH-consensus scoring method. Similar results were found in the per-protocol analysis (appendix p16).

Major bleeding occurred solely in the intervention group (in four [5%] of 77 patients), most within 10 days after start of treatment (median 5.5 days [0.8–12.5]). No intracranial or intraspinal bleeds occurred; however, in one patient the major bleeding resulted in neuropraxia of the peroneal nerve. All events were related to the assigned thrombolytic treatment and required additional medical intervention. None of the four deaths, of which one (1%) occurred in the intervention group and three (4%) in the standard treatment group, were related to the instituted treatment or procedure.

During follow-up, a total of 24 thrombotic events occurred in 20 patients: 14 (18%) of 77 patients from the intervention group had a total of 17 events (five recurrent [non-stent] deep-vein thromboses in five [6%] patients and 12 in-stent thromboses in ten [13%] patients) versus six (8%) of 75 patients from the standard treatment group who had seven events (five recurrent [non-stent] deep-vein thromboses in four [5%] patients and two pulmonary emboli in two [3%] patients). All of the thrombotic events (in-stent or non-stent) involved the index leg (table 3, appendix p15).

Table 3 *Safety outcomes*

	Additional thrombolysis group (n=77)	Standard treatment group (n=75)	Difference between treatment groups (95% CI)	Odds ratio (95% CI)
Primary outcome				
Major bleeding*[27]	4 (5%)	0	5·2% (–0·4 to 2·7)	9·25 (0·49 to 174·7)
Secondary outcomes				
Pulmonary embolism	0	2 (3%)	–2·6% (–7·1 to 1·8)	0·19 (0·01 to 4·02)
Recurrent (non-stent) deep-vein thrombosis†	5 (6%)	4 (5%)	1·2% (–6·3 to 8·7)	1·23 (0·32 to 4·78)
In-stent thrombosis‡	10 (13%)	..	..	..
Death	1 (1%)	3 (4%)	–2·7% (–7·8 to 2·4)	0·32 (0·03 to 3·11)

Data are n (%). None of the comparisons in this table showed a statistically significant difference between groups. *Bleeding was associated with neuropraxia of the peroneal nerve. †In the standard treatment group, four patients developed a recurrent deep-vein thrombosis, of which one had two separate events; after the first event, which occurred when the patient had no anticoagulant treatment, treatment was reinstalled using direct oral anticoagulants; the second event developed despite anticoagulant treatment; thrombolysis was attempted, however it was unsuccessful; anticoagulant therapy will be continued indefinitely. ‡Of the ten patients who developed an in-stent-thrombosis, two patients encountered two separate events; in both cases, the second event was treated conservatively by lifelong continuation of anticoagulant therapy.

In the intervention group, all recurrent (non-stent) thrombotic events occurred while patients were on anticoagulant treatment, whereas in the standard treatment group, all patients were off anticoagulant treatment at the time of recurrence. In-stent thrombosis, which occurred solely in the intervention group because patients from the standard treatment group did not undergo venous stenting, occurred 12 times in ten patients (13%). Four of these occurred within 2 weeks after the primary intervention. Repeated thrombolysis was initiated in six (60%) of ten patients and was combined with adjunctive endovascular procedures in two of these patients and hybrid procedures (a combination of surgical and endovascular) in three patients. Two of these patients had a second event of in-stent thrombosis, after which lifelong conservative anticoagulation therapy was initiated. No serious adverse events occurred.

Allocated treatment was monitored and is summarised in the appendix (pp 13–14). Incidences of accidental unmasking were not recorded. In three (4%) of 77 patients assigned to the intervention group, the procedure was not performed. In all other patients in the intervention group, thrombolysis was started at a median of 10.0 days (IQR 6.8–15.0) after onset of symptoms and was continued for a median of 2.0 days (1.0–3.0). Treatment was terminated early in 22 (30%) of the 74 patients who received thrombolytic treatment: in 19 patients because no progress in thrombus resolution was seen, in two patients because of a persisting low fibrinogen level, and one patient no longer wished to continue with thrombolysis. Adjunctive procedures were done in 42 (55%) of 77 patients, including venous stenting in 35 patients.

Stenting involved the common iliac vein in 29 patients and stenting caudal to the iliofemoral ligament was only done in three patients.

Adherence to compression therapy of more than 80% of days at 12-month follow-up was seen in 49 (66%) of 74 patients in the intervention group and 51 (72%) of 71 patients receiving standard treatment. Few patients refrained from compression therapy: 12 (16%) in the intervention group and 11 (15%) in the standard treatment group. In the intervention group, 63 (82%) of 77 had adherence of more than 80% of days at 3 months and 61 (80%) of 76 had more than 80% adherence at 6 months compared with the control group, in which 60 (81%) of 74 at 3 months and 61 (82%) of 74 at 6 months had more than 80% adherence. In the intervention group, 75 (97%) of 77 patients at 3 months, 73 (96%) of 76 at 6 months, and 36 (49%) of 74 at 12 months were using anticoagulant therapy, compared with 69 (93%) of 74 patients at 3 months, 66 (89%) of 74 at 6 months, and 43 (61%) of 71 patients at 12 months in the standard treatment group.

The complete quality of life data from baseline until month 12 for both treatment groups is in the appendix (p 17). Change between baseline and 12 months in general health-related quality of life measures (SF36 and EQ5D) and disease-specific quality-of-life measures (VEINES-QOL/sym T and intrinsic scores) were similar between treatment groups (appendix p17). Except for the VEINES-QOL/sym T score ($p=0.71$), all quality of life measurements significantly increased over time ($p<0.04$).

Discussion

Our study did not show a benefit from additional ultrasound-accelerated catheter-directed thrombolysis over standard treatment for the prevention of post-thrombotic syndrome 1 year after acute iliofemoral deep-vein thrombosis. Results were consistent in the modified intention-to-treat and per-protocol analyses and did not depend on predefined patient characteristics.

A non-significant absolute difference of –6.1% was associated with additional ultrasound-accelerated catheter-directed thrombolysis versus standard treatment. This difference is far less than the anticipated –17% difference.

Additionally, our results as presented according to the ISTH definition are in concordance with the main results of the ATTRACT trial,[16] both showing a more modest non-significant risk reduction than our primary analysis using the original Villalta scoring and thus unable to confirm the outcomes of the CaVenT trial,[14] which demonstrated an absolute risk reduction of 14.4% for the development of post-thrombotic syndrome with additional catheter-directed thrombolysis.

We observed a significantly higher incidence of recurrent thrombotic events in the additional ultrasound-accelerated catheter-directed thrombolysis group because of the occurrence of in-stent-thromboses. Furthermore, even though without severe consequences, major bleeding occurred solely in the intervention group. Moreover, additional ultrasound-accelerated catheter-directed thrombolysis did not significantly affect quality of life: both the generic as

well as disease-specific patient-reported health-related quality of life scores showed a similar improvement in both groups during follow-up.

Outcomes might have been influenced by differences in study design or selected study populations. The number of patients in our trial was lower than in the ATTRACT trial[16] but similar to the number in the CaVenT trial.[14] However, our number of patients with iliofemoral deep-vein thrombosis was about twice as high as in the CaVenT-trial. Thrombus location can influence the risk of developing post-thrombotic syndrome[10,11] as well as the efficacy of thrombolytic treatment.[13] The CAVA trial included patients with iliofemoral thrombosis only, providing a more homogeneous study population, which was considered an important advantage over the CaVenT trial. However, contrary to our expectations, this homogeneous selection of high-risk patients did not result in greater benefit for the patients. To that effect, the ATTRACT trial also did not show unequivocally better results in patients with iliofemoral thromboses than those with isolated femoropopliteal thromboses, which are clinically less severe or less therapy resistant. Moreover, a subanalysis involving exclusively patients with iliofemoral thromboses showed no preventive effect of catheter-directed thrombolysis on the development of any (mild to severe) post-thrombotic syndrome. However, the intervention did result in less severe post-thrombotic complaints and higher quality of life after 24 months.[17]

Both trials used catheter-directed thrombolysis with a mechanical component, which could potentially have induced vein wall damage, thereby blurring the effects of thrombolysis. However, this confusion is unlikely given the results of a study by Engelberger and colleagues[32] that showed no difference in post-thrombotic syndrome incidence whether the mechanical component of the Ekos Endowave-system was activated during thrombolytic treatment or not. Also, the ATTRACT trial,[16] which assessed multiple different thrombolytic treatment strategies, did not report any differential effect on outcomes related to the use of different treatment modalities. In our study, patients who received additional ultrasound-accelerated catheter-directed thrombolysis had treatment according to a single protocol used in all centres. Adjunctive procedures (mainly percutaneous transluminal angioplasty and venous stenting), were complicated by a high proportion of in-stent thromboses. This high proportion might have affected the clinical outcomes because recurrent thrombosis is one of the main risk factors for the development of post-thrombotic syndrome.[29,33]

The 12-month follow-up of this trial was shorter than the follow-up in the other two trials. Previous studies, including the ATTRACT trial, suggest that although post-thrombotic syndrome can still develop years after the acute event, it usually occurs within the first year.[10,16,29,33,34] Since the CaVenT trial[14] did not show a difference in incidence of post-thrombotic syndrome until 24 months, a longer follow-up theoretically might have led to different results.[4]

Our study has several limitations. Stringent inclusion criteria were used that resulted in a lengthy period of recruitment and could affect the generalisability of the results. For example, the use of direct oral anticoagulants was introduced during the inclusion period. Multiple patients

withdrew informed consent immediately after randomisation because of disappointment when allocated to standard treatment only, which reduced our sample size, and although it did not result in a numerical misbalance between the treatment groups, it might have resulted in imbalance of prognostic factors. The higher-than-expected proportion of patients with post-thrombotic syndrome in the standard treatment group might also have negatively affected the power of the trial. However, in patients that did receive assigned treatment, few were lost to follow-up during the trial. In addition, both treatment groups showed high compliance with compression therapy, maybe because in the Netherlands the use of compression stockings is more commonly accepted and is officially part of treatment than in most other European or North American countries, which might have rendered standard treatment as comparative treatment relatively successful.

The perceived advantage of selecting a homogenous population of patients with iliofemoral thrombosis might have turned out to be a disadvantage for the outcomes of our study, as these types of thromboses might be more treatment resistant. Whether this treatment resistance is associated with the location of the thrombosis resulting in impaired venous outflow or with characteristics of the clot is uncertain.[35] Furthermore, catheter-based intervention protocols encourage physicians to apply additional procedures, including stent placement, introducing an extra risk factor for in-stent-thrombosis. Stents are not sufficiently equipped to reduce clot formation and new generations of stents might be required. Additionally, no robust evidence supports a particular anticoagulant regimen to prevent in-stent-thrombosis.[36] Thus, a multidisciplinary approach is probably needed to solve the remaining problems, including better selection of patients, optimisation of treatment protocols, improvement of the quality of the reperfusion process, assessment of the need for stenting, and enhancement of the quality of stent materials as well as optimisation of the (post-interventional) antithrombotic policy. These problems need to be addressed in concert in order to make further steps towards successful reperfusion therapy in venous thrombosis.

In conclusion, this study showed that additional ultrasound-accelerated catheter-directed thrombolysis does not change the risk of post-thrombotic syndrome 1 year after an acute iliofemoral deep-vein thrombosis compared with standard therapy alone. Although this trial is inconclusive, the outcome suggests the possibility of a moderate effect. Further research is therefore warranted to better understand our results in the context of previous trials, preferably by combining the available evidence in an individual patient data meta-analysis.

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Chapter 7: Association of Successful Ultrasound-Accelerated Catheter-Directed Thrombolysis with Postthrombotic Syndrome: A Post Hoc Analysis of the CAVA Trial

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Abstract:

Background: The CAVA trial did not show the anticipated risk reduction for postthrombotic syndrome (PTS) after thrombus removal via additional ultrasound-accelerated catheter-directed thrombolysis (UACDT) in patients with acute iliofemoral deep vein thrombosis (IFDVT). Difficulties in achieving an effective degree of recanalization through thrombolysis may have influenced outcomes. We therefore
assessed whether successful UACDT (restored patency > 90%) did reduce the development of PTS.

Methods: This CAVA trial post hoc analysis compared the proportion of PTS at 1-year follow-up between patients with successful UACDT and patients that received standard treatment only. In addition, clinical impact as well as determinants of successful thrombolysis were explored.

Results: UACDT was initiated in 77 (50.7%) patients and considered successful in 41 (53.2%, interrater agreement κ . 0.7, 95% confidence interval 0.47–0.83). PTS developed in 15/41 (36.6%) patients in the successful UACDT group versus 33/75 (44.0%) controls (p . 0.44). In this comparison, successful UACDT was associated with lower Venous Clinical Severity Score (3.50 2.57 vs. 4.82 2.74, p . 0.02) and higher EuroQOL-5D (EQ-5D) scores (40.2 36.4 vs. 23.4 34.4, p . 0.01). Compared with unsuccessful UACDT, successful UACDT was associated with a shorter symptom duration at inclusion (p . 0.05), and higher rates of performed adjunctive procedures (p < 0.001) and stent placement (p < 0.001).

Conclusion: Successful UACDT was not associated with a reduced proportion of PTS 1 year after acute IFDVT compared with patients receiving standard treatment alone. There was, however, a significant reduction in symptom severity and improvement of generic quality of life according to the EQ-5D. Better patient selection and optimization of treatment protocols are needed to assess the full potential of UACDT for the prevention of PTS.

Introduction

Postthrombotic syndrome (PTS) is a serious complication that occurs in 40 to 60% of patients who have experienced deep vein thrombosis of the leg.[1–3] The risk of postthrombotic morbidity depends on the location and extent of thrombosis,[2,4,5] the highest risk being associatedwith iliofemoral thrombosis.[2,5–7] Current thrombosis management entails immediate anticoagulant therapy, therapeutic compression therapy, and earlymobilization.[8,9] Although overall successful, it does not sufficiently prevent the development of PTS in those patients most at risk.[10] Based on the concept of the "open vein hypothesis," early thrombus removal is anticipated to be promising for the reduction of PTS incidence.[11,12] Catheter-directed thrombolysis (CDT) was demonstrated to be safe and successful in regaining venous patency after acute deep vein thrombosis[13–15] however, results of recent controlled clinical trials have been inconsistent: while the CaVenT trial showed a substantial reduction in PTS upon CDT, the large ATTRACT trial and the recent CAVA trial performed specifically in patients with iliofemoral deep vein thrombosis (IFDVT), failed to confirm this positive outcome.[16–19]

Secondary analyses of the previous trials[16–19] also addressed the success rate of thrombolytic treatment in relation to the degree of patency that was actually achieved: a factor known to influence the risk of PTS.[6,10] Secondary analysis of the CaVenT trial showed an inverse correlation of residual thrombosis following thrombolysiswith patency at 24months; however, without a direct correlation between postthrombolysis residual thrombosis and PTS.[20] This post hoc analysis of the CAVA trial aims to explore whether successful ultrasoundaccelerated CDT (UACDT) is associated with better outcomes for the development of PTS and quality of life (QoL) as well as whether thrombolytic success is influenced by certain patient, thrombus, or treatment characteristics.

Methods

This study is an exploratory post hoc analysis from the CAVA trial, an investigator-initiated, multicenter, randomized, single-blind, allocation-concealed, parallel group, superiority trial which assessed the development of PTS in patients with acute IFDVT receiving additional UACDT compared with standard treatment alone. The study was approved by the review boards of all participating centers and written informed consent was obtained before randomization. The results of the CAVA trial and the full research protocol were published earlier.[16] In short, patients aged 18 to 85 years with an objectified, first-time IFDVT with a maximum symptom duration of 14 days and meeting the inclusion criteria were eligible for inclusion. IFDVT was defined as partial or complete thrombosis of the common femoral vein ormore cranial vein segments.[21] A total of 184 patientswas randomly (1:1) assigned to treatment with additional UACDT (intervention group) or to standard treatment only (control group).[9] In the final modified intention-to-treat analysis, 152 (82.6%) of the 184 randomized patients were included: 77 (50.7%) patients from the intervention group in which thrombolysiswas initiated and 75 (49.3%) patients from the control group. Patients allocated to the intervention

group were admitted to the medium care unit at one of the six interventional centers and UACDT was started no later than 21days after onset of symptoms. Treatmentdecisions (e.g.,dose adjustments, interruption, or termination of treatment) were based on the progress of thrombolysis demonstrated on daily venous angiograms as well as on the coagulant status determined by repetitive 6-hourly laboratory measurements.The intervention was terminated in case of successful treatment (defined as regained venous patency of 90%), in case there was 48 hourswithout change inpatency, persistent deviance of the coagulation status (activated partial thromboplastin time> 80 seconds, fibrinogen< 8mm in FIBTEM, or plasma fibrinogen< 1.8 g/L), or when the maximum duration of treatment (96 hours) was reached. Adjunctive procedures (e.g., thrombosuction, percutaneous transluminal angioplasty, stenting using dedicated venous stents, endophlebectomy, and/or creating an arteriovenous fistula)were at the discretion of the physician performing the procedure yet recommended in case of a 0% residual venous obstruction and/or compression syndromes.

Clinical follow-up was performed at 1 of the 15 participating centers by the patient's treating physician or study personnel who were informed on the patient's study participation but not on treatment allocation. Therefore, patients were asked not to disclose their allocated treatment during follow-up visits. For this post hoc analysis, patients in the intervention group were classified as either having received successful or unsuccessful thrombolysis. Thrombolysis was considered to be successful with an accomplished patency of > 90% with adequate in- and outflow in all affected vein segments as established on venous angiogramat the end of interventional treatment.All three reviewers have ample experience in the diagnosis and treatment of venous pathology either as dedicated venous vascular surgeon (C.W.) or interventional radiologists (C.A. and R.B.).They reviewed all interventions
independently using a standardized clinical registration form reporting on thrombus localization, venous anomalies, and patency following thrombolysis and/or additional interventions (i.e., stenting). None of them had any knowledge regarding the linical outcomes.

Primary Efficacy Outcome

The primary outcome for the analysis between successful thrombolysis and standard treatment was the proportion of PTS at 12 months according to the International Society of Thrombosis and Haemostasis consensus definition, based on a singular Villalta score of 5 at least 6 months after the primary event or the presence of venous ulceration, between successful thrombolysis and standard treatment.[22]

Secondary Outcomes

The severity of PTS between successful thrombolysis and standard treatment was represented by the Villalta scale (0–33) which categorizes into no (0–4), mild (5–9), moderate (10–14), and severe (15 or venous ulceration)[22–24] as well as by the Venous Clinical Severity Score (VCSS, 0–30) with more severe burden leading to a higher score.[25] In addition, generic QoL according

to the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)[26] and the EuroQOL-5D (EQ-5D)[27] was assessed as well as disease-specific QoL (Venous Insufficiency Epidemiological and Economic Study Quality of Life [VEINES-QOL] questionnaire)[28–30] and the Pain Disability Index.[31] In addition, a comparison was made between successful thrombolysis versus unsuccessful thrombolysis. The latter comparison was performed to explore whether treatment characteristics differed andwhether unsuccessful thrombolysis resulted in other (disadvantageous or harmful) consequences apart from the recanalization being unsuccessful.

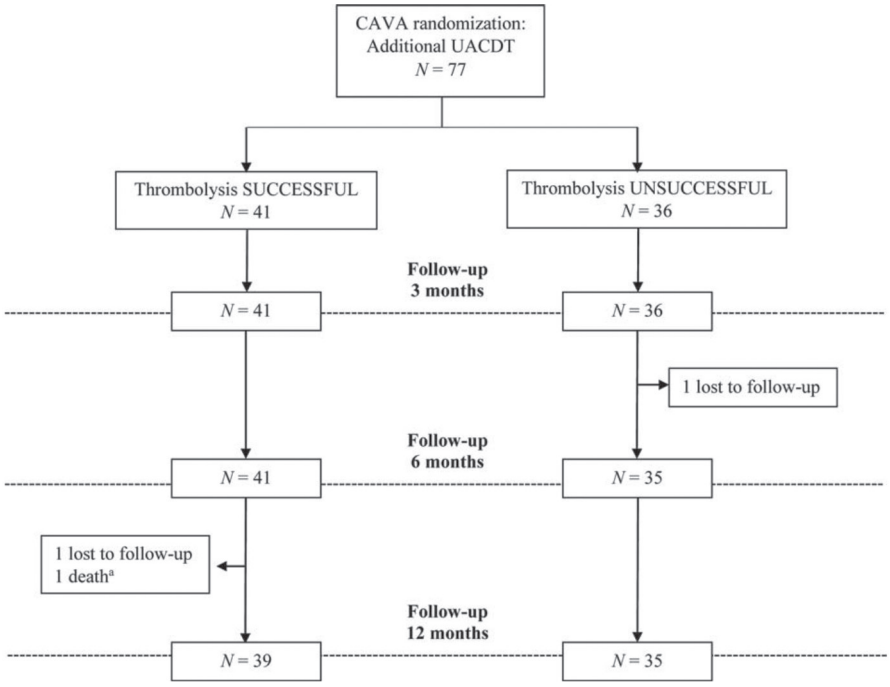
Statistical Analysis

An exploratory post hoc analysis of the CAVA trial was performed to assess the impact of successful thrombolysis on the proportion of PTS. The interrater agreement for identification of successful procedures was determined using Cohen's . To assess the difference in proportion of patientswith PTS between groups, univariate analysis of proportions with logistic regression (chi-square) was used and associated odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were calculated. Additionally, we used the Kaplan–Meier method to calculate the cumulative incidence of PTS at 12 months adjusted for center to compare incidences between the two treatment groups. Withdrawal, loss to follow-up, and deathwere censored at the last available date. Cox regression analysis adjusted for age, sex, clinical presentation (idiopathic or provoked) of the thrombotic event, and extent of the index thrombus at the diagnostic ultrasound using the Lower Extremity Thrombosis classification32 was applied to determine the hazard ratios with their accompanying 95% CIs. Repeated QoL measurements and changes over time were assessed using a mixed design analysis of variance. The minimal clinically important difference was calculated as proposed by Norman et al.[33] or validated values were used when available.[30,34] For all analyses, a p-value of < 0.05 was considered statistically significant. The statistical analyseswere performed using SPSS, version 25 (IBM corporation, Armonk, New York, United States).

Results

Following the independent review of the procedural venous angiographs, consensus was reached in 65 of 77 patients (84.4%), resulting in a κ of 0.7. After a second review, thrombolysis was considered successful in 53.2% (41 out of 77 interventions) (Figure. 1).

Figure 1



Adapted detailed flowchart segment for patients included in the subanalysis successful versus unsuccessful thrombolysis. The trial profile of the CAVA trial has been published previously.[16] Thrombolysis was considered successful if an overall patency of ≥ 90% with an adequate in- and outflow in all of the initially affected vein segments was seen on venous angiogram at the end of interventional treatment. aThe cause of death was not study-related. UACDT, ultrasound-accelerated catheter-directed thrombolysis.

Baseline Characteristics

Baseline characteristics were balanced between treatment groups except for median age which, with a median of 44.5 years, appeared slightly lower in patients with unsuccessful thrombolysis. The number of days that symptoms were present was more often 14 to 21 days in patients with unsuccessful thrombolysis compared with patients with successful thrombolysis or standard treatment alone ($p < 0.05$) (Table 1).

Table 1 *Baseline characteristics*

	Successful additional UACDT $N = 41$	Unsuccessful additional UACDT $N = 36$	Standard treatment $N = 75$
Age, y – median (IQR)	51.0 (40.0–68.0)	44.5 (35.3–59.3)	52.0 (38.0–65.0)
Age, category – no. (%)			
< 40 y – no. (%)	10 (24.4)	13 (36.2)	20 (26.6)
40–65 y – no. (%)	17 (41.5)	16 (44.4)	38 (50.7)
> 65 y – no. (%)	14 (34.1)	7 (19.4)	17 (22.7)
Sex – no. (%)			
Male – no. (%)	23 (56.1)	16 (44.4)	38 (50.7)
Female – no. (%)	18 (43.9)	20 (55.6)	37 (49.3)
Body mass index – mean ± SD[a]	28.4 ± 5.3	27.6 ± 5.9	27.4 ± 4.1
Body mass index, category – no. (%)[a]			
< 25.0–no. (%)	12 (29.3)	12 (33.3)	22 (29.3)
25.0–30.0–no. (%)	15 (36.6)	16 (44.4)	33 (44.0)
≥ 30.0–no. (%)	13 (31.7)	6 (16.7)	15 (20.0)
Unknown – no. (%)	1 (2.4)	2 (5.6)	5 (6.7)
Provoked deep vein thrombosis – no. (%)	18 (43.9)	22 (61.1)	32 (42.7)
Number of known risk factors – no. (%)[b]			
One – no. (%)	15 (36.6)	17 (47.2)	22 (29.3)
More than one – no. (%)	3 (7.3)	5 (13.9)	10 (13.3)
Thrombus location – no. (%)			
Left – no. (%)	30 (73.2)	24 (66.6)	55 (73.3)
Right – no. (%)	10 (24.4)	11 (30.6)	17 (22.7)
Bilateral[c] – no. (%)	1 (2.4)	1 (2.8)	3 (4.0)
Duration of symptoms at inclusion, d – median (IQR)	5.0 (3.0–9.8)	7.0 (4.0–13.0)	7.0 (3.0–10.0)
Duration of symptoms at inclusion, category – no. (%)			
0–7 d – no. (%)	24 (58.6)	17 (47.2)	37 (49.3)
7–14 d – no. (%)	14 (34.1)	10 (27.8)	31 (41.3)
14–21 d – no. (%)	2 (4.9)	8 (22.2)[d]	6 (8.0)
> 21 d – no. (%)	0	0	1 (1.3)
Unknown – no. (%)	1 (2.4)	1 (2.8)	0
VCSS – mean ± SD	7.1 ± 3.2	6.8 ± 3.3	7.3 ± 2.8
Anticoagulant therapy at inclusion – no. (%)			
Acenocoumarol – no. (%)	24 (58.5)	22 (61.1)	53 (70.7)
Phenprocoumon – no. (%)	10 (24.4)	6 (16.7)	10 (13.3)
Direct oral anticoagulants – no. (%)	6 (14.6)	6 (16.7)	6 (8.0)
LMWH – no. (%)	0	1 (2.8)	0
Unknown – no. (%)	1 (2.4)	1 (2.8)	6 (8.0)

Abbreviations: IQR, interquartile range; LMWH, low-molecular-weight heparin; SD, standard deviation; UACDT, ultrasound-accelerated catheter-directed thrombolysis; VCSS, Venous Clinical Severity Score. Note: Data are n (%), mean SD, or median (IQR). With the exception of the outcome marked with "d," none of the variables mentioned in this table showed significant difference between groups in the comparisons of successful additional UACDT versus standard therapy or versus unsuccessful additional UACDT, respectively.

a Body mass index (BMI) is defined as the patient's weight in kilograms divided by the square of the patient's height in meters (kg/m2).

b An acute deep vein thrombosis is considered "idiopathic" or "unprovoked" in the absence of the following risk factors: surgery in the previous 2 months, trauma in the previous 2 months, pregnancy or child birth in the previous 3 months, use of hormone replacement therapy, use of oral contraceptives, and active malignancy.

c In the case of bilateral deep vein thrombosis, the leg with the most proximal localization was considered to be the index leg. dp 1⁄4 0.05.

Successful Thrombolysis versus Standard Treatment

At 12-month follow-up, PTS occurred in 15 of 41 patients (36.6%) with successful thrombolysis versus 33 of 75 patients (44.0%) receiving standard treatment only; p = 0.44, OR 0.73 (95% CI 0.34–1.61) (Table 2).

Table 2 *Efficacy outcomes*

	Successful additional UACDT *n* = 41	Unsuccessful additional UACDT *n* = 36			Standard treatment *n* = 75		
			Difference between treatment groups[a] (95% CI)	Odds ratio[a] (95% CI)		Difference between treatment groups[b] (95% CI)	Odds ratio[b] (95% CI)
Primary outcome							
Postthrombotic syndrome by ISTH[22]–no. (%)	15 / 41 (36.6)	17 / 36 (47.2)	–10.6% (–34.0 to 13.7)	0.65 (0.26–1.61)	33 / 75 (44.0)	–7.4% (–26.4 to 13.3)	0.73 (0.34–1.61)
Postthrombotic syndrome by ISTH[22] severity – no. (%)							
None (0–4) – no. (%)	26 / 41 (63.4)	19 / 36 (52.8)	10.6% (–13.7 to 34.0)	1.55 (0.62–3.86)	42 / 75 (56.0)	7.4% (–13.3 to 26.4)	1.36 (0.62–2.98)
Mild (5–9) – no. (%)	12 / 41 (39.3)	11 / 36 (30.6)	–1.3% (–23.5 to 20.5)	0.94 (0.35–2.50)	17 / 75 (22.7)	6.6% (–10.7 to 25.1)	1.41 (0.60–3.35)
Moderate (10–14) – no. (%)	2 / 41 (4.9)	6 / 36 (16.7)	–11.8% (–20.3 to 4.1)	0.26 (0.05–1.36)	12 / 75 (16.0)	–11.1% (–17.3 to 3.5)	0.27 (0.06–1.27)
Severe (≥ 15) – no. (%)	1 / 41 (2.4)	0	2.2% (–4.4 to 4.8)	2.70 (0.11–68.5)	4 / 75 (5.3)	–2.9% (–6.5 to 6.4)	0.44 (0.05–4.11)
Moderate/Severe (≥ 10) – no. (%)	3 / 41 (7.3)	6 / 36 (16.7)	–9.3% (–20.7 to 6.8)	0.40 (0.09–1.71)	16 / 75 (21.3)	–14.0% (–22.3 to 2.1)	0.29 (0.08–1.07)
Additional outcomes							
Villalta score[24] at 12 mo – mean ± SD	3.35 ± 3.10	4.72 ± 3.19[c]	1.37 (–0.15 to 2.88)	–	4.93 ± 5.06	1.58 (–0.23 to 3.39)	–
VCSS[25] at 12 mo – mean ± SD	3.50 ± 2.57	4.88 ± 2.25[d]	1.38 (0.20–2.55)	–	4.82 ± 2.74[e]	1.32 (0.24–2.40)	–
Ulceration at any follow-up assessment – no. (%)	0	0	–0.2% (–2.7 to 2.4)	0.88 (0.02–45.5)	4 / 75 (5.3)	–4.7% (–6.6 to 4.8)	0.19 (0.01–3.65)

Abbreviations: CI, confidence interval; ISTH, International Society of Thrombosis and Haemostasis; SD, standard deviation; UACDT, ultrasound-accelerated catheter-directed thrombolysis; VCSS, Venous Clinical Severity Score.

Note: Data are n (%) or mean + SD. Numbers concerning the diagnosis of postthrombotic syndrome include all participating patients at 12-month follow-up as well as patients that deceased after development of postthrombotic syndrome. In the case of bilateral deep vein thrombosis, the least favorable clinical scores were used.

a Values based on comparison between patients with successful additional UACDT (n = 41) versus patients with unsuccessful additional UACDT (n = 36).

b Values based on comparison between patients with successful additional UACDT (n = 41) versus patients with standard treatment alone (n = 75).

c p = 0.05.

d p = 0.03.

e p = 0.02.

The cumulative incidence of PTS at 12-month follow-up was 37.5% in the successful thrombolysis group versus 45.2% in the standard treatment group: hazard ratio adjusted for center 0.75 (95% CI 0.40–1.41), p = 0.33. The overall mean Villalta scores did not differ between the groups and were 3.35 ± 3.10 versus 4.93 ± 5.06, p = 0.11. The subscores were 1.32 ± 1.77 versus 2.16 ± 3.68 for the objective items (p = 0.09) and 2.03 ± 2.17 versus 2.80 ± 2.94 for the subjective items (p = 0.35). There were no differences in the occurrence of mild, moderate, severe, or for the combination moderate–severe PTS. However, patients in the successful thrombolysis group had a lower symptom severity according to the VCSS (3.50 ± 2.57 vs. 4.82 ± 2.74, p = 0.02).

The health-related QoL scores at 12-month follow-up differed compared with those at inclusion for the different health measures used (p < 0.002) with the exception of the SF-36-General Health score (p . 0.13) and the VEINES-QOL total score (p . 0.56) (Table 3). Changes over time between groups only resulted in a significant difference for the EQ-5D (p = 0.01) score. The difference between groups was 9.2 and exceeded the calculated minimal clinically important difference.

No differences in standard postthrombotic management (use of anticoagulation and adherence to compression therapy) were seen during follow-up with the exception of anticoagulation being prescribed more often at 6-month follow-up in patients with successful thrombolysis compared with patients on standard treatment (100.0% vs. 89.2%, p = 0.03).

Successful versus Unsuccessful Thrombolysis

No difference in proportion of PTS at 12-month follow-up was found between patients with successful and unsuccessful thrombolysis: 15 (36.6%) versus 17 (47.2%) patients, p = 0.35, OR 0.65 (95%CI 0.26–1.61) (Table 2). However, successful thrombolysis did result ina lower symptom severity compared with unsuccessful thrombolysis both according to the total Villalta score (3.35 ± 3.10 vs. 4.72 ± 3.19, p = 0.05) and to the VCSS (3.50 ± 2.57 vs. 4.88 ± 2.25, p = 0.03). At 12-month follow-up, the SF-36-Physical Health, EQ-5D, and VEINES-QOL intrinsic scores differed significantly compared with inclusion (p < 0.001) (Table 3).

The change in scores over time was significantly different between groups for the EQ-5D (p < 0.001), the VEINES-QOL total score (p . 0.05), and the VEINES-QOL intrinsic score (p = 0.002) (Table 3). The changes over time in the aforementioned domains are all clinically relevant exceeding the validated or calculated minimal clinically important difference.

Characteristics of Successful Thrombolysis

The median time between onset of symptoms and start of UACDT (and therefore the presumed thrombus age) did not differ between patients with successful and unsuccessful thrombolysis: 10.0 days (interquartile range [IQR] 6.0–14.0) versus 11.5 days (IQR 8.0–17.0), p = 0.09 (Table 4).

	Successful additional UACDT $n = 41$			Unsuccessful additional UACDT[a] $N = 36$			Standard treatment[b] $n = 75$		
Generic quality of life									
	SF-36, Physical Health – mean ± SD[26]	***N***	**Δ From inclusion**	**SF-36, Physical Health – mean ± SD[26]**	***N***	**Δ From inclusion**	**SF-36, Physical Health – mean ± SD[26]**	***N***	**Δ From inclusion**
Inclusion	46.1 ± 33.5	35	–	35.7 ± 26.6	29	–	40.1 ± 32.7	59	–
3 mo	78.8 ± 21.6	33	37.1 ± 35.5	68.1 ± 29.6	24	22.5 ± 37.0	70.8 ± 25.9	50	27.4 ± 33.5
6 mo	82.3 ± 22.3	31	39.8 ± 37.4	70.5 ± 25.4[c]	28	31.3 ± 32.0	74.7 ± 23.2	49	33.1 ± 33.9
12 mo	82.4 ± 20.3	35	36.0 ± 41.1	79.3 ± 25.2	28	43.3 ± 38.9	76.6 ± 25.8	64	35.1 ± 39.6
				Δ From inclusion to 12 mo: $p < 0.001$ Δ From inclusion to 12 mo between groups: $p = 0.08$			Δ From inclusion to 12 mo: $p < 0.001$ Δ From inclusion to 12 mo between groups: $p = 0.21$		
	SF-36, Mental Health – mean ± SD[26]	***N***	**Δ From inclusion**	**SF-36, Mental Health – mean ± SD[26]**	***N***	**Δ From inclusion**	**SF-36, Mental Health – mean ± SD[26]**	***N***	**Δ From inclusion**
Inclusion	71.3 ± 17.6	**35**	–	70.7 ± 17.7	29	–	73.4 ± 17.8	59	–
3 mo	78.3 ± 14.6	32	8.2 ± 14.5	75.6 ± 17.8	24	1.4 ± 14.2	74.8 ± 17.6	49	2.4 ± 16.5
6 mo	78.2 ± 16.3	30	6.8 ± 18.5	78.0 ± 21.5	27	6.2 ± 4.2	78.6 ± 17.2	47	6.9 ± 16.7
12 mo	76.8 ± 16.3	34	4.7 ± 19.8	91.3 ± 52.0	28	19.6 ± 54.5	79.8 ± 16.7	64	6.2 ± 20.5
				Δ From inclusion to 12 mo: $p = 0.18$ Δ From inclusion to 12 mo between groups: $p = 0.30$			Δ From inclusion to 12 mo: $p = 0.002$ Δ From inclusion to 12 mo between groups: $p = 0.52$		
	SF-36, General Health – mean ± SD[26]	***N***	**Δ From inclusion**	**SF-36, General Health – mean ± SD[26]**	***N***	**Δ From inclusion**	**SF-36, General Health – mean ± SD[26]**	***N***	**Δ From inclusion**
Inclusion	65.0 ± 16.3	35	–	62.8 ± 18.5	29	–	63.5 ± 20.0	58	–
3 mo	66.3 ± 16.7	32	0.9 ± 14.5	59.8 ± 19.6	24	−3.6 ± 15.9	61.9 ± 20.5	49	−0.11 ± 15.7
6 mo	64.8 ± 19.0	30	1.1 ± 18.7	61.3 ± 22.4	26	0.8 ± 20.2	66.9 ± 20.2	47	4.0 ± 16.8
12 mo	66.2 ± 17.5	34	−0.7 ± 16.8	64.8 ± 18.5	28	2.0 ± 19.3	64.9 ± 22.8	64	0.7 ± 19.4
				Δ From Inclusion to 12 months: $p = 0.11$ Δ From Inclusion to 12 months between groups: $p = 0.55$			Δ From Inclusion to 12 months: $p = 0.13$ Δ From Inclusion to 12 months between groups: $p = 0.97$		
	EQ-5D – mean ± SD[27]	***N***	**Δ From inclusion**	**EQ-5D – mean ± SD[27]**	**N**	**Δ From inclusion**	**EQ-5D – mean ± SD[27]**	***N***	**Δ From inclusion**
Inclusion	48.5 ± 36.7	35	–	54.8 ± 31.2	29	–	59.2 ± 31.7	57	–
3 mo	85.3 ± 16.9	33	39.3 ± 35.3	82.2 ± 13.2	24	15.1 ± 24.5[d]	77.3 ± 27.2	48	18.6 ± 30.0[d]
6 mo	87.0 ± 12.0	31	40.7 ± 36.6	80.9 ± 20.9	27	21.5 ± 32.9	84.6 ± 18.0	48	24.4 ± 30.7
12 mo	86.3 ± 11.9	35	40.2 ± 36.4	85.0 ± 18.4	28	28.9 ± 35.3	82.3 ± 21.0	64	23.4 ± 34.4[e]
				Δ From inclusion to 12 mo: $p < 0.001$ Δ From inclusion to 12 mo between groups: $p = 0.001$			Δ From inclusion to 12 mo: $p < 0.001$ Δ From inclusion to 12 mo between groups: $p = 0.01$		
	Pain Disability Index – mean ± SD[31]	***N***	**Δ From inclusion**	**Pain Disability Index – mean ± SD[31]**	***N***	**Δ From inclusion**	**Pain Disability Index – mean ± SD[31]**	***N***	**Δ From inclusion**

	Successful additional UACDT $n = 41$			Unsuccessful additional UACDT[a] $N = 36$			Standard treatment[b] $n = 75$		
Inclusion	33.4 ± 23.0	27	–	38.3 ± 19.8	27	–	33.0 ± 20.2	55	–
3 mo	9.3 ± 15.1	30	−26.4 ± 24.5	16.7 ± 14.1[d]	20	−15.7 ± 21.9	18.9 ± 18.1[c]	46	−18.5 ± 18.9
6 mo	9.9 ± 15.1	28	−25.0 ± 27.1	10.7 ± 11.6	22	−23.9 ± 20.1	12.7 ± 15.0	47	−23.8 ± 19.9
12 mo	7.4 ± 11.0	30	−26.6 ± 23.2	10.3 ± 13.9	26	−28.9 ± 24.7	13.1 ± 16.3	62	−21.1 ± 19.4
				Δ From inclusion to 12 mo: $p < 0.001$ Δ From inclusion to 12 mo between groups: $p = 0.27$			Δ From inclusion to 12 mo: $p < 0.001$ Δ From inclusion to 12 mo between groups: $p = 0.26$		
Disease-specific quality of life									
	VEINES-QOL – mean ± SD[28–30]	*N*	Δ From inclusion	VEINES-QOL – mean ± SD[28–30]	*N*	Δ From inclusion	VEINES-QOL – mean ± SD[28–30]	*N*	Δ From inclusion
Inclusion	49.9 ± 10.8	35	–	50.0 ± 10.0	27	–	49.9 ± 10.2	59	–
3 mo	53.0 ± 9.6	33	2.21 ± 9.5	46.9 ± 9.7[f]	22	−5.6 ± 11.5[d]	49.1 ± 10.1	46	0.29 ± 9.1
6 mo	50.8 ± 10.3	30	0.78 ± 13.8	48.3 ± 10.6	24	−3.4 ± 12.3	50.0 ± 9.7	48	0.21 ± 8.6
12 mo	50.1 ± 12.9	30	−1.53 ± 11.7	50.1 ± 8.7	23	−0.5 ± 9.6	49.7 ± 9.0	57	−0.29 ± 9.1
				Δ From inclusion to 12 mo: $p = 0.53$ Δ From inclusion to 12 mo between groups: $p = 0.05$			Δ From inclusion to 12 mo: $p = 0.56$ Δ From inclusion to 12 mo between groups: $p = 0.25$		
	VEINES-QOL Intrinsic – mean ± SD[28–30]	*N*	Δ From inclusion	VEINES-QOL Intrinsic – mean ± SD[28–30]	*N*	Δ From inclusion	VEINES-QOL Intrinsic – mean ± SD[28–30]	*N*	Δ From inclusion
Inclusion	50.8 ± 18.1	35	–	50.5 ± 19.2	28	–	49.5 ± 19.1	59	–
3 mo	71.6 ± 17.2	33	21.1 ± 17.6	62.3 ± 15.7[e]	23	6.1 ± 20.7[d]	64.0 ± 19.3	48	0.17 ± 0.17
6 mo	71.2 ± 17.7	31	20.3 ± 24.7	63.2 ± 20.6	27	8.1 ± 21.5[f]	67.6 ± 20.2	48	0.19 ± 0.17
12 mo	69.6 ± 20.2	35	16.8 ± 22.7	72.2 ± 14.3	28	20.1 ± 18.2	68.6 ± 17.9	64	0.19 ± 0.18
				Δ From inclusion to 12 mo: $p < 0.001$ Δ From inclusion to 12 mo between groups: $p = 0.002$			Δ From inclusion to 12 mo: $p < 0.001$ Δ From inclusion to 12 mo between groups: $p = 0.17$		

Abbreviations: EQ-5D, EuroQOL-5D; SD, standard deviation; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; UACDT, ultrasound-accelerated catheter-directed thrombolysis; VEINES-QOL, Venous Insufficiency Epidemiological and Economic Study Quality of Life.

Note: Data are mean ± SD. Post hoc correction for multiple comparisons according to Bonferroni was performed. Although not shown in this table, analyses were performed on all SF-36 domains (including Social Health, Role of Physical Limitations, Role of Mental Limitations, Vitality, Pain, and Health Change).

a Values based on comparison between patients with successful additional UACDT (n = 41) versus patients with unsuccessful additional UACDT (n = 36).

b Values based on comparison between patients with successful additional UACDT (n = 41) versus patients with standard treatment alone (n = 75).

c p = 0.02.

d p = 0.01.

e p = 0.04.

f p = 0.03.

Table 4 *Treatment characteristics: successful versus unsuccessful additional UACDT*

	Successful additional UACDT *N* = 41	Unsuccessful additional UACDT *N* = 36	*p*-Value
Intervention performed – no. (%)	41 / 41 (100.0)	33 / 36 (91.7)	0.09
Duration of symptoms at start UACDT, d – median (IQR)	10.0 (6.0–14.0)	11.5 (8.0–17.0)	0.09
Duration of symptoms at start UACDT, category – no. (%)			
0–7 d – no. (%)	12 / 41 (29.3)	6 / 36 (16.7)	0.19
7–14 d – no. (%)	17 / 41 (41.5)	14 / 36 (38.9)	0.82
14–21 d – no. (%)	10 / 41 (24.4)	13 / 36 (36.1)	0.26
> 21 d – no. (%)	1 / 41 (2.4)	1 / 36 (2.8)	1.00
Unknown – no. (%)	1 / 41 (2.4)	2 / 36 (5.6)	0.60
Duration between inclusion and start UACDT, d – median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	0.95
Duration between inclusion and start UACDT, category – no.(%)			
0–7 d – no. (%)	35 / 41 (85.4)	27 / 36 (75.0)	0.25
7–14 d – no. (%)	6 / 41 (14.6)	5 / 36 (13.9)	1.00
UACDT not started – no. (%)	0	3 / 36 (8.3)	0.52
Unknown – no. (%)	0	1 / 36 (2.8)	1.00
Duration of UACDT, d – median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.98
Vein segments affected – LET classification – no. (%)[a]			
LET IV – no. (%)	9 / 41 (22.0)	6 / 36 (16.7)	0.56
LET III – no. (%)	29 / 41 (70.7)	27 / 36 (75.0)	0.68
LET II – no. (%)	3 / 41 (7.3)	1 / 36 (2.8)	0.62
Unknown – no. (%)	0	2 / 36 (5.6)	0.90
Suspect for preexistent pathology – no. (%)	30 / 41 (73.1)	19 / 36 (52.8)	0.06
Thrombolysis terminated prematurely – no. (%)	0	18 / 36 (50.0)	< 0.001
No progress – no. (%)	n/a	13 / 18 (72.2)	
Persistent abnormality in coagulation status – no. (%)	n/a	2 / 18 (11.1)	
Suspicion of neoplasia on study imaging – no. (%)	n/a	1 / 18 (5.6)	
Considered as screen failure – no. (%)	n/a	1 / 18 (5.6)	
Termination by patient – no. (%)	n/a	1 / 18 (5.6)	
Adjunctive procedure – no. (%)	31 / 41 (75.6)	5 / 36 (13.9)	< 0.001
Endovascular – no. (%)	31 / 31 (100.0)	4 / 5 (80.0)	0.04
Hybrid (including arteriovenous fistula) – no. (%)	0	1 / 5 (20.0)	0.59
Stenting – no. (%)[b]	31 / 41 (75.6)	4 / 36 (11.1)	< 0.001
Inferior caval vein, suprarenal – no. (%)[c]	3 / 31 (9.7)	0	1.00
Inferior caval vein, infrarenal – no. (%)[d]	5 / 31 (16.1)	0	0.78
Common iliac vein – no. (%)[e]	26 / 31 (83.9)	4 / 4 (100.0)	1.00
External iliac vein – no. (%)[f]	11 / 31 (35.5)	1 / 4 (25.0)	1.00
Common femoral vein – no. (%)[g]	2 / 31 (6.5)	0	1.00
Femoral vein – no. (%)	0	0	1.00
Deep femoral vein – no. (%)[h]	1 / 31 (3.2)	0	1.00
Stent placement: additional underlying pathology – no. (%)[i]	27 / 31 (87.1)	4 / 4 (100.0)	1.00
Agenesis – no. (%)	1 / 27 (3.7)	0	1.00
May–Thurner syndrome – no. (%)	9 / 27 (33.3)	3 / 4 (75.0)	0.30

Table 4 *(continued)*

Abbreviations: IQR, interquartile range; LET, Lower Extremity Thrombosis; UACDT, ultrasound-accelerated catheter-directed thrombolysis.
Note: Data are n (%), or median (IQR).

a LET classification was based on venous angiogram performed before start of UACDT.
b Options are not mutually exclusive: multiple vein segments could be stented in a single patient.
c In the successful thrombolysis group the following stents were used: 3 x Sinus XL.
d In the successful thrombolysis group the following stents were used: 4 x Sinus XL, 1 x Sinus Venous.
e In the successful thrombolysis group the following stents were used: 15 x Sinus Venous, 4 x Veniti, 3 x Silver Vena, 2 x Sinus XL, 2 x unknown. In the unsuccessful thrombolysis group the following stents were used: 4 x Sinus Venous.
f In the successful thrombolysis group the following stents were used: 8 x Sinus Venous, 1 x Veniti, 2 x Silver Vena. In the unsuccessful thrombolysis group the following stents were used: 1 x Sinus Venous.
g In the successful thrombolysis group the following stents were used: 1 x Sinus Venous, 1 x Silver Vena.
h In the successful thrombolysis group the following stents were used: 1 x Sinus Venous.
i Additional findings are not mutually exclusive. Multiple additional findings could be seen in a single patient.

There were no differences in duration of thrombolysis, thrombus localization, or presence of preexisting vascular findings (e.g., anatomical anomalies, intraluminal obstructions, or extraluminal compression). Termination of thrombolytic treatment before the maximum duration of 96 hours for reasons other than successful recanalization occurred in 18 of 36 patients (50.0%) in the unsuccessful thrombolysis group only andwas mainly due to no or limited progress in 13 out of 18 (72.2%).

Adjunctive procedures were performed in 31 of 41 patients (75.6%) in the successful thrombolysis group versus 5 of 36 (13.9%) in the group with unsuccessful thrombolysis ($p < 0.001$) and more frequently also involved stent placement (31 out of 31 [100.0%] vs. 4 out of 5 [80.0%], $p = 0.04$). There was no difference in periprocedural complications; however, postinterventional in-stent thrombosis occurred in 6 out of 31 (19.4%) stented patients after successful thrombolysis versus 4 out of 4 (100.0%) after unsuccessful thrombolysis, $p = 0.04$.

Discussion

This exploratory post hoc analysis of the CAVA trial 16 did not show a lower proportion of PTS 1 year after acute IFDVT in patients with successful recanalization through additional thrombolysis compared with patients receiving standard anticoagulant therapy alone.

However, we observed a tendency toward lower ORs for treatment effect after successful thrombolysis (OR 0.73 [0.34–1.61]) compared with the overall treatment effect observed in the CAVA-trial (OR 0.91 [0.48–1.72]).[16] This difference was even more pronounced comparing successful thrombolysis to unsuccessful thrombolysis (OR 0.65 [0.26–1.61]). This may suggest a potential treatment effect for thrombolysis when early recanalization with restoration of flow is accomplished.

This finding is corroborated by the early positive impact of successful thrombolysis on health-related QoL, although this was not consistent in the various QoL questionnaires used.

Inconsistencies between EQ-5D and SF-36 have been described more often and may reflect differences in sensitivity between these metrics.35 In addition, while there was a significant reduction in mean Villalta scores in patients after successful thrombolysis, its clinical relevance remains uncertain as these scores were within the normal range for both treatment groups.

The low rate of thrombolytic success in the CAVA trial (53%) does not stand on its own. Although based on ultrasound assessment at 1 month, thereby possibly introducing confounders regarding maintenance of patency rather than purely achieving successful thrombolysis, subanalysis of the ATTRACT trial reported a regained venous compressibility in 61% of the subgroup of patients with common femoral vein thrombosis and even lower rates for femoral and popliteal thrombosis.[36]

Shorter symptom duration at inclusion and the application of adjunctive procedures or stent placement following thrombolysis were the most important factors associated with successful thrombolysis. Apart from the symptom duration at inclusion, emphasizing the importance of strict patient selection and the time frame in which treatment should be initiated, no additional patient characteristics were found to indicate successful or unsuccessful thrombolysis at baseline. However, by selecting patients based on treatment success a disbalance of unidentified prognostic factors between the compared groups could have been introduced.

A remarkable finding was the high incidence of fibrotic residual venous obstructions following thrombolysis in this population of first-time IFDVT patients. It is known that repetitive mechanical endothelial microtrauma, for example, due to extravascular compression as seen in compression syndromes, evokes an inflammatory response which might result in intraluminal fibrosis and subsequent flow obstructions.[37]

One might speculate that these preexisting intravascular fibrotic changes are instrumental in the lack of spontaneous recanalization in the iliofemoral tract. These findings should be interpreted with caution as these were not based on pathological studies. In the absence of uniform treatment protocols, thrombolytic strategies vary widely between studies.[13,16,17] This lack of consensus extends into multiple aspects of this treatment modality and ranges from peri- and postinterventional treatment protocols (e.g., thrombolytic and anticoagulant regimens, agents, dosages, and devices), to monitoring of the hemostatic status (preferred measurements, its necessity, and implications for treatment), indications for adjunctive procedures, and outcomes to pursue at the postinterventional angiogram to achieve a positive long-termoutcome. Indicators for successful treatment outcomes are therefore difficult to detect.

Reasonable uniformity is reached for the diagnosis of PTS, and although the Villalta score has been criticized it is currently the preferred diagnostic score.[22,24] Therefore, to increase comparability with previous trials, we reported PTS using the definition as proposed by the consensus method of the International Society of Thrombosis and Haemostasis.[22,24]

The results of this analysis should be interpreted with caution. First of all, the CAVA trial was not designed or powered for this post hoc analysis. Furthermore, our analyses involved multiple

testing enhancing the risk of false positive findings. Although classification was performed by experienced specialists using a prespecified definition for successful thrombolysis, the interrater agreement may be considered unsatisfactory low. This may be due to the current lack of evidence regarding the influence and quantification of peri-interventional parameters (e.g., flow, degree of stenosis, etc.) on thrombolytic treatment success and long-term outcomes. Furthermore, although clear recommendations were provided, adjunctive procedures were performed at the discretion of the operating physician without a standardized documentation of the decision-making process. Despite these shortcomings, our results comparing successful and unsuccessful thrombolysis are very similar to the results found in previous studies showing an increased risk of PTS in case of a greater residual venous obstruction[1,38] and studies indicating the importance of restored patency and venous flow in preventing postthrombotic morbidity.[19,20] Furthermore, since this study had a lowloss to follow-up and a high uniformity regarding baseline characteristics and standard thrombosis management (i.e., anticoagulant therapy and compression therapy), we were well able to analyze the impact of additional thrombolysis compared with standard treatment alone.

In conclusion, this post hoc analysis of the CAVA trial did not show a significant reduction in the proportion of PTS 1 year after acute IFDVT in patients with a successful thrombolysis. However, it did result in a lower severity of postthrombotic complaints and better generic QoL. Further research is mandatory to determine the required terms of thrombolytic success, the optimal treatment strategy, and patient selection criteria.

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Chapter 8: Clinical impact of assessing thrombus age using magnetic resonance venography prior to catheter-directed thrombolysis

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Abstract

Objectives: Magnetic resonance venography (MRV) is underutilized in the evaluation of thrombus properties prior to endovascular treatment but may improve procedural outcomes. We therefore investigated the clinical impact of using a dedicated MRV scoring system to assess thrombus characteristics prior to endovascular intervention for iliofemoral deep vein thrombosis (DVT).

Methods: This is a post hoc analysis of data from the CAVA trial (Clinicaltrials.gov: NCT00970619). MRV studies of patients receiving ultrasound-accelerated catheter-directed thrombolysis (CDT) for iliofemoral DVT were reviewed. Thrombus age related imaging characteristics were scored and translated into an overall score (acute, subacute, or old). MRV scores were compared to patient-reported complaints. MRV-scored groups were compared for CDT duration and success rate.

Results: Fifty-six patients (29 men; age 50.8 ± 16.4 years) were included. Using MRV, 27 thrombi were classified acute, 17 subacute, and 12 old. Based on patient-reported complaints, 11 (91.7%) of these old thrombi would have been categorized acute or subacute, and one (3.7%) of the acute thrombi as old. Average duration of CDT to > 90% restored patency differed significantly between groups ($p < 0.0001$): average duration was 23 h for acute thromboses (range: 19–25), 43 h for subacute (range: 41–62), and 85 h for old thromboses (range: 74–96). CDT was almost eleven times more successful in thromboses characterized as acute and subacute compared to old thromboses (OR: 10.7; 95% CI 2.1–55.5).

Conclusion: A dedicated MRV scoring system can safely discriminate between acute, subacute, and old thromboses. MRV-based selection is predictive of procedural duration and success rate and can help avoid unnecessary complications.

Introduction

The growing availability of minimally invasive treatment options for deep vein thrombosis (DVT), in particular for iliofemoral DVT, has led to increased use of imaging modalities other than duplex ultrasound in DVT evaluation.[1–3] Accurate pre-interventional imaging of iliofemoral DVT requires evaluation of both abdomino-pelvic and lower extremity veins. In the abdomino-pelvic region, ultrasound is not routinely used or adequate.[4,5] Both adjunctive magnetic resonance venography (MRV) and computed tomography venography (CTV) have been shown to be feasible. However, CTV has limitations regarding intraluminal changes and beam-hardening artifacts (due to hip replacements for example) and should be avoided in young and pregnant patients. A major disadvantage of CTV is the radiation dose, which is not trivial and should be carefully considered, especially given the oftentimes younger patient population and the need for (long term) repeat examinations.[6] Magnetic resonance venography (MRV) does not require radiation or iodine contrast material and has been shown to be a good option.[7–9] MRV is not only a useful tool for assessing the presence and location of thrombi in the abdominopelvic veins, but also for detailed evaluation of thrombus properties. MRV enables

identification of several thrombus imaging characteristics.[10, 11] A previous study showed that identifying MRV-specific thrombus characteristics is not only feasible but also reproducible[12] However, identifying thrombus characteristics is only the first step in utilizing the potential of MRV. atients undergoing minimally invasive thrombus removal procedures are at increased risk of thrombolysis-related complications. Therefore, predicting the probability of CDT success prior to treatment is desirable, especially since not all treatments are successful and long-term success depends on adequate primary treatment of acute disease.[2,13,14] Being able to predict procedural success could alter preferred treatment strategies. It has previously been shown that MRV imaging characteristics are more accurate than clinical information regarding thrombus age and treatability.[15] To further understand the potential of MRV in iliofemoral DVT, we aim to investigate the relation between treatment outcome and thrombus imaging characteristics on MRV.

The aim of this study was to evaluate if pre-procedural identification of thrombus-age related MRV characteristics of iliofemoral DVT could predict treatment outcomes of catheter-directed thrombolysis (CDT).

Material and methods

Patients

This study is a post hoc analysis of the CAVAtrial (Clinicaltrials. gov: NCT00970619), an investigator-initiated, multicentre, randomized, single-blind, allocation-concealed, parallel group, superiority trial assessing the development of post-thrombotic syndrome in patients with a first time acute iliofemoral DVT and comparing additional ultrasound-accelerated CDT to standard treatment.[3] The CAVA trial enrolled 184 patients aged 18 to 85 years old, with an objectively documented first time iliofemoral deep-vein thrombosis (i.e. complete or partial thrombosis of the common femoral vein or more cranial vein segments) with acute symptoms for no longer than 14 days.

The patient complaint–based classification included pain and leg swelling as main symptoms and a more detailed analysis using the venous clinical severity score (VCSS). For the full description, we refer to the main trial publication and appendix.[3] Ninety-one of 184 patients were randomly assigned to receive additional ultrasound-accelerated CDT. Fourteen patients did not start the assigned treatment due to early withdrawal (8) or screening failures (6). Therefore, CDT was initiated in 77 patients. Patients allocated to additional ultrasound-accelerated CDT were admitted to a medium care unit at one of the six participating interventional centres, and CDT was started no later than 21 days after onset of patient reported symptoms. The intervention was terminated in case of successful treatment (defined as regained venous patency of > 90% on control angiography, performed every 24h); after 48h treatment without any change in patency on control angiography; in case of persistent fibrinogen levels < 1.8 g/L; or when the maximum duration of treatment (96 h) was reached. Major bleedings were defined as a bleeding associated with a ≥ 2 g/dL fall in haemoglobin, the need for transfusion of two

or more units of packed red blood cells or whole blood, a symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular), or contributing to the death of the patient.[16]

MRV protocols

All MRV studies of patients in the group receiving additional ultrasound-accelerated CDT of the CAVA trial were reviewed. MRV examinations were performed on clinical MRI systems, based on a master protocol of the principal trial site. The other participating hospitals adapted local scan protocols accordingly. A dedicated 12-element phased-array peripheral vascular coil with a cranio-caudal coverage of 128 cm (Philips Medical Systems) on a 1.5 T MR system (Intera; Philips Medical Systems), was used for signal reception. Patients were imaged in a supine position. An overview of detailed scan parameters is provided in Table 1.

Table 1 *Scan parameters per participating centre*

Hospital	MUMC+	Nijsmellinghe	AMC	Maasstad
Scanner	1.5T Philips Intera	1.5T Siemens Magnetom	1.5T Siemens Magnetom	1.5T Siemens Magnetom
Sequence	Ultrafast GE	T1 VIBE	T1 VIBE	T1 VIBE
Contrast	yes	yes	yes	Yes
Scan mode	3D	3D	3D	3D
Repetition time (TR) (ms)	7.8	4.73	5.9	3.2
Echo time (TE) (ms)	3.9	2.17	2.44	1.28
Flip angle (degrees)	10	10	20	10
AVG Acquisition time (TA) (min)	14:52	12:42	15:39	07:12
Bandwidth (BW) (Hz)	181.8	390	240	521
Acquisition voxel (mm)	0.95 x 0.95 x 3.00	0.91 x 0.91 x 1.80	0.8 x 0.8 x 0.8	1.0 x 1.0 x 6.00
Reconstructed voxel (mm)	0.95 x 0.95 x 1.50	0.91 x 0.91 x 1.80	0.8 x 0.8 x 2.0	0.9 x 0.9 x 1.5
Number of slices	750 (5 x 150)	768 (3 x 256)	537 (3 x 176)	864(6 x 144)
Acquisition matrix	380 x 266	230 x 256	263 x 350	400 x 313
FoV	400	490	500	400
Fat Supression	yes	yes	yes	yes
Cardiac synchronization (ECG)	yes	no	no	yes
Breath hold	no	no	no	no

Prior to contrast delivery, all patients underwent a standard 2D non-contrast enhanced balanced turbo field echo (BTFE) sequence to visualize the abdominal and pelvic veins. The latter was acquired in 2 volumes to cover the abdomen and pelvis. This was followed by injection of a bloodpool contrast agent (Gadofosveset-trisodium, Ablavar, Lantheus Medical Imaging). A fixed dose of 10 mL Gadofosveset-trisodium (0.25 mmol/mL) was administered intravenously at 1 mL/s in the median cubital vein, followed by a 20 mL saline flush injected at the same flow rate, using a remote-controlled dual head injector (Spectris; Bayer Medrad). Acquisition of the first scan volume was started 30 s after contrast administration.

A three-dimensional (3D) ultrafast gradient echo sequence with fat suppression (spectral presaturation with inversion recovery, (SPIR) was used for high-resolution imaging of the venous vasculature. Coverage of the deep vein system from the IVC to the distal popliteal vein/proximal calf veins was ensured by a coronal acquisition scheme in 3 volumes covering abdomen, pelvis, and (upper) legs, which were then stitched and reconstructed in the axial plane on the scanner. Angiography and catheter-directed thrombolysis Routinely, the deep vein system was accessed from the popliteal vein and contrast angiography was performed from the popliteal vein to the inferior caval vein. After positioning of the thrombolysis catheter in the thrombotic occlusion, thrombolytic treatment was started (T0). Control angiography was performed every 24h.[3]

Evaluation of imaging studies

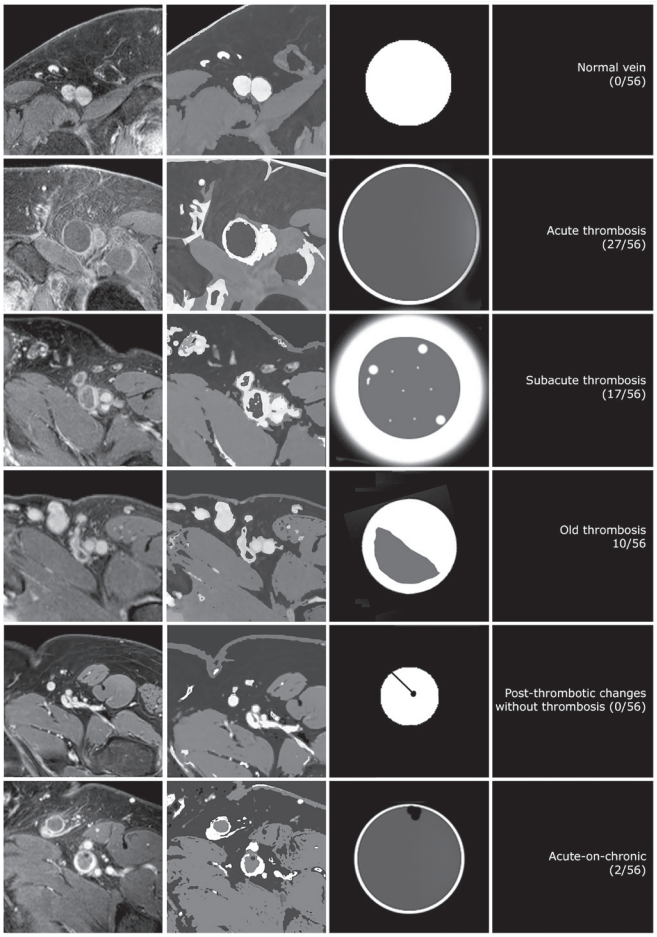
Thrombus age-related imaging characteristics were scored for the common femoral vein of the affected limb. The following items were subjectively scored: image quality, confidence of image interpretation, and thrombus characteristics. Image quality was assessed subjectively on a 5-point scale modified from Danias et al: 1 poor-quality information, nondiagnostic; 2 structures visible but with significant blurring/artifacts, diagnosis suspected but not established; 3 anatomy visible with moderate blurring/artifacts, able to establish diagnosis; 4 minimal blurring/artifacts, good-quality diagnostic information with definite diagnosis; and 5 sharply defined borders, excellent quality diagnostic information.[17, 18]

Confidence of image interpretation was scored on a scale from 1 to 4, with 1 = unsure (definite interpretation unsure), 2 = mildly confident (evaluation of major findings possible), 3 = moderately confident (definite interpretation possible), and 4 = confident (exact interpretation possible)[17–19].

Thrombus age-related imaging characteristics were based on a previously developed and validated scoring system [12], described as dilatation of the vein (increased size), hypointense signal intensity within the vein lumen, signs of recanalization, presence of wall thickening with a halo sign, or post-thrombotic scarring (Fig. 1).

Figure 1

Thrombuscharacteristics identified using MR-venography. Normal vein: homogeneously opacified hyperintense vein lumen. No luminal defect or perivascular) wall changes. Acute thrombosed vein: dilated homogeneously hypointense vein lumen with small enhancing rim of contrast depicting the vein wall. No (perivascular) wall changes (no halo sign). Subacute thrombosed vein: Still dilated low intensity vein lumen with thick enhancing rim of contrast, part vein wall thickening and part perivascular edema (halo sign). There are some small hyperintense areas within the thrombus as sign of recanalization. Old thrombosed vein: the vein lumen is reduced to a more 'normal' vein size with an opacified part (open lumen/vein wall) and a low intensity part that is still filled with thrombus-like tissue. Post-thrombotic vein: the vein lumen is smaller than the normal vein and homogeneously opacified except for 1 or more sharply demarcated very low intensity black dots and/or lines adhering to the vein wall. This represents (fibrotic) scar tissue (post-thrombotic venous scarring). Acute-on-chronic thrombosed vein: as in an acute deep vein thrombosis there is a dilated lumen with mostly hypointense material but additionally there are signs of a previous thrombotic event that has left scar tissue markings (very hypointense dots and lines)



Finally, an overall thrombus score was assigned. Interobserver agreement for the identification of thrombus characteristics based on this scoring system was previously reported to be excellent between expert radiologist (k 0.97) and good for novice radiologists (k 0.82).[12]

A dilated vein with hypointense signal intensity was assigned the overall score 'acute'. A dilated vein showing wall thickening, the halo sign, hypointense signal intensity, and signs of recanalization was scored as 'subacute'. A nondilated vein showing a (partial) hypointense signal intensity with or without signs of post-thrombotic scarring and wall thickening was labelled as 'old'. A dilated vein with hypointense signal intensity and additionally signs of postthrombotic scarring (possibly so-called acute-on-chronic characteristics) was also labelled as 'old'.

All sequences for this study were evaluated by 2 independent reviewers (CA, cardiovascular and interventional radiologist with 11 years of expertise, and RB, interventional radiologist with 7 years of expertise). The reviewers had access to source images as well as common post-processing tools (MPR/curved planar reconstruction, MIP). In patients with a DVT on both sides, whether

both sides were intervened on was left to the treating specialist's discretion. Only the most severely diseased side (clinically) was evaluated in the CAVA analysis. The reviewers were informed whether the left or right side was to be evaluated, but otherwise blinded for duplex ultrasound findings and clinical records of the patients. After independently reviewing the images, consensus was reached for all cases between the reviewers. These outcomes were used for the overall statistical analysis.

Statistical analysis

To compare outcomes for continuous variables between groups, one-way analysis of variance (ANOVA) or Kruskal-Wallis was used, as appropriate. In case of overall significant findings, pairwise comparisons were examined using Tukey post hoc adjustment or Mann-Whitney U test, as appropriate. To assess the difference in proportions, univariate analysis with logistic regression (chi-square) was used, and associated odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were calculated. Interobserver agreement was calculated using the kappa statistic.
For all analyses, a p-value of < 0.05 was considered statistically significant. The statistical analyses were performed using SPSS, version 24 (IBM corporation).

Results

Patients

Figure 2 shows the inclusion profile for this post hoc analysis of CAVA study data. Twenty-one of the 77 patients receiving additional ultrasound-accelerated CDT in the CAVA study did not undergo MRV prior to the start of the procedure due to logistic reasons and were excluded from this analysis, leaving a total of 56 patients available for inclusion.

Figure 2 *Trial profile*

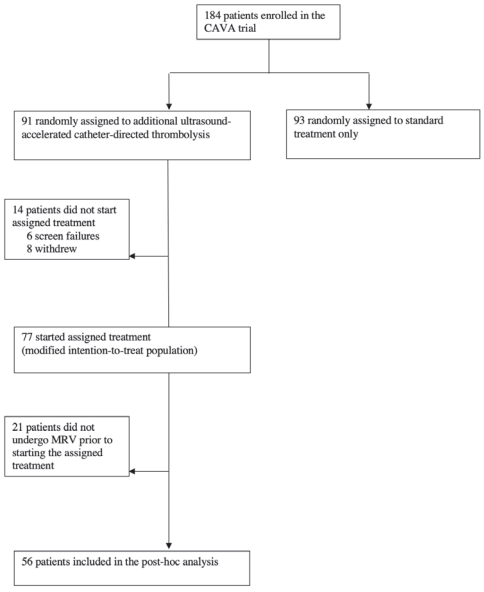


Image quality

Overall MRV image quality was rated as excellent with an average score of 4.61 ± 0.59. Confidence of image interpretation was high with an average score of 3.86 ± 0.35.

Interobserver agreement

Overall interobserver agreement was excellent with a kappa of 0.85, confirming the previously reported high level of agreement between observers.[12]

Thrombus age-related MRV-imaging characteristics

Distribution of the six thrombus age-related imaging elements in relation to the overall scores (acute, subacute, and old) is shown in Table 2. Dilated vein segments were significantly more often present in acute and subacute thrombosis. Signs of recanalization were most often present in subacute thrombosis), as was a halo sign around the vein. Partial very hypointense vein lumen was only present in old thrombosis as were all but 1 sign of post-thrombotic scarring of the vein wall.

Table 2 *Overall thrombus age in relation to imaging characteristics*

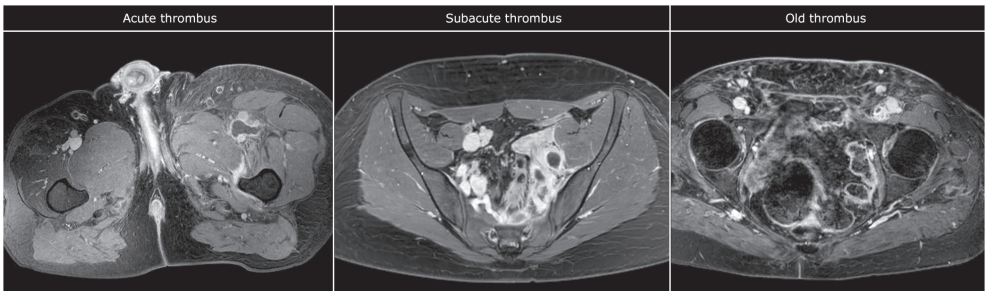
	Acute N = 27	Subacute N = 17	Old N = 12	Total N = 56
Hypointense signal intensity vein lumen	27 (100.0%)	17 (100.0%)	12 (100.0%)	56 (100.0%)
Dilated vein *	27 (100.0%)	16 (94.1&)	3 (25.0%)	46 (82.1%)
Signs of recanalization *	2 (7.4%)	17 (100.0%)	9 (75.0%)	28 (50.0%)
Thickened vein wall with halo sign around the vein *	0	17 (100.0%)	4 (33.3%)	21 (37.5%)
Partial very hypointense vein lumen *	0	0	10 (83.3%)	10 (17.9%)
Post-thrombotic scarring †	0	1 (5,9%)	4 (33.3%)	5 (8.9%)

The above table shows the scores of individual thrombus characteristics.
Data are n (%). * $p < 0.0001$, † $p = 0.007$

Overall thrombus score

Of the 56 cases evaluated, 27 were characterized as acute thrombus, 17 as subacute thrombus, and 12 as old thrombus. Examples are shown in Fig. 3.

Figure 3



Examples of variations in characteristics of iliofemoral DVT. From left to right: examples of left-sided acute common femoral, subacute iliac and old femoro-iliac thrombi as identified in the studies examined. Notice how the acute case shows a very homogenous 'clean' image with subcutaneous edema. In contrast, there is extensive perivascular edema in the subacute image and more inhomogeneous signal intensities in the old image

The old group included 3 cases with so-called mixed characteristics. They were described as showing 'acute-on-chronic' thrombosis implying a rethrombosis of the affected iliofemoral vein(s), showing both post-thrombotic scarring and dilation of a vein filled with hypointense signal.

Patient and treatment characteristics versus overall thrombus score

Table 3 shows patient and treatment characteristics stratified per thrombus-age group, as determined using MRV. The average thrombolysis time was 23 (19–25) hours for acute, 43 (41–62) hours for subacute, and 85 (74–96) hours for old thrombi ($p < 0.0001$). Thrombolysis was successful in 32 of 56 patients (57.1%) and was more often successful in combined acute and subacute thrombosis groups, with 30 of 44 (68.2%) successful interventions, than in the old group, with 2 of 12 successful interventions (16.7%) (OR = 10.71 (2.07–55.5), $p = 0.006$). Ten out of 12 thrombolysis procedures in the old thrombus group were unsuccessful, either due to premature termination or incomplete lysis at 96 h (per protocol maximum duration of thrombolytic therapy). Of the 12 thrombi categorized as old using MRV assessment,11 (91.7%) were categorized as acute or subacute based on patient-reported duration of complaints. On the other hand, one (3.7%) of the thrombi classified as acute using MRV was categorized as old based on patient-reported complaints. Treatment of the thrombus with CDT in this case (clinically 'old', MRV 'acute') was successful. Three cases of major bleeding occurred (5,4%): one in a patient with acute thrombosis, two in patients with subacute thromboses, and none in patients with old thromboses.

Table 3 *Patient characteristics per MRV-based thrombus age group*

	Acute N = 27	Subacute N = 17	Old N = 12	Total N = 56
Age, years – mean ± SD	51.7 ± 16.0	54.1 ± 17.5	44.1 ± 15.2	50.8 ± 16.4
Age, years – categories				
-< 40 years	6 (22.2%)	4 (23.5%)	4 (33.3%)	14 (25.0%)
-40-65 years	15 (55.6%)	6 (35.3%)	6 (50.0%)	27 (48.2%)
-> 65 years	6 (22.2%)	7 (41.2%)	2 (16.7%)	15 (26.8%)
Sex, Male	16 (59.3%)	8 (47.1%)	5 (41.7%)	29 (51.8%)
Affected side ⋆				
- Left †	18 (66.7%)	17(100.0%)	3 (25.0%)	38 (67.9%)
- Right †	8 (29.6%)	0	8 (66.7%)	16 (28.6%)
- Bothsided	1 (3.7%)	0	1 (8.3%)	2 (3.6%)
BMI – mean ± SD	28.1 ± 5.9	28.2 ± 3.7	29.2 ± 8.3	28.4 ± 5.9
BMI, categories				
- <25.0	9 (33.3%)	4 (23.5%)	4 (33.3%)	17 (30.4%)
- 25.0-29.9	10 (37.0%)	8 (47.1%)	5 (41.7%)	23 (41.1%)
- ≥30.0	7 (25.9%)	5 (29.4%)	3 (25.0%)	15 (26.8%)
- Unknown	1 (3.7%)	0	0	1 (1.8%)
Duration of complaints at MRV imaging, days – mean ± SD ‡	8.5 ± 4.5	9.8 ± 5.5	14.0 ± 4.2	10.1 ± 5.2
Duration between MRV and start thrombolysis, days – mean ± SD	0.96 ± 2.0	1.59 ± 2.7	1.08 ± 1.93	1.2 ± 2.2
Duration of complaints at start thrombolysis, days – mean ± SD §	9.5 ± 5.1	11.4 ± 4.9	15.1 ± 4.0	11.3 ± 5.2
Duration of complaints at start thrombolysis, categories				
- 0-7 days	9 (33.3%)	2 (11.8%)	0	11 (19.6%)
- 7-14 days	12 (44.4%)	9 (52.9%)	4 (33.3%)	25 (44.6%)
- 14-21 days ¶	4 (14.8%)	6 (35.3%)	7 (58.3%)	17 (30.4%)
- >21 days	1 (3.7%)	0	1 (8.3%)	2 (3.6%)
- Unknown	1 (3.7%)	0	0	1 (1.8%)
Successful thrombolysis §	19 (70.4%)	11 (64.7%)	2 (16.7%)	32 (57.1%)
Total time of thrombolysis, hours – mean ± SD †	23.3 ± 7.4	47.9 ± 19.3	85.3 ± 16.3	44.1 ± 27.8
Complications, Major bleeding‖	1 (3.7%)	2 (11.8%)	0	3 (5.4%)

Data are n (%) or mean (SD) ⋆ p = 0.002, † p = 0.000, ‡ p = 0.007, § p = 0.006, ¶ p = 0.026

Discussion

The results of this study show that MRV may be a useful diagnostic modality for assessing thrombus age-related characteristics prior to CDT in iliofemoral DVT. Using MRV, thromboses could be identified as acute, subacute, and old in all cases. There was a clear discrepancy between patient complaint–based classification and MRV-based classification, in particular in the old thromboses group. Moreover, MRV-estimated thrombus age was found to be associated with both the duration and success rate of the intervention. The average thrombolysis time significantly differed between MRV-based groups with favourable results (shorter thrombolysis times and higher procedural success rate) in the acute and subacute versus the old thromboses group. MRV therefore enables a pre-selection of patients who are most likely to benefit from CDT, and those for whom the better option is to withhold thrombolysis (i.e. in cases where old thrombus age predicts poor success rate). The latter patients, being exposed to the risk of thrombolytic therapy with little to no benefit regarding thrombus removal, potentially stand to gain most from this preinterventional assessment.

It is generally accepted that thrombi older than 21 days are resistant to thrombolytic therapy.[1,2] The current findings show that MRV-based thrombus age is almost eleven times more likely to be accurate than thrombus age based on patient complaints. The latter was inaccurate in 21% of cases, most of which failed to reach adequate recanalization following thrombolytic therapy. This might explain the relatively high failure rate of the CDT found in the CAVA trial.[3] Had thrombolysis been withheld in patients with a thrombus characterized as old on MRV in this series, the overall procedural success rate could have increased by 11%. No benefit concerning procedural related bleeding complications could be identified in this series, but this may be due to the limited number of adverse events in the CAVA trial. Unexpectedly, signs of a previous DVT event with remnant scarring within the femoral veins were found in three patients with acute-on-chronic thrombus characteristics. These vein wall changes are common in post-thrombotic deep vein disease but were not anticipated in patients with first-time acute DVT. Clinically, these previous thrombotic events were asymptomatic and had not been identified during patient intake, emphasizing the need for a better diagnostic work-up before proceeding to CDT.

There is an evolution of the thrombus characteristics over time and these characteristics are clearly distinctive. However, there are gradual changes when the thrombus evolves from the acute to the subacute and later old phase in iliofemoral DVT cases: in addition to the well-defined criteria of the described scoring system, the presence and extent of not only perivascular but also subcutaneous edema were observed. In the acute phase, the latter can be very extensive. In the subacute phase, edema was still present but tended to organize more around the vein (wall) as perivascular edema. In the old phase, the (visible) edema was mostly resolved. While the confidence of image interpretation with the imaging features studied was already excellent, assessment of subcutaneous edema could potentially be an additional visual aid for radiologists starting to assign a thrombus score in daily practice. Extensive venous

collateralization is generally a sign of a more chronic venous occlusive state, and should not be present in acute DVT.[19] It was not observed in any of the cases in this study.

However, there are some limitations to this study. First, this is a post hoc analysis with a small sample size. However, distinctions between the three categories of MVR-based thrombus age are clear and associations with clinical outcomes strong. A second limitation is that the MRV scan protocol for the CAVA trial included the bloodpool contrast agent gadofosveset-trisodium, the use of which is no longer current daily practice. Studies have shown the benefits of using a standard extracellular gadolinium agent.[20,21] The bloodpool contrast agent can be substituted with a standard extracellular gadolinium agent containing gadobutrol (Gadovist, Bayer HealthCare) without loss of image quality or diagnostic value. This standard agent is now routinely administered in our practice and has replaced bloodpool contrast agents for MRV.[22] Third, although widely used, patient-reported complaints are not a robust indicator for exact thrombus age[15]; in fact, a partial thrombosis may last for a prolonged period of time before becoming occlusive and therefore symptomatic.[23] In this study, MRV was shown to provide a more objective and robust indication for thrombus age than patient-reported complaints. Fourth, CDT was not successful in all acute thromboses and ultimate success of reperfusion therapy may not rely solely on adequate assessment of thrombus age. Other patient characteristics and properties of the thrombus which influence clot resolution may be important additional determinants. For example, differences in endogenous clot lysis due to individual patient variation in clot structures influence turbidity and permeation and are independent of thrombus age.[24]

In conclusion, thrombus aging based on MRV imaging enables preprocedural selection of patients with iliofemoral DVT most likely to undergo successful CDT, as well as those most likely to be resistant to thrombolytic therapy. This helps to avoid unnecessary risk associated with unsuccessful catheter-directed thrombolysis and extensive treatment duration.

In view of these results, magnetic resonance venography should be considered a prerequisite for patients opting to undergo catheter-directed thrombolysis for iliofemoral deep vein thrombosis.

Summary statement

Pre-interventional magnetic resonance venography–based assessment of thrombus age in patients with iliofemoral deep vein thrombosis can identify patients most likely to undergo successful catheter-directed thrombolysis and may thus prevent unnecessary catheter-directed thrombolysis-related complications.

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Part III:

Summary, general discussion, impact

Chapter 9: Summary and general discussion

Deep vein thrombosis (DVT) has a considerable societal impact.[1,2] Preventive measures are essential, but for those affected by the disease we need to optimize strategies to ensure early diagnosis and invest in treatment algorithms that preserve QoL.[3,4] In addition to extensive iliofemoral deep vein thrombosis being a risk factor for post-thrombotic syndrome, it is also most difficult to accurately analyze with routine duplex ultrasound (DUS) imaging. Furthermore, the current obesity pandemic hampers DUS imaging and can further complicate early and correct diagnosis. These factors pose a challenge to improve diagnostic and therapeutic efforts.[5]

As outlined in the introduction, the results presented in this thesis can be divided into 2 parts. The first part focusses on providing (imaging) tools to improve the added value and accessibility of imaging, specifically magnetic resonance venography (MRV). The following questions are posed and answered:

- How can we improve reporting standards for deep vein thrombosis (chapter 2).
- Can we evaluate specific thrombus imaging characteristics to estimate clot age and does this affect treatment outcome (chapter 3).
- How can diagnostic work up be improved using MRV, and how can MRV be made more accessible to non-academic hospitals for standard assessment of iliofemoral deep vein thrombosis (chapter 4).
- Can using MRV improve patient selection for ultrasound-assisted catheter-directed thrombolysis in patients with iliofemoral deep vein thrombosis (**chapter 5**).

The second part of this thesis describes the results of the Dutch CAVA trial, which was the third randomized controlled trial that specifically focused on the added value of ultrasound-assisted catheter-directed thrombolysis for the prevention of post-thrombotic syndrome in acute iliofemoral deep vein thrombosis.[6] There is a particular focus on how imaging and minimal invasive interventions can affect treating deep vein thrombosis in clinical practice:

- When treating iliofemoral deep vein thrombosis, does the addition of ultrasound-assisted catheter-directed thrombolysis prevent or reduce the risk of developing post-thrombotic syndrome (chapter 6).
- How does technical success of ultrasound-assisted catheter-directed thrombolysis and adjunctive interventions (e.g., iliac vein stenting) affect outcome regarding post-thrombotic syndrome (chapter 7).
- Does assessment of specific thrombus imaging characteristics on pre-interventional MR imaging allow for more accurate patient selection (chapter 8).

Part 1

In **chapter 2** we discuss the need for a classification that helps to identify patients with deep vein thrombosis potentially requiring additional interventional treatment based on thrombus location. Numerous, mostly observational studies have reported on the outcome after 'proximal' or 'distal' deep vein thrombosis. However, proximal and distal are adjectives used liberally without a clear underlying definition on when exactly a thrombus is considered proximal or distal, complicating comparison of results between studies.

The 'open vein hypothesis' was formulated as a concept postulating that aggressive early thrombus removal and restoration of vein patency prevents the development of post-thrombotic syndrome.[7] An indwelling thrombus induces vein wall injury and may lead to chronic vein wall changes beyond repair if venous patency and flow are not restored as soon as possible.[8]

An important risk factor for suboptimal outcomes of anticoagulant therapy is the location of the thrombus: in the larger deep veins in pelvis and groin (e.g. common femoral vein, iliac veins and inferior caval vein) patients tend to develop more and more severe post-thrombotic syndrome.[9] By correctly identifying patients with iliofemoral deep vein thrombosis (defined as 'proximal') compared to femoropopliteal (defined as 'distal') the effects and outcomes of any treatment algorithm chosen for either group can be compared more accurately. This particularly holds true for a comparison between study populations as often these deep vein thrombosis 'entities', 'proximal' and 'distal' are not treated differently. Additionally, one could argue that any (positive or negative) outcome effect of more invasive treatment algorithms might be underestimated by analysing proximal and distal deep vein thrombosis as one entity. Since dividing lower extremity deep vein thrombosis in 2 entities might still limit analysis, the lower extremity thrombosis (LET) classification was proposed as a comprehensible reporting standard distinguishing four different levels of thrombosis: calf vein, upper leg, groin and pelvis, and inferior caval vein thrombosis. In a study by Strijkers et al. using the LET classification for a deep vein thrombosis subgroup analysis was shown to be feasible.[10] Additionally, part of the hypothesis on which the LET classification is based, i.e., more extensive deep vein thrombosis and iliofemoral involvement resulting in a higher LET classification, was shown to be indicative of developing more severe post-thrombotic syndrome (PTS). Nevertheless, we have to keep in mind that, while the LET classification focusses on the larger, more central veins as being a potential major discriminating factor for PTS development, the big picture is far more complex. Disease state definitions can have an important impact on the interpretation of treatment effectiveness. Our imaging-based test alone is most likely not sufficient to define the disease.

The study of PTS is complex and has to rely on the currently available scoring systems. The Villalta score assesses severity of PTS, documents change in severity over time and has a good interobserver reliability. Limitations are however its subjective nature and diagnostic accuracy.[11,12] In recent years, patient-reported outcomes have become more important and, if widely adopted, can potentially contribute more to comparisons across different trials. The aim

of the LET classification to compare deep vein thrombosis patients more accurately between trials based on the anatomical distribution of thrombi in the lower extremities remains valid and could still be a valuable contribution to interpreting the bigger picture.

To accurately evaluate the location and extend of the thrombus in acute deep vein thrombosis is not always easy. In particular in more extensive thromboses, or when only standard ultrasound evaluation protocols are used, reporting limitations occur.[13] Multiple studies have reported on the added value of MRI and CT specifically in those cases.[14-18] Furthermore, evidence emerged that it was possible to distinguish acute from chronic thrombus material using magnetic resonance direct thrombus imaging.[19,20] Our contrast enhanced magnetic resonance venography protocol combined with the initial experience published by Spritzer et al., allowed for an evaluation of imaging characteristics that might be of value in interpreting thrombus image evolution in acute deep vein thrombosis.[21] In **chapter 3** we report our thrombus image interpretation concept and the feasibility of such an interpretation. As outlined in the previous paragraph, in deep vein thrombosis, restoring flow and patency of the vein is considered vital. The sooner treatment is started, and flow is restored, the less thrombus organization and vein wall remodeling potentially has occurred. Experts in the field regard thrombus that has developed less than two weeks ago as acute, up to three weeks as subacute, and persisting for more than three weeks as chronic or 'old'.[22] Susceptibility to thrombolytic agents diminishes as the thrombus organizes and the vein wall remodels and develops more chronic changes.[23] Long-term follow up after catheter-directed thrombolysis in the series of Baekgaard et al. has shown functional veins without reflux in up to 82% of patients treated.[24] One of the strict inclusion criteria was a patient reported duration of complaints < 14 days. It is however not optimal to have to depend on a patient reported duration of complaints to estimate thrombus age or suitability for invasive treatment as a patient's perception or memory of the onset of complaints can be inaccurate. The question was whether we could improve on this by using thrombus imaging characteristics identified on our magnetic resonance venography examinations to virtually age thrombus in a more objective and standardized way. The results in chapter 3 show that it is feasible to identify specific imaging characteristics of thrombus and vein wall changes in MRV studies with good to excellent interobserver agreement.[25] Key findings were the fact that it could be applied on all MRV studies and that the imaging thrombus age score in each patient seemed to have a distribution comparable, though not exactly equal, to that of patient reported duration of complaints. Some patients would be labelled as acute deep vein thrombosis based on imaging information but reported a relative long duration of complaints and vice versa. Unfortunately, there was no true gold standard to compare the results too, such as for example in vivo thrombus samples. Nevertheless, the outcome of this study has served as a base to further investigate the consequences of these image findings regarding the treatment of iliofemoral deep vein thrombosis.

In **chapter 5** we further discuss the importance of taking into account thrombus age when treating iliofemoral deep vein thrombosis with catheter-directed thrombolysis. We demonstrated that both duration of complaints as a measure to 'age thrombus' and specific thrombus MRV imaging characteristics could be predictive for treatment outcome. It is important to note that there were specific differences between the analysis of patient reported duration of complaints and MRV imaging characteristics. Patient reported duration of complaints as evaluated in this study was compared to long term outcome (patency, no reflux) with a median of 5 years. The imaging data focused on providing proof of concept and were correlated to short term outcome (duration of and success rate of catheter-directed thrombolysis). Interestingly, specific differences between patient reported duration of complaints and the MRV analysis indicated that patient reported duration of complaints was important in particular for the long-term outcome, but for short term outcomes MRV analysis provided an edge for patient selection. Thus there could additional value to combining both evaluations in future to further improve patient selection and outcome.

Several studies have shown that the use of blood pool agents is favourable, due to a long steady state imaging window for high-resolution acquisition of the entire deep venous system in the lower extremities, allowing for detailed depiction of the entire venous system and (intra)luminal changes.[26-28] Unfortunately, in 2011 the most frequently used contrast agent for magnetic resonance venography, named Ablavar ® (Gadofosveset-trisodium, Lantheus Medical), was taken off the market in Europe. It is important to mention that this was a marketing decision, not a flaw in the contrast agent itself or complications after administering it. The implications were nevertheless clear and urged us to revisit our contrast enhanced approach to magnetic resonance venography. **Chapter 4** presents our comparison of two contrast agents, a regular gadolinium-based agent gadobutrol (Gadovist, Bayer HealthCare) and Gadofosveset-trisodium. Furthermore, we evaluated 3 separate imaging protocols including a non-contrast enhanced protocol, which resulted in 3 important study outcomes. First, we found that the use of a contrast agent was superior to a non-contrast enhanced protocol for evaluation of the deep venous system. Second, gadobutrol was found to be able to replace Ablavar without decline in image quality or interpretation. Third, by updating our scan protocol and applying new, now generally available, fat suppression techniques, we were able to significantly reduce the required scan time, making MRV even more accessible.

Part 2

In November 2019, results of the CAVA randomized controlled trial, evaluating the value of adding catheter-directed thrombolysis to standard anticoagulation therapy for iliofemoral deep vein thrombosis, were published (**chapter 6**).[8] The rationale for selecting iliofemoral deep vein thrombosis patients specifically was that spontaneous recanalization in these patients is less likely, hence the potential benefit of thrombolysis might outweigh bleeding risks associated with

catheter-directed thrombolysis. Results after one-year follow-up did not show a significant difference in proportions with post-thrombotic syndrome between the two study groups: 29% in the ultrasound accelerated catheter-directed thrombolysis (UA-CDT) group versus 35% in the standard treatment group. Treatment of underlying deep vein stenosis, however, was more actively executed with 76% in the CAVA trial, compared to 28% in the ATTRACT trial, and 16% in the CaVenT trial.[29,30] These higher numbers were closer to expectations of the experts in the field but did not result in a reduction in post-thrombotic syndrome at one-year follow-up. Furthermore, there was a low inclusion rate and the number of cases treated by each specialist team was limited which could have affected the (long-term) outcome as was reported before.[31]
Taking the above points into consideration a post hoc analysis of the CAVA trial was performed (**chapter 7**) to look specifically at those patients in which the treatment (ultrasound accelerated catheter-directed thrombolysis) was technically successful. Again, the proportion of post-thrombotic syndrome at one year, the primary endpoint of the CAVA-trial, did not differ significantly between the catheter-directed thrombolysis group and control group. There was, however, a lower severity of post thrombotic complaints and the generic QoL was higher. This finding stresses the importance of accurate evaluation of eligible patients prior to treatment selection, ideally non-invasive as described in **chapter 5**.

Most patients develop PTS within the first two years following the initial deep vein thrombosis diagnosis. There is however a steady increase in incidence reported over 10 to 20 years after the event.[32] The earlier trial by Plate et al. that evaluated open venous thrombectomy and the CaVent-trial, suggested that there could be benefits to restoring unimpeded venous flow, showing a reduction of up to 28% in PTS incidence. [33] It is important to note, when comparing these results to the ATTRACT- and CAVA-trials, that the most compelling data emerged at five-year follow-up. [34] The ATTRACT-trial was published in 2017 with an endpoint of two-year follow-up and the CAVA-trial was published in 2020 with one-year follow-up.[7,8] Taking this into account, one- and two-year follow-up might be too short to measure the full effects of additional treatments. Notten et al. published additional long-term follow-up results for the CAVA-trial.[35] In this analysis, 120 patients (79,8%) of the total CAVA-trial study population participated in a final follow-up visit, 62 patients from the intervention group (52%). The median follow-up was 39 months (interquartile range 23,3-63,8 months). PTS developed in 19 (30,6%) in the intervention group versus 26 (44,8%) in the standard treatment group. Using the International Society on Thrombosis and Haemostasis consensus definition (Villalta score $\geq$ 5 or venous ulceration at 6-month assessment or later) the absolute reduction was 22.2%. Although this study was limited by its sample size, the overall findings indicate a reduction of (mild) PTS without impact on quality of life. This strengthens the concept that the impact of ultrasound-accelerated catheter-directed thrombolysis on the prevention of PTS increases with time and future studies should consider a longer follow-up to evaluate the definitive outcome.

In the observational studies, involvement of the iliofemoral veins was identified as a risk factor for PTS.[3] In the CAVA-trial we incorporated a more precise identification of proximal (iliofemoral) deep vein thrombosis, not only analyzed with DUS, but also confirmed with MRV. The goal was to be more precise in selecting patients, since an iliofemoral deep vein segment specifically needed to be involved. The results however, are inconclusive; no significant overall reduction in PTS at one-year follow-up was shown. However, as outlined in the previous paragraph, longer term follow up did indicate a reduction in PTS. Furthermore, a subgroup analysis of the ATTRACT-trial focusing on patients with specific iliofemoral vein involvement comparing pharmaco-mechanical thrombolysis to standard treatment did show a difference in patients with moderate to severe PTS (Villalta score >9 or ulcer) and severe PTS (Villalta >14 or ulcer).[36] PTS was 18% versus 28% in the moderate to severe group, and 8,7% versus 15% in the severe group, both in favor of pharmacomechanical catheter-directed thrombolysis (PCDT). When the venous clinical severity score (VCSS) was used as primary outcome measure the difference was 6,6% versus 14% in favor of PCDT. This subgroup analysis combined with the long-term follow up results of the CAVA-trial suggests that there might still be merit to the observational concept of iliofemoral involvement, thus in future trials, involvement of these deep vein segments should be taken into account.

In order to achieve better outcomes following thrombolysis, optimization of the treatment strategy and better selection criteria for eligible patients are essential. Ideally those patients that are to benefit most from the proposed treatment are to be selected. In particular for catheter-directed thrombolysis and its associated bleeding risk, being able to improve on selection prior to treatment can greatly benefit patients and outcomes. C**hapter 8** details the results of our study on the potential for a MRV imaging-based thrombus-aging system to aid selecting iliofemoral deep vein thrombosis patients eligible for catheter-directed thrombolysis. Imaging thrombus assessment could also be used to identify those most likely to be resistant to thrombolytic therapy. The study has shown that there is merit to this concept. Using MRV thrombus characteristics, thrombi could be identified as acute, sub-acute and old. Moreover, MRV-estimated thrombus age was found to be associated with both duration and success rate of the intervention, as was shown in the significant difference between average thrombolysis time in the MRV-based groups: 23 (19–25) hours for acute, 43 (41–62) hours for subacute, and 85 (74–96) hours for old thrombi ($p < 0.0001$). This would help to avoid (unnecessary) risks associated with unsuccessful catheter-directed thrombolysis: an extensive treatment duration and complications such as bleeding. In view of the results, MRV should be considered a prerequisite for patients potentially eligible for catheter-directed thrombolysis for iliofemoral deep vein thrombosis.

Daily practice in the experienced centers has evolved from (strictly) catheter-directed thrombolysis to more aggressive mechanical thrombectomy, including rheolytic thrombectomy as used in the ATTRACT-trial and various aspiration catheters and pump-assisted aspiration

systems. These approaches might change the selection criteria and eligibility of patients for minimally invasive thrombus removal. Whether using our image-based thrombus assessment could be an aid in these treatment options is yet to be investigated. Furthermore, we do not know if more aggressive, mechanical approaches affect the vein wall and valves. The damage to the vein wall and valves, the concept of early thrombus removal intends to prevent, could very well be induced by these more aggressive techniques for thrombus removal. [37,38]

Future research

As outlined in the introduction, there are two processes hypothesized to cause venous hypertension which leads to PTS which are part of the foundation of the research in this thesis. The first is obstruction of deep venous flow by persistent residual thrombus. The second is the conversion of a compliant vein to a stiff fibrotic vein with afunctional valves. [33,39]

With regard to the first process, obstruction of deep venous flow, elaborating on the studies in this thesis, and taking the open vein hypothesis into account, research should continue to investigate the potential for early resolution of thrombus to reduce post-thrombotic syndrome. The CAVA subgroup analysis data presented in this thesis indicates that further improving patient selection could be paramount. Hence research to achieve further optimization of patient selection, supported by dedicated imaging techniques to evaluate (residual) thrombus should be a focus. For example, the long-term evolution of deep vein (wall) changes after DVT, including remnant sequalae or scars, could be analyzed with sequential MR imaging to map both acute and chronic changes in great detail, in order to further unravel their relationship with post-thrombotic syndrome.

From an interventional radiologist point of view, it would be interesting to investigate the evolution of thrombosis in vivo versus the corresponding imaging characteristics in more detail. If MRV could provide insights into the timing of and development of vein damage based on imaging characteristics, this could be taken into account when considering (additional) treatment options. One could hypothesize that, early on in the process of deep vein thrombosis, a more careful approach and technique might be preferred to prevent any (iatrogenic) damage to the veins whilst supporting rapid clot lysis. If, however the disease has progressed to a point where vein damage is already present, more aggressive approaches aimed at maximal lumen gain might be more appropriate. A threshold would have to be established for the MRV analysis, for which our MRV thrombus score could be the starting point.

Besides optimization of patient selection, improvement of thrombus removal techniques should be part of the research agenda as these two factors are vital for both technical and clinical success. Prevention of post-thrombotic syndrome was the most important outcome in all deep vein thrombosis intervention trials up till now. However, additional outcomes such as the impact of the disease on patients' QoL are important and should be given more emphasis and might even be included as primary endpoint in future trials.

Finally, clinical experience shows it is vital to improve on post-interventional treatment strategies to better maintain gained treatment results.

The greatest challenge for imaging research may be the secondary process of fibrosis and valvular dysfunction. To date no new techniques have been established or investigated to evaluate smaller, more distal (calf) veins which might be of importance in the development of post-thrombotic syndrome. The question remains whether restoration of (proximal) outflow is vital enough to prevent post-thrombotic syndrome when distal damage has already occurred or cannot be prevented by current medicinal or catheter interventions.
In view of the current incorporation of artificial intelligence and machine learning into radiology systems, there are opportunities for looking at imaging information in new ways. Instead of the more traditional slice-by-slice, the total imaged volume could be analyzed in both qualitative and quantitative ways, contributing to the overall picture rather than just the affected deep vein(s). For example, imaging based venous flow and/or pressure measurements which have been shown to be valuable when analyzed invasively,[40] or imaging-based quantification of leg oedema could be incorporated.
The evolution from (lack of) thrombus resolution to vein wall fibrosis might not be as directly linked as we anticipated. There are studies that suggest that these processes occur independently. [34,35] While the central veins might require (minimally invasive) interventional treatment, a biological agent that modulates the vein wall response to thrombosis, with or without concurrent thrombus removal, would represent a potential major advancement in PTS prevention.
Finally, the high morbidity burden mandates researchers to continue exploring both interventional and noninterventional strategies to improve patient quality of life following acute deep vein thrombosis.

In conclusion, the work presented in this thesis shows that whilst available data available on catheter-directed thrombolysis for the prevention of post-thrombotic syndrome in iliofemoral deep vein thrombosis has greatly increased, this has not led to a definitive conclusion on the usefulness of this intervention.
In this thesis, the focus lies on improvement after minimally invasive treatment, measured as reduction in PTS, but the overall high risk of developing PTS after acute deep vein thrombosis regardless of treatment is a concern for all deep vein thrombosis patients and mandates further research.

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Chapter 10: Impact paragraph

In this chapter, the relevance and the socio-economic, clinical and scientific impact of the research described in this thesis is discussed. The research in this thesis was performed over the course of the past decade. Our knowledge and understanding of deep venous system imaging interpretation have expanded with each year and each chapter of this thesis. After completion of the CAVA trial the full scope of our magnetic resonance venography (MRV) approach became clear, in particular how it could affect clinical management of (acute) deep vein thrombosis. At the same time it may be that, even after a decade of evolution in our views and interpretations, we have only 'scratched the surface' of imaging deep venous disease.

Socio-Economic impact

As it stands, evaluation of lower extremity deep vein thrombosis with duplex ultrasound (DUS) provides a good medical imaging tool to support an optimized referral pathway. Based on current criteria and guidelines the outcome of a diagnostic DUS generally leads to correct referral for patients. We should however not underestimate the current socio-economic impact of deep vein thrombosis with its associated high morbidity and long-term complications, which not only affect patient QoL but also impose a financial burden on society. This holds true in particular for the development of post-thrombotic syndrome (PTS) after acute deep vein thrombosis. PTS is a complication that occurs in 40% to 60% of deep vein thrombosis patients when treated according to the current guidelines.[1,2] It has serious negative implications for the quality of life and contributes to rising healthcare costs.[3,4] In view of these facts, developing and implementing more advanced (non-invasive) imaging tools like MRV provides an opportunity to ensure an early and more precise diagnosis, essential for treatment success and prevention of (long-term) complications. In this thesis we have shown that, for patients with extensive iliofemoral deep vein thrombosis, MRV can provide additional imaging information to help guide an optimized treatment plan, which potentially reduces therapy associated risks and costs since invasive treatment can be applied in those with potential high yield and avoided in those with expected low yield.

Clinical impact

Deep venous thrombosis is a complex disease in which the main contribution of imaging is and has been the evaluation of the presence or absence of a deep vein thrombosis. Most efforts have been invested in supporting the treatment of deep vein thrombosis with anticoagulant therapies.[5,6]

With the publication of the first successful studies on minimally invasive, catheter-directed thrombolysis (CDT) for deep vein thrombosis between 1995 and 2000 a renewed interest in thrombolysis as treatment option for deep vein thrombosis was created.[7,8] The first randomized

controlled trial, the CaVent study, underlined the potential of catheter directed thrombolysis for the prevention of the post-thrombotic syndrome.[9] However, this trial and consequent trials did not deliver on this promise.[10,11] It was argued that adequate patient selection could be an important contributor to success of the intervention. Furthermore, it was argued that CDT in addition to anticoagulation was only the starting point of the treatment. Without treating any underlying obstruction, the potential benefits regarding outcome will be suboptimal. The aim of the CAVA-trial was to focus on evaluating and treating iliofemoral deep vein thrombosis. At that time, experts considered duplex ultrasound and venography the only established imaging modalities for deep vein thrombosis. We included MRV in our evaluation of patients suspected of iliofemoral deep vein thrombosis which contributed to the awareness of underlying deep venous disease (deep vein stenosis and / or chronic obstruction) as an important factor for (long-term) clinical success. More importantly we developed an imaging assessment technique that allows for virtual thrombus aging based on imaging alone, providing a prognostic tool for CDT success or failure. This technique proved to yield a clinically relevant parameter which can be used by clinicians to decide when (not) to opt for CDT, minimizing unnecessary patient exposure to the risks of CDT. Additionally virtual thrombus aging reinforced the concept of treating (iliofemoral) deep vein thrombosis as soon as possible since this ensures the shortest required thrombolysis time.

Current medical practice shows that patient selection and treatment is relying more and more on medical imaging information. Our MRV protocol will enable radiologists to better consult their clinicians in selecting patients eligible for venous interventions. Our MRV protocol can thus help the selection process and treatment of deep vein thrombosis patients and benefits patients directly.

Scientific impact

Deep vein thrombosis is a relatively common disease, both spontaneous and after surgery.[12] Identifying deep vein thrombosis early is of great importance in improving outcomes for patients by preventing pulmonary emboli, extension of deep vein thrombosis and reduce long-term risks such as PTS.[13-15] In this thesis we have shown that we could improve outcomes by adding MRV to the diagnostic algorithm for patients with iliofemoral deep vein thrombosis, and that MRV can help guide therapy choices by interpreting imaging characteristics of thrombus. This information is useful for both clinicians and researchers as it represents 'a piece of the puzzle' for the explanation of the (lack of) long term success in treating deep vein thrombosis with CDT. Completely unraveling the pathophysiology of DVT might be out of reach, but medical imaging can contribute to the evaluation of treatment strategies for deep vein thrombosis patients. Introducing MRV as part of the routine assessment of (extensive) iliofemoral deep vein thrombosis currently has limited clinical applications. We managed to present an MRV image interpretation technique useful as a non-invasive diagnostic tool to assess virtual thrombus morphology, thereby creating the possibility of future MR imaging

research on imaging-based deep vein thrombosis assessment and treatment. As outlined in the discussion, a potential research application would be detailed analysis of MR imaging features in the acute phase coupled with histological clot analysis.

MRV has long been considered inaccessible or highly complex and reserved for academic specialty centers only. In this thesis we demonstrated the potential of performing MRV on a mainstream 1.5T MRI machine, with an acceptable exam duration, utilizing a regular gadolinium-based contrast agent. Both the reduction in acquisition time and the alternative for more complex contrast agents deemed mandatory in the past (and now virtually unobtainable) improved accessibility and utilization of MRV for deep vein thrombosis. With less requirements, more sites can participate in both research and clinical utilization of MRV.
There is a rapid expansion of new minimally invasive treatment options for thrombus removal. When to use these techniques or how pre-interventional imaging can guide (technical) treatment choices has yet to be established. The virtual thrombus aging imaging technique described in this thesis could already be used to evaluate the use of pharmaco-mechanical and strictly mechanical thrombectomy devices which have been introduced in recent years.

This thesis shows that there is potential to improve on the imaging work up in deep vein thrombosis patients by performing MRV, when considering treating these patients with minimally invasive techniques, such as catheter-directed thrombolysis and/or stent placement. Current data do not support routine implementation of catheter directed thrombolysis in clinical care. However, the expectation is that there is room for improvement and better results might be achieved by better patient selection, better device selection and more supportive treatment after initial care, so that long-term risks of minimally invasive thrombolysis and/or thrombectomy will ultimately outweigh the gains.

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Appendices

Nederlandse samenvatting

Diep veneuze trombose (DVT) heeft een aanzienlijke maatschappelijke impact.[1,2] Preventieve maatregelen zijn essentieel, maar voor degenen die door de ziekte worden getroffen, moeten we strategieën optimaliseren om vroege diagnose te waarborgen en te investeren in behandelalgoritmen die de kwaliteit van leven behouden.[3,4] Naast uitgebreide iliofemorale diepe veneuze trombose als een risicofactor voor post-trombotisch syndroom, is het ook het moeilijkst om nauwkeurig te analyseren met routinematige duplex-echografie (DUS) beeldvorming. Bovendien belemmert de huidige obesitasepidemie DUS-beeldvorming en kan deze de vroege en juiste diagnose verder compliceren. Deze factoren vormen een uitdaging om diagnostische en therapeutische inspanningen te verbeteren.[5]
Zoals beschreven in de inleiding, kunnen de resultaten gepresenteerd in deze scriptie worden onderverdeeld in 2 delen. Het eerste deel richt zich op het verstrekken van (beeldvormings) tools om de toegevoegde waarde en toegankelijkheid van beeldvorming, specifiek magnetische resonantie-venografie (MRV), te verbeteren. De volgende vragen worden gesteld en beantwoord:

- Hoe kunnen we rapportagestandaarden voor diepe veneuze trombose verbeteren (**hoofdstuk 2**).
- Kunnen we specifieke beeldkenmerken van trombus evalueren om de leeftijd van de stolsel te schatten en heeft dit invloed op de behandelingsuitkomst (**hoofdstuk 3**).
- Hoe kan de diagnostische werkzaamheid worden verbeterd met behulp van MRV en hoe kan MRV toegankelijker worden gemaakt voor niet-academische ziekenhuizen voor standaardbeoordeling van iliofemorale diepe veneuze trombose (**hoofdstuk 4**).
- Kan het gebruik van MRV de patiëntenselectie verbeteren voor echo-geaccelereerde kathetergerichte trombolyse bij patiënten met iliofemorale diepe veneuze trombose (**hoofdstuk 5**).

Het tweede deel van deze scriptie beschrijft de resultaten van de Nederlandse CAVA-studie, die de derde gerandomiseerde gecontroleerde studie was die specifiek gericht was op de toegevoegde waarde van echogeleide kathetergerichte trombolyse voor de preventie van post-trombotisch syndroom bij acute iliofemorale diepe veneuze trombose.[6] Er is bijzondere aandacht voor hoe beeldvorming en minimaal invasieve interventies van invloed kunnen zijn op de behandeling van diepe veneuze trombose in de klinische praktijk:

- Bij de behandeling van iliofemorale diepe veneuze trombose, voorkomt of vermindert de toevoeging van echo-geaccelereerde kathetergerichte trombolyse het risico op het ontwikkelen van post-trombotisch syndroom (hoofdstuk 6).
- Hoe beïnvloedt technisch succes van echo-geaccelereerde kathetergerichte trombolyse en aanvullende interventies (zoals iliacale veneuze stenting) de uitkomst met betrekking tot post-trombotisch syndroom (hoofdstuk 7).

- Leidt de beoordeling van specifieke beeldkenmerken van de trombus op pre-interventionele MR-beeldvorming tot een meer nauwkeurige selectie van patiënten (hoofdstuk 8).

Deel 1

In **hoofdstuk 2** bespreken we de noodzaak van een classificatie die helpt bij het identificeren van patiënten met diepe veneuze trombose die mogelijk extra interventionele behandeling nodig hebben op basis van de locatie van de trombus. Talloze, voornamelijk observationele studies hebben gerapporteerd over de uitkomst na 'proximale' of 'distale' diepe veneuze trombose. Echter, proximaal en distaal zijn bijvoeglijke naamwoorden die vrijelijk worden gebruikt zonder een duidelijke onderliggende definitie wanneer een trombus precies als proximaal of distaal wordt beschouwd, wat vergelijking van resultaten tussen studies bemoeilijkt.

De 'open ader-hypothese' werd geformuleerd als een concept dat postuleert dat agressieve vroege verwijdering van de trombus en het herstel van de ader doorgankelijkheid het ontwikkelen van post-trombotisch syndroom voorkomt.[7] Een aanwezige trombus veroorzaakt letsel aan de aderwand en kan leiden tot chronische veranderingen in de aderwand die niet meer kunnen worden hersteld als veneuze doorgankelijkheid en doorstroming niet zo snel mogelijk worden hersteld.[8]

Een belangrijke risicofactor voor suboptimale resultaten van anticoagulantia is de locatie van de trombus: bij een trombose in de grotere diepe aderen in het bekken en de lies (bijv. de gemeenschappelijke femorale ader, iliaca-aderen en inferieure vena cava) ontwikkelen patiënten nadien vaker een ernstiger post-trombotisch syndroom.[9] Door patiënten met zo een iliofemorale diepe veneuze trombose (gedefinieerd als 'proximaal') te identificeren in vergelijking met femoropopliteale (gedefinieerd als 'distaal') kunnen de effecten en uitkomsten van elk gekozen behandelschema voor beide groepen nauwkeuriger worden vergeleken. Dit geldt met name voor een vergelijking tussen onderzoekspopulaties, omdat deze diep veneuze trombose 'entiteiten', 'proximaal' en 'distaal', vaak niet verschillend worden behandeld. Bovendien kan men stellen dat elk (positief of negatief) effect op uitkomst van meer invasieve behandelingsmethoden onderschat kan worden door proximale en distale diepe veneuze trombose als één entiteit te analyseren in de wetenschap dat de uitkomsten van de huidige behandelingen tussen deze twee groepen al verschillend zijn. Aangezien het verdelen van diepe veneuze trombose in twee entiteiten nog steeds de analyse kan beperken, werd de classificatie voor diepe veneuze trombose in het onderbeen (LET-classificatie) voorgesteld als een begrijpelijke rapportagestandaard die vier verschillende niveaus van trombose onderscheidt: kuitader, bovenbeen, lies en bekken en inferieure vena cava trombose. In een studie door Strijkers et al. bleek het gebruik van de LET-classificatie voor een subgroepanalyse van diepe veneuze trombose haalbaar te zijn.[10]

Bovendien werd aangetoond dat het LET-classificatie systeem, gebaseerd op de hypothese dat uitgebreide diepe veneuze trombose en iliofemorale betrokkenheid leiden tot een hogere LET-classificatie, een indicatie is van het ontwikkelen van ernstiger post-trombotisch syndroom

(PTS). We moeten echter in gedachten houden dat, terwijl de LET-classificatie zich richt op de grotere, meer centrale aderen als een potentieel belangrijke onderscheidende factor voor de ontwikkeling van PTS, het grotere geheel veel complexer is. De definitie van de ziektestatus kan desalniettemin een belangrijke impact hebben op de interpretatie van de effectiviteit van de behandeling. We moeten ons realiseren dat onze enkel op beeldvorming gebaseerde test waarschijnlijk niet voldoende is om de ziekte in zijn geheel te definiëren.
Het onderzoek naar PTS is complex en moet steunen op de momenteel beschikbare scoresystemen. De Villalta-score beoordeelt de ernst van PTS, documenteert de verandering in ernst in de loop van de tijd en heeft een goede interbeoordelaarsbetrouwbaarheid. De beperkingen zijn echter de subjectiviteit en diagnostische nauwkeurigheid. [11,12] In de afgelopen jaren zijn patiëntgerapporteerde uitkomsten belangrijker geworden en kunnen ze, indien wijdverbreid aangenomen, potentieel bijdragen aan vergelijkingen tussen verschillende onderzoeken. Het doel van de LET-classificatie om diepe veneuze trombose patiënten tussen onderzoeken nauwkeuriger te vergelijken op basis van de anatomische verdeling van trombi in de onderste ledematen blijft valide en kan nog steeds een waardevolle bijdrage leveren aan het interpreteren van het grotere geheel.

Het nauwkeurig beoordelen van de locatie en omvang van de trombus bij acute diepveneuze trombose is niet altijd eenvoudig. Met name bij meer uitgebreide tromboses of wanneer alleen standaard echografieprotocollen worden gebruikt, treden beperkingen in de rapportage op.[13] Verschillende studies hebben gerapporteerd over de toegevoegde waarde van MRI en CT in het algemeen en specifiek in die voor echografie lastige gevallen.[14-18] Bovendien is bewijs ontstaan dat het mogelijk was om acuut van chronisch trombusmateriaal te onderscheiden met behulp van directe MRI-beeldvorming van de trombus.[19,20] Ons contrastversterkte magnetische resonantie-venografieprotocol, gecombineerd met de initiële ervaring gepubliceerd door Spritzer et al., maakte een evaluatie mogelijk van beeldvormingskenmerken die van waarde zouden kunnen zijn bij het interpreteren van trombusbeeldvorming bij acute diepveneuze trombose.[21] In **hoofdstuk 3** rapporteren we ons concept van trombusbeeldinterpretatie en de haalbaarheid van een dergelijke interpretatie. Zoals beschreven in de vorige alinea wordt bij diep veneuze trombose het herstellen van de doorstroming en patency van de ader als cruciaal beschouwd. Hoe eerder de behandeling wordt gestart en de doorstroming in de aders wordt hersteld, des te minder trombusorganisatie en veneuze wandhermodellering mogelijk hebben plaatsgevonden. Experts op het gebied beschouwen trombus die minder dan twee weken geleden is ontwikkeld als acuut, tot drie weken als subacuut en persisteert gedurende meer dan drie weken als chronisch of 'oud'.[22] De gevoeligheid voor trombolytische middelen neemt af naarmate de trombus zich organiseert en de veneuze wand zich herstructureert en meer chronische veranderingen ontwikkelt.[23] Langdurige follow-up na kathetergerichte trombolyse in de serie van Baekgaard et al. heeft aangetoond dat functionele aderen zonder reflux voorkwamen bij maximaal 82% van de behandelde patiënten.[24] Een van de strikte

inclusiecriteria was een gemelde duur van klachten < 14 dagen. Het is echter niet optimaal om afhankelijk te zijn van de gemelde duur van klachten van een patiënt om de leeftijd van de trombus te schatten of de geschiktheid voor invasieve behandeling te bepalen, omdat de perceptie of het geheugen van een patiënt over het begin van klachten onnauwkeurig kan zijn. De vraag was of we dit konden verbeteren door trombusbeeldkenmerken die op onze magnetische resonantie venografie-onderzoeken waren geïdentificeerd te gebruiken om de trombus leeftijd virtueel in te schatten op een meer objectieve en gestandaardiseerde manier.

De resultaten in **hoofdstuk 3** tonen aan dat het haalbaar is om specifieke beeldkenmerken van trombus en aderwandveranderingen te identificeren in MRV-studies met een goede tot uitstekende interbeoordelaarsovereenkomst.[25] Belangrijke bevindingen waren het feit dat het op alle MRV-studies kon worden toegepast en dat de beeldscore voor trombusleeftijd in elke patiënt een vergelijkbare, zij het niet exacte, distributie leek te hebben als de door patiënten gerapporteerde duur van klachten. Sommige patiënten zouden worden geclassificeerd als een acute diepe veneuze trombose op basis van beeldvormingsinformatie, maar rapporteerden een relatief lange duur van klachten en vice versa. Helaas was er geen echte gouden standaard om de resultaten mee te vergelijken, zoals bijvoorbeeld in vivo trombusmonsters. Desondanks heeft de uitkomst van deze studie als basis gediend om de gevolgen van deze beeldvondsten verder te onderzoeken met betrekking tot de behandeling van iliofemorale diepe veneuze trombose.

In **hoofdstuk 5** bespreken we verder het belang van het in aanmerking nemen van de leeftijd van het trombus bij de behandeling van iliofemorale diepe veneuze trombose met kathetergerichte trombolyse. We hebben aangetoond dat zowel de duur van de klachten als maatstaf voor 'trombus veroudering' als specifieke trombus MRV-beeldvormingskenmerken voorspellend kunnen zijn voor de behandelingsuitkomst. Het is belangrijk op te merken dat er specifieke verschillen waren tussen de analyse van de door de patiënt gerapporteerde duur van de klachten en de MRV-beeldvormingskenmerken. De door de patiënt gerapporteerde duur van de klachten, zoals in deze studie geëvalueerd, werd vergeleken met de langetermijnresultaten (doorgankelijkheid aders, geen reflux) met een mediane follow-up van 5 jaar. De beeldvormingsgegevens richtten zich op het leveren van het bewijs van concept en werden gecorreleerd met de kortetermijnresultaten (duur en succespercentage van de kathetergerichte trombolyse). Interessant genoeg duiden specifieke verschillen tussen de door de patiënt gerapporteerde duur van de klachten en de MRV-analyse erop dat de door de patiënt gerapporteerde duur van de klachten met name belangrijk was voor de langetermijnresultaten, maar dat de MRV-analyse een voordeel bood bij de patiëntenselectie voor de kortetermijnresultaten. Daarom zou er in de toekomst mogelijk aanvullende waarde kunnen zijn door beide evaluaties te combineren om de patiëntenselectie en uitkomsten verder te verbeteren.

Verschillende studies hebben aangetoond dat het gebruik van zogenaamde 'bloedpoel' contrastmiddelen gunstig is, vanwege een lange retentie van deze middelen in het bloed. Hierdoor is hoge resolutie beeldvorming in een stabiele aankleuring toestand van bloed en weefsel mogelijk van het gehele diepe veneuze systeem in de onderste ledematen. Dit resulteert in gedetailleerde afbeelding van het gehele veneuze systeem en (intra)luminale veranderingen in 1 scan.[26-28] Helaas werd in 2011 het meest gebruikte 'bloedpoel' contrastmiddel voor magnetische resonantie venografie, genaamd Ablavar ® (Gadofosveset-trinatrium, Lantheus Medical), van de markt gehaald in Europa. Het is belangrijk op te merken dat dit een marketingbeslissing was, geen gebrek in het contrastmiddel zelf of complicaties na toediening ervan. De implicaties waren echter duidelijk en hebben ons ertoe aangezet om onze contrastversterkte benadering van magnetische resonantie venografie opnieuw te bekijken. **Hoofdstuk 4** worden de resultaten van onze vergelijking van twee contrastmiddelen, een regulier gadolinium-gebaseerd middel gadobutrol (Gadovist, Bayer HealthCare) en Gadofosveset-trinatrium beschreven. Bovendien hebben we naast contrastmiddelen, 3 afzonderlijke beeldvormingsprotocollen geëvalueerd, waaronder een niet-contrastversterkt protocol, wat resulteerde in 3 belangrijke onderzoeksresultaten. Ten eerste ontdekten we dat het gebruik van een contrastmiddel superieur was aan een niet-contrastversterkt protocol voor evaluatie van het diepe veneuze systeem. Ten tweede bleek gadobutrol in staat om Ablavar te vervangen zonder afname van beeldkwaliteit of interpretatie mogelijkheden. Ten derde waren we door het updaten van ons scanprotocol en het toepassen van nieuwe, nu algemeen verkrijgbare, vetonderdrukkingstechnieken in staat om de vereiste scantijd aanzienlijk te verminderen, waardoor MRV nog toegankelijker werd.

Deel 2

In november 2019 werden de resultaten van de gerandomiseerde gecontroleerde CAVA-studie gepubliceerd, waarin de waarde van toevoeging van kathetergerichte trombolyse aan standaard antistollingstherapie voor iliofemorale diepe veneuze trombose werd geëvalueerd (**hoofdstuk 6**).[8] De reden om specifiek iliofemorale diepe veneuze trombosepatiënten te selecteren was dat spontane rekanalisatie bij deze patiënten minder waarschijnlijk is, waardoor het potentiële voordeel van trombolyse mogelijk groter is dan de bloedingsrisico's die gepaard gaan met kathetergerichte trombolyse. Resultaten na één jaar follow-up toonden geen significant verschil in proporties met post-trombotisch syndroom tussen de twee onderzoeksgroepen: 29% in de groep met echo-geaccelereerde kathetergerichte trombolyse (UA-CDT) versus 35% in de standaardbehandelingsgroep. De behandeling van onderliggende diepe veneuze stenose werd echter actiever uitgevoerd met 76% in de CAVA-studie, vergeleken met 28% in de ATTRACT-studie en 16% in de CaVenT-studie.[29,30] Deze hogere aantallen waren dichter bij de verwachtingen van de experts in het veld, maar resulteerden niet in een vermindering van post-trombotisch syndroom bij follow-up na één jaar. Bovendien was er een lage inclusie ratio en was het aantal gevallen dat door elk specialistisch team werd behandeld beperkt, wat het (langetermijn) resultaat zou kunnen hebben beïnvloed, zoals eerder werd gerapporteerd.[31]

Bovenstaande punten in overweging nemend, werd een post-hoc analyse van de CAVA-studie uitgevoerd (**hoofdstuk 7**) om specifiek te kijken naar die patiënten waarbij de behandeling (echo-geaccelereerde kathetergerichte trombolyse) technisch succesvol was. Opnieuw verschilde de proportie van post-trombotisch syndroom na één jaar, het primaire eindpunt van de CAVA-studie, niet significant tussen de groep met kathetergerichte trombolyse en de controlegroep. Er was echter een lagere ernst van post-trombotische klachten en de generieke kwaliteit van leven was hoger. Deze bevindingen benadrukken het belang van nauwkeurige evaluatie van geschikte patiënten vóór de behandelingselectie, idealiter niet-invasief, zoals beschreven in **hoofdstuk 5**.

De meeste patiënten ontwikkelen PTS binnen de eerste twee jaar na de initiële diagnose van diepe veneuze trombose. Er wordt echter een gestage toename van het incidentiepercentage gemeld over 10 tot 20 jaar na het evenement.[32] De eerdere studie van Plate et al. die open veneuze trombectomie evalueerde en de CaVent-studie, suggereerden dat er voordelen zouden kunnen zijn bij het herstellen van ongehinderde veneuze doorstroming, met een vermindering van maximaal 28% in het incidentiepercentage van PTS.[33] Belangrijk is op te merken, dat bij het vergelijken van deze resultaten met de ATTRACT- en CAVA-studies, de meest overtuigende gegevens naar voren kwamen bij een follow-up van vijf jaar.[34] De ATTRACT-studie werd gepubliceerd in 2017 met een eindpunt van twee jaar follow-up en de CAVA-studie werd gepubliceerd in 2020 met een follow-up van één jaar.[7,8] Het is aldus de vraag of één- en tweejarige follow-up wellicht te kort kan zijn om de volledige effecten van de aanvullende behandelingen te meten. Notten et al. publiceerden aanvullende langetermijnresultaten voor de CAVA-studie.[35] In deze analyse namen 120 patiënten (79,8%) van de totale CAVA-studiepopulatie deel aan een laatste follow-upbezoek, 62 patiënten uit de interventiegroep (52%). De mediane follow-up was 39 maanden (interkwartielafstand 23,3-63,8 maanden). PTS ontwikkelde zich bij 19 (30,6%) patiënten in de interventiegroep versus 26 (44,8%) in de standaardbehandelingsgroep. Bij gebruik van de consensusdefinitie van de International Society on Thrombosis and Haemostasis (Villalta-score > 5 of veneuze ulceratie bij 6-maandenbeoordeling of later) was de absolute vermindering 22,2%. Hoewel deze studie beperkt was door de steekproefomvang, geven de algemene bevindingen aan dat er een vermindering van (milde) PTS was zonder invloed op de kwaliteit van leven. Dit versterkt het concept dat de impact van echo-geaccelereerde cathetergerichte trombolyse op de preventie van PTS toeneemt met de tijd en toekomstige studies zouden een langere follow-up moeten overwegen om het definitieve resultaat te kunnen evalueren.

In de observationele studies werd betrokkenheid van de iliofemorale aderen geïdentificeerd als een risicofactor voor PTS.[3] In de CAVA-trial hebben we een nauwkeurigere identificatie van proximale (iliofemorale) diepe veneuze trombose opgenomen, niet alleen geanalyseerd met DUS, maar ook bevestigd met MRV. Het doel was om preciezer te zijn in het selecteren

van patiënten, omdat een iliofemoraal diep veneus segment specifiek betrokken moest zijn. De resultaten zijn echter inconclusief; er werd geen significante algehele vermindering van PTS bij een follow-up van één jaar getoond. Zoals echter beschreven in de vorige alinea, duidde de langere follow-up wel op een vermindering van PTS. Bovendien toonde een subgroepanalyse van de ATTRACT-trial, die zich richtte op patiënten met specifieke iliofemorale veneuze betrokkenheid en farmaco-mechanische trombolyse vergeleek met standaardbehandeling, wel een verschil in patiënten met matige tot ernstige PTS (Villalta-score >9 of ulcus) en ernstige PTS (Villalta >14 of ulcus).[36] PTS was 18% versus 28% in de matige tot ernstige groep, en 8,7% versus 15% in de ernstige groep, beide ten gunste van farmaco-mechanische cathetergerichte trombolyse (PCDT). Toen de veneuze klinische ernst score (VCSS) als primaire uitkomstmaat werd gebruikt, was het verschil 6,6% versus 14% ten gunste van PCDT. Deze subgroepanalyse in combinatie met de resultaten van langdurige follow-up van de CAVA-trial suggereert dat er nog steeds waarde kan worden gehecht aan het observationele concept van iliofemorale betrokkenheid. Bij toekomstige onderzoeken zou dus rekening moeten worden gehouden met de betrokkenheid van deze diep veneuze segmenten.
Om betere resultaten te behalen na trombolyse zijn optimalisatie van de behandeling en betere selectiecriteria voor geschikte patiënten essentieel. Idealiter worden die patiënten geselecteerd die het meeste baat hebben bij de voorgestelde behandeling. Met name voor kathetergestuurde trombolyse en het daarmee geassocieerde bloedingsrisico kan een verbeterde selectie voorafgaand aan de behandeling de patiënten en uitkomsten aanzienlijk ten goede komen. **Hoofdstuk 8** geeft de resultaten weer van ons onderzoek naar het potentieel van een MRV-beeldvormingssysteem voor het selecteren van iliofemorale diepe veneuze trombosepatiënten die in aanmerking komen voor kathetergestuurde trombolyse. Beeldvormende beoordeling van trombi kan ook worden gebruikt om diegenen te identificeren die waarschijnlijk resistent zijn tegen trombolytische therapie. Het onderzoek heeft aangetoond dat er waarde zit in dit concept. Met behulp van MRV-trombuskenmerken konden trombi worden geïdentificeerd als acuut, subacuut en oud. Bovendien bleek dat de op MRV geschatte trombusleeftijd geassocieerd was met zowel de duur als het succespercentage van de interventie, zoals bleek uit het significante verschil tussen de gemiddelde trombolysetijd in de MRV-gebaseerde groepen: 23 (19-25) uur voor acute, 43 (41-62) uur voor subacute en 85 (74-96) uur voor oude trombi ($p < 0{,}0001$). Dit zou helpen om (onnodige) risico's geassocieerd met onsuccesvolle kathetergestuurde trombolyse te vermijden: een uitgebreide behandelduur en complicaties zoals bloedingen. Gezien de resultaten moet MR-Venografie worden beschouwd als een voorwaarde voor patiënten die potentieel in aanmerking komen voor kathetergestuurde trombolyse voor iliofemorale diepe veneuze trombose.

De dagelijkse praktijk in ervaren centra is geëvolueerd van (strikt) cathetergerichte trombolyse naar meer agressieve mechanische trombectomie, inclusief rheolytische trombectomie zoals gebruikt in de ATTRACT-trial en verschillende aspiratiecatheters en pomp-ondersteunde

aspiratiesystemen. Deze benaderingen kunnen de selectiecriteria en de geschiktheid van patiënten voor minimaal invasieve trombusverwijdering veranderen. Of het gebruik van onze beeldgebaseerde trombusbeoordeling een hulpmiddel kan zijn bij deze behandelingsopties, moet nog worden onderzocht. Bovendien weten we niet of meer agressieve, mechanische benaderingen de veneuze wand en kleppen ook negatief beïnvloeden. De potentiële schade aan de veneuze wand en kleppen, waar het concept van vroege trombusverwijdering op gericht is, zou heel goed kunnen worden veroorzaakt door deze meer agressieve technieken voor trombusverwijdering. [37,38]

Toekomstig onderzoek

Zoals beschreven in de inleiding, zijn er twee processen die verondersteld worden veneuze hypertensie te veroorzaken, wat leidt tot PTS en die de basis vormen van het onderzoek in deze thesis. Het eerste is obstructie van de diepe veneuze bloedstroom door rest trombus. De tweede is de verandering van een (gezonde) flexibele ader naar een (zieke), stijve, fibrotische ader met afunctionele kleppen. [33,39]
Met betrekking tot het eerste proces, obstructie van de diepe veneuze bloedstroom, en rekening houdend met de 'open-ader hypothese', zou onderzoek verder moeten worden gericht op de potentie van vroege oplossing van de trombus om post-trombotisch syndroom te verminderen. De CAVA-subgroepanalysegegevens gepresenteerd in deze scriptie geven aan dat verdere verbetering van de selectie van patiënten van cruciaal belang kan zijn. Daarom zou onderzoek gericht op verdere optimalisatie van patiëntenselectie, ondersteund door toegewijde beeldvormingstechnieken om (rest) trombus te evalueren, een focus moeten zijn. Bijvoorbeeld, de lange termijn evolutie van diepe veneuze (wand) veranderingen na DVT, inclusief resterende trombus of littekens. Dit zou kunnen worden geanalyseerd met sequentiële MRV-beeldvorming om zowel acute als chronische veranderingen in detail in kaart te brengen, om hun relatie met post-trombotisch syndroom verder te ontrafelen.

Vanuit het perspectief van een interventieradioloog zou het interessant zijn om de evolutie van trombose in vivo versus de overeenkomstige beeldkenmerken gedetailleerder te onderzoeken. Als MRV inzicht kan bieden in het tijdstip en de ontwikkeling van veneuze schade op basis van beeldkenmerken, kan hiermee rekening worden gehouden bij het overwegen van (aanvullende) behandelingsopties. Men zou kunnen veronderstellen dat in een vroeg stadium van diepe veneuze trombose een meer voorzichtige aanpak en techniek de voorkeur geniet om (door de behandeling toegebrachte) schade aan de aderen te voorkomen terwijl snelle stolsel oplossing wordt ondersteund. Als de ziekte echter al gevorderd is tot het punt waarop aderbeschadiging al aanwezig is, kunnen meer agressieve benaderingen gericht op maximale lumenvergroting meer geschikt zijn. Er zou een drempel moeten worden vastgesteld voor de MRV-analyse, waarvoor onze MRV-trombusscore het startpunt zou kunnen zijn.

Naast optimalisatie van patiëntenselectie, moet verbetering van de technieken voor trombusverwijdering onderdeel zijn van de onderzoeksagenda, omdat deze twee factoren essentieel zijn voor zowel technisch als klinisch succes. Het voorkomen van het posttrombotisch syndroom was tot nu toe het belangrijkste resultaat in alle interventietrials voor diepe veneuze trombose. Echter, aanvullende uitkomsten, zoals de impact van de ziekte op de kwaliteit van leven van patiënten, zijn belangrijk en moeten meer nadruk krijgen en zelfs als primaire uitkomstmaat worden opgenomen in toekomstige trials. Ten slotte toont klinische ervaring aan dat het essentieel is om post-interventionele behandelstrategieën te verbeteren om de behaalde behandelresultaten beter te behouden.

De grootste uitdaging voor beeldvormingsonderzoek kan het secundaire proces van fibrose en klepstoornissen zijn. Tot op heden zijn er geen nieuwe technieken vastgesteld of onderzocht om kleinere, meer distale (kuit)aders te evalueren die mogelijk belangrijk zijn bij de ontwikkeling van posttrombotisch syndroom. De vraag blijft of het herstel van (proximale) uitstroom van bloed vitaal genoeg is om post-trombotisch syndroom te voorkomen wanneer distale schade al is opgetreden of niet kan worden voorkomen door huidige medicinale of katheterinterventies. Gezien de huidige ontwikkelingen en toekomstige integratie van kunstmatige intelligentie en machine learning in radiologische systemen, zijn er mogelijkheden om op nieuwe manieren naar beeldinformatie te kijken. In plaats van de meer traditionele 'slice-by-slice' methode, kan het totale afgebeelde volume op zowel kwalitatieve als kwantitatieve manieren worden geanalyseerd, wat bijdraagt aan het totaalbeeld in plaats van alleen de aangetaste diepe ader(s). Bijvoorbeeld, op beeldvorming gebaseerde veneuze bloedstroom- en/of drukmetingen die waardevol blijken bij invasieve analyse,[40] of beeldvorming gebaseerde kwantificering van beenoedeem kunnen worden geïntegreerd.
De evolutie van (het gebrek aan) trombusresolutie tot veneuze wandfibrose is mogelijk niet zo direct gekoppeld als we hadden verwacht. Er zijn studies die suggereren dat deze processen onafhankelijk van elkaar plaatsvinden.[34,35] Hoewel de centrale aders mogelijk (minimaal invasieve) interventionele behandeling vereisen, zou een medicijn dat de veneuze wandrespons op trombose moduleert, al dan niet in combinatie met gelijktijdige trombusverwijdering, een potentieel grote vooruitgang betekenen in de preventie van PTS.
Tot slot verplicht de hoge ziektelast onderzoekers om zowel interventionele als niet-interventionele strategieën te blijven verkennen om de kwaliteit van leven van patiënten na een acute diepe veneuze trombose te verbeteren.

Concluderend laat het werk gepresenteerd in deze thesis zien dat, hoewel er meer data beschikbaar is gekomen over kathetergerichte trombolyse voor de preventie van post-trombotisch syndroom bij iliofemorale diepe veneuze trombose, dit nog niet heeft geleid tot een definitieve conclusie over de bruikbaarheid van deze interventie. In deze thesis ligt de focus op verbetering na minimaal invasieve behandeling, gemeten als vermindering van PTS, maar het algehele hoge risico op het ontwikkelen van PTS na acute diepe veneuze trombose ongeacht de behandeling is een zorg voor alle patiënten met diepe veneuze trombose en vereist verder onderzoek.

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Curriculum Vitae

Carsten Arnoldussen was born 25th of august 1978, in Sittard, the Netherlands. In 1997 he graduated from the Atheneum at Gymnasium Augustinianum in Eindhoven. Thereafter, he went to study information technology, health sciences and law prior to finally starting medicine in 2001. In 2007 he earned his medical degree at the Maastricht University in Maastricht and was immediately selected to start his formal radiology residency at Maastricht University Medical Centre+. In 2009 he came into contact with em. prof. dr. C.H.A. Wittens who was creating a dedicated (deep) venous practice at Maastricht University Medical Centre+. In addition to the treatment of deep vein obstruction, the imaging assessment of deep vein disease was of particular interest to both of them and together with Irwin Toonder an assessment algorithm was created to assess these patients prior to (minimally invasive) interventions. This clinical collaboration would become the basis of the imaging-based research projects to come, including the CAVA-trial, working together with many other PhD students.

Meanwhile, he completed his training in Radiology at the Maastricht University Medical Centre+ and obtained his board license in 2012 including his cardiovascular imaging and interventional radiology subspecialties. He further specialized in interventional radiology, and after completing his fellowship, started working at VieCuri Medical Centre (Venlo) in 2013. Meanwhile he maintained his clinical and research position at Maastricht University Medical Centre.

In addition to his clinical work at Hart+Vaat Centrum MUMC+, he continued to conduct research as part of the venous disease research team at the Maastricht University Medical Centre+. The focus of his research is on (non-)invasive imaging of deep venous disease, both acute and chronic. In more recent years an additional focus has been imaging pelvic venous disease, developing dedicated (MR) imaging protocols and finetuning interventional treatment techniques. Nowadays, his specific research interest is in investigating the relationship between clinical presentation, image findings and treatment outcomes for minimally invasive (venous) interventions.

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Maar dit boekje was niet tot stand gekomen met enkel zelfstandigheid. Er zijn andere leermeesters essentieel geweest voor mijn route door het academische onderzoek landschap. In de eerste plaats professor Wittens, die met zijn visie en toekomstgerichte plannen voor de veneuze chirurgie, interventieradiologie en beeldvorming in het MUMC+ mij wist te prikkelen. Zijn komst en plannen creëerde de mogelijkheid om aan een tot op dat moment openstaand hiaat in mijn ontwikkeling, namelijk zelf klinisch onderzoek doen, invulling te geven. Wie had gedacht dat dat traject hier zou worden voltooid. Beste Cees, dank voor jouw visie, steun, vertrouwen en volharding.
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