Deep vein thrombosis : diagnostic and prognostic challenges

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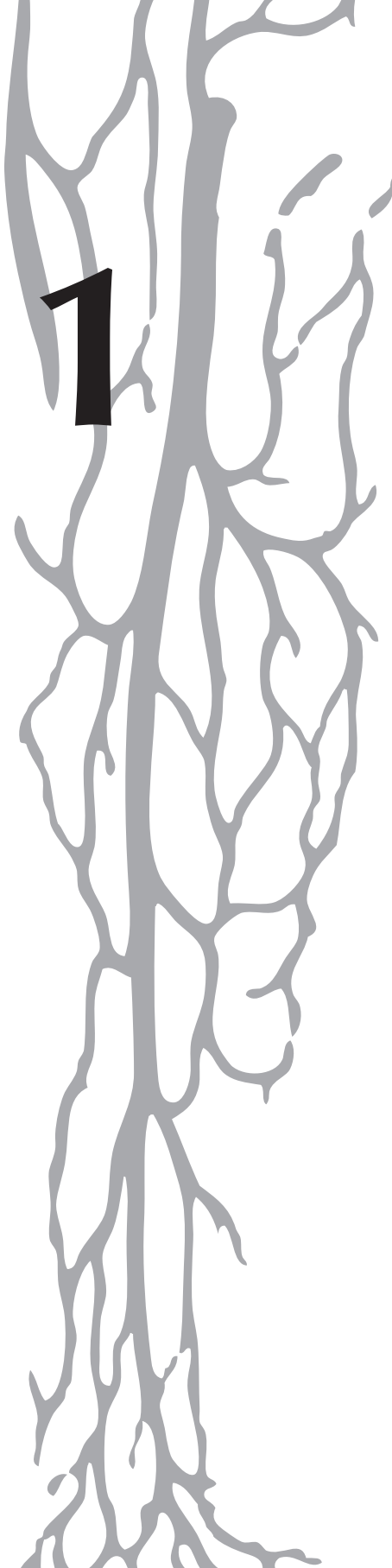
CONTENTS

1

Introduction and outline of this thesis



Deep vein thrombosis (DVT) is characterized by the formation of a blood clot in one of the deep veins. DVT occurs most frequent in the deep veins of the lower extremities, but can also occur in one of the veins of the upper extremity, splanchnic veins or cerebral veins. When DVT detaches, it can embolise into the lungs, causing acute pulmonary embolism (PE), which is potential life threatening. DVT and acute PE are together defined as one disease: venous thromboembolism (VTE). The understanding of the pathophysiologic mechanism of VTE is still based on Virchow's triad described in 1856: venous stasis, vessel injury and hypercoagulability.[1] Signs and symptoms of VTE are nonspecific. Therefore diagnostic tests are needed in addition to questioning and physical examination to establish definite diagnosis.

Although VTE diagnostic management and imaging techniques have rapidly evolved over the past decades, a correct diagnosis remains challenging in many cases. **Chapter 2** provides an overview of the current challenges in the diagnostic management of suspected VTE, which are subsequently further discussed in the first part of this thesis. New, promising diagnostic management strategies are being developed all over the world, and continuously tested in diagnostic management studies. The safety threshold against which all this studies are evaluated is the failure rate of invasive venography, because this is still the 'golden standard' for DVT according to current guidelines. However, over the last years, the disease prevalence in DVT diagnostic management study populations has significantly decreased. In line with the association between disease prevalence and failure rate as proposed by Bayes in 1764, we aimed to develop a new disease prevalence dependent diagnostic safety threshold for future diagnostic management studies (**chapter 3**).[2]

The current favoured strategy of diagnostic management of a first DVT is the use of a diagnostic algorithm starting with a clinical decision rule to estimate the pre-test probability of having DVT.[3] The most widely used clinical decision rule is the Wells rule, consisting of 10 items with allocated different number of points to a total score.[4] In case of a low clinical probability (Wells rule < 2 points) combined with a negative D-dimer test, DVT can be ruled out without additional imaging tests such as compression ultrasonography (CUS). In clinical practice this decision rule is however often incorrectly used leading to unneeded excessive diagnostic tests and diagnostic failures.[5] In **chapter 4** we therefore aimed to design and test a simpler rule which consisted of only 4 items, the so-called 'I-DVT' score.

The diagnostic management of DVT is more difficult in specific patient groups, including pregnant women, patients with suspected ipsilateral recurrent DVT and patients with suspected upper extremity DVT (UEDVT). Magnetic Resonance Direct Thrombus Imaging (MRDTI), a non-contrast enhanced MRI technique, can be a potential solution in diagnosing DVT in these patients. With this technique a thrombus can be directly visualised, based on the oxygenation of haemoglobin when blood clots, which results

in the formation of methemoglobin. This acts as an endogenous contrast agent and appears as high/'white' signal when imaged using a T1-weighted MRI sequence.[6,7]

A DVT diagnosis in pregnant patients may be difficult because of the relatively high incidence of isolated pelvic vein thrombosis. For obvious reasons, compression ultrasonography is inadequate due to anatomical reasons.[8] Alternative conventional diagnostic tests include direct, CT- or MRI venography, that expose mother and foetus to ionizing radiation and/or contrast material. **Chapter 5** describes a case of a pregnant woman with suspected DVT in whom conventional diagnostic tests failed to establish a definite diagnosis. The diagnosis could however be finally confirmed by MRDTI.

The current strategy of diagnosing patients with a suspected ipsilateral recurrent DVT is also complicated, mainly because of highly prevalent chronic thrombus remains that are present in up to 50% of patients despite adequate anticoagulation. A distinction between residual vein thrombosis and acute recurrent DVT with CUS is impossible.[9] In a previous study, it was shown that MRDTI accurately distinguishes acute recurrent DVT from chronic thrombus remains.[10] An alternative direct thrombus imaging technique is the T1 weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery (TSE-SPAIR) sequence. This sequence is characterised by the visualisation of the vessel wall in a high resolution, which is not the case with MRDTI.[11] In **chapter 6** we investigate the additional value in diagnostic accuracy and diagnostic confidence of the TSE-SPAIR sequence on top of the MRDTI sequence in 15 patients with suspected recurrent ipsilateral DVT.

One other diagnostic challenge is the diagnosis of upper extremity deep vein thrombosis (UEDVT). Compression ultrasonography is often inconclusive because of overlying anatomic structures that hamper adequate compression of the veins. Contrast venography is needed in many cases, which is associated with complications due to exposure to radiation and contrast material.[12] In **chapter 7,** we explored the feasibility of the MRDTI and TSE-SPAIR sequences for diagnosing UEDVT.

The second part of this thesis focuses on the prognosis of patients diagnosed with and treated for DVT. To prevent complications as acute PE and the post-thrombotic syndrome (PTS), adequate anticoagulant treatment for DVT is required. The current treatment of choice is direct oral anticoagulants (DOACs).[13] The main advantage of DOACs over the more old-fashioned vitamin K antagonists is that they have a lower risk of bleeding. Moreover, neither monitoring nor dose titrations are needed.[14] A potential drawback of DOACs is a higher risk of decreased drug persistence, i.e. prematurely discontinuing treatment. In **chapter 8** we explored the incidence of prematurely cessation of anticoagulant therapy for incident venous thromboembolism based on Dutch pharmacy registry data.

Inadequate treatment of DVT is one of the main risk factors of PTS. PTS is a chronic complication occurring in 20-50% of patients with DVT, and is characterised by a spectrum of mild to severe symptoms of chronic venous insufficiency.[15] Several risk factors

for PTS at the time of the DVT diagnosis have been identified, such as more proximal DVT, older age, obesity and history of ipsilateral recurrent DVT.[16] Whether ultrasound-measured chronic vein obstruction by residual clots and/or valvular reflux may be helpful in better predicting PTS remains controversial. Therefore, the primary aim of **chapter 9** was to perform a systematic review and meta-analysis to identify ultra-sonographic parameters, assessed during or after treatment of proximal DVT of the leg, that predict post thrombotic syndrome.

It has been shown that elastic compression stocking (ECS) therapy may prevent PTS, but only in case patients are compliant to wearing the stocking on a daily base for 2 full years.[17-19] Importantly, stockings are costly, cumbersome to apply, and can be hot, constricting, and itchy. These factors are the main cause of the poor compliance of patients to ECS therapy in clinical practice. The primary aim of **chapter 10** was to find independent predictors for PTS development in patients who compliantly used ECS up to one year after DVT, to select patients who may safely stop ECS therapy.

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Part 1

Challenges in diagnostic management and imaging of deep vein thrombosis

2

Current and future perspectives in imaging of venous thromboembolism

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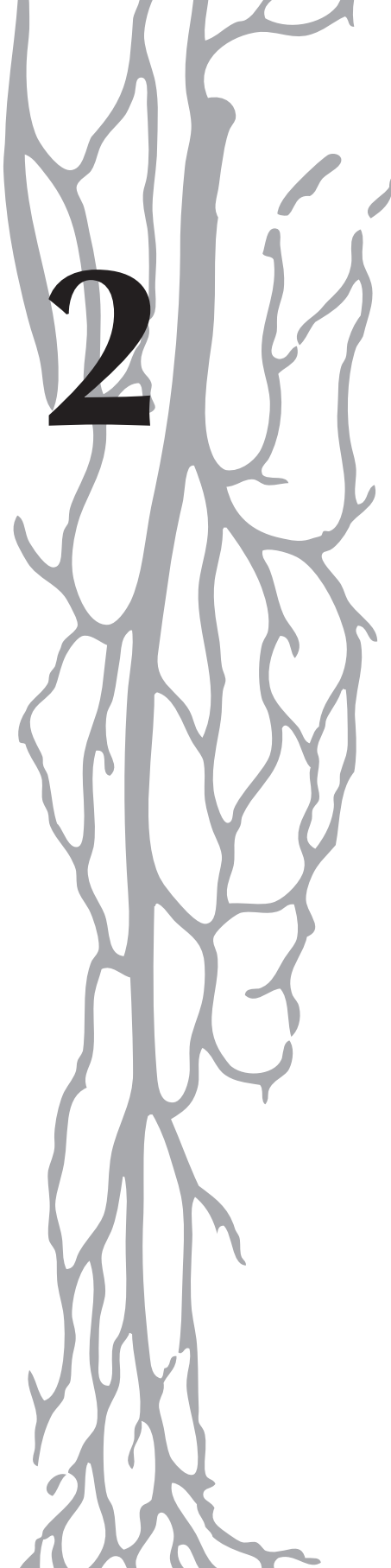

ABSTRACT

Several thrombus imaging techniques for the diagnosis of venous thromboembolism (VTE) are available. The most prevalent forms of VTE are deep vein thrombosis of the lower extremities and pulmonary embolism. However, VTE may also occur at more unusual sites such as deep veins of the upper extremity and the splanchnic and cerebral veins. Currently, the imaging techniques most widely used in clinical practice are compression ultrasonography and Computed Tomography Pulmonary Angiography (CTPA). Moreover, Single Photon Emission Computed Tomography (SPECT), CT venography (CT-V), Positron Emission Tomography (PET) and different MRI techniques, including Magnetic Resonance Direct Thrombus Imaging (MRDTI), have been evaluated in clinical studies. This review provides an overview of the technique, diagnostic accuracy and potential pitfalls of these established and emerging imaging modalities for the different sites of venous thromboembolism.

INTRODUCTION

Over the past decades, techniques for imaging of venous thromboembolism (VTE) have rapidly evolved. Traditionally, contrast venography was standard of reference for diagnosing deep vein thrombosis (DVT) of the extremities and conventional invasive pulmonary angiography for pulmonary embolism (PE).[1,2] These techniques have been replaced by compression ultrasonography (CUS) and Computed Tomography Pulmonary Angiography (CTPA).[3,4] To standardize the diagnostic process, imaging tests have been implemented in diagnostic algorithms that have been proven safe and efficient in clinical practice.[5]

CUS and CTPA are however not suitable for all patients with suspected VTE. CUS is, for example, not appropriate in patients with plaster casts, for the subclavicular part of the arm veins, or in splanchnic or cerebral veins. Moreover, the difficulty of making a distinction between chronic residual thrombosis and acute recurrent DVT remains challenging.[6,7] To overcome these shortcomings, new imaging techniques have been developed and tested, such as single-photon emission computed tomography (SPECT), CT venography (CT-V), positron emission tomography (PET), and different magnetic resonance imaging (MRI) techniques. In this review, we will provide an overview of the current available and emerging imaging techniques for VTE and briefly discuss the advantages and limitations of these modalities at different thrombus sites (DVT, PE, Upper Extremity Deep Vein Thrombosis [UEDVT], Splanchnic Vein Thrombosis (SVT) and Cerebral Vein Thrombosis [CVT]) (**table 1**). It is beyond the scope of this review to describe diagnostic algorithms, which have been well described elsewhere,[8,9] as well as to consider the relative costs and cost-effectiveness of different diagnostic modalities, either as stand-alone test or within the context of these diagnostic algorithms. However, test availability, costs and safety are important considerations in choosing diagnostic tests.

Ultrasonography

Technique

Ultrasonography (US) is widely accepted as the primary diagnostic procedure for the work up of suspected DVT of the leg. Ultrasound images are created by the turnaround time of sound waves. Using the images to directly diagnose clots has varying success because clot echogenicity is variable and unpredictable, and a fresh clot is often anechoic.[10] With compression US(CUS), veins are compressed with the ultrasound probe. In the absence of a DVT, gentle pressure with the probe causes the venous lumen to collapse. The lack of compressibility of a venous segment under the ultrasound probe is diagnostic for DVT (**Fig. 1**).[11]

Table 1. Overview of available imaging techniques for different locations of venous thrombosis.

Thrombus location	Available Techniques					Test of choice	Future perspectives
	CUS	**CT**	**SPECT**	**MRI**	**PET**		
Deep veins of the leg [3,59,76,93]	Se:94%(93-95) Sp:94%(93-94) L: Detection of recurrent DVT	Se:96%(93-98) Sp:95%(94-97) L: radiation dose		Se:92%(88-95) Sp:95%(93-97) L: low availability, long imaging time	Se: 88% Sp:100%# L: technique has to be further developed	CUS (2-point or whole-leg)	MRDTI for recurrent ipsilateral DVT
Deep veins of the arm[32,87]	Se:82%(70-93) Sp:82%(72-92) L: compression not possible due to overlying bone	Se: unknown Sp: unknown L: not enough evidence		Se:71%(29-96) Sp:89%(52-100) L: no accuracy		CUS	MRDTI for inaccessible vein segments
Pulmonary artery (acute PE)[37,84,100]	Se:87% (79-92) Sp:82%(71-89) L: small amount of accessible lung area	Se:83%(76-92) Sp:96%(93-97) L: contrast allergy + CI-AKI,radiation dose	Se:83%(61-95) Sp:98%(92-100) L: not validated in a prospective management study	Se:78%(67-86) Sp:99%(96-100) L: high proportion of inconclusive scans	Se: unknown Sp: unknown L: technique has to be further developed	CTPA	MR-PA, Molecular MRI with target specific- contrast agents for reduction of radiation
Pulmonary artery (CTEPH)[52,86]		Se:76%(69-82) Sp:96%(93-98) L: not diagnostic for CTEPH as single test		Se: 83%(77-85) Sp: 99%(89-99)* L: low accuracy from segmental arteries		VQ lung scanning/ DSA	MR techniques for reduction of radiation
Abdominal/ pelvic veins [36,88]	Se:89%(55-99) Sp:92%(88-94)* L: low accuracy due to overlying bowel gas	Se: unknown Sp: unknown L: radiation dose		Se:100%(93-100) Sp:98%(93-98)* L: low evidence		CTV	MRDTI for more accurate diagnosis
Cerebral veins[69]		Se: 75-100% Sp: 82-100% L: low sensitivity		Se: unknown Sp: unknown L: false positives due to artefacts		MRV	MRBTI for direct visualisation of the thrombus

Se, sensitivity; Sp, specificity; L, limitations; CUS, compression ultrasonography; CTV, computed tomography venography; SPECT, single-photon emission tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; MRDTI, magnetic resonance direct thrombus imaging; DSA, digital subtraction angiography; MRV, magnetic resonance venography; MRBTI, magnetic resonance black-blood thrombus imaging; PE, pulmonary embolism; DVT, deep vein thrombosis; CTEPH, chronic thromboembolic pulmonary hypertension *Confidence intervals derived from original article # Confidence interval not derivable from original article

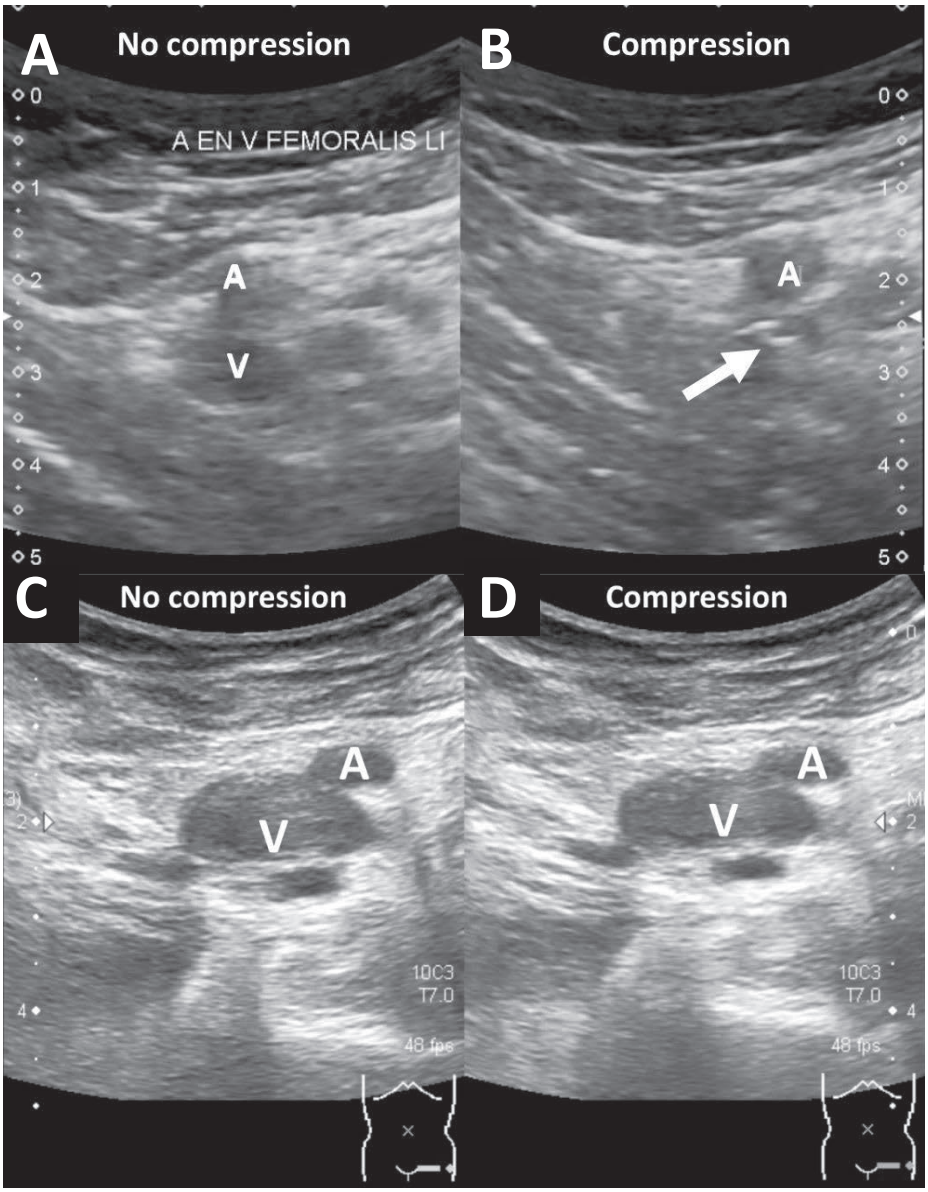

Figure 1. (A,B) A 66-year-old female patient presenting with suspected deep vein thrombosis (DVT). Compression ultrasonography of the left upper leg in axial view at the level of the femoral vein showing good compressible common femoral vein (white arrow), excluding DVT.
(C,D) A 64-year-old female patient with oesophagus carcinoma presenting with suspected DVT. Compression ultrasonography of the left upper leg in axial view at the level of the femoral vein showing incompressible common femoral vein, indicating DVT. A, artery; V, vein.

Color-coded Doppler US may serve as additional technique in the diagnosis of thrombosis. It provides visualization of flow, color-coded for velocity and direction. Absent or partially absent color-coded flow is diagnostic for thrombosis.[3,12] Using Doppler US, proximal vein segments in the pelvis and abdomen that are difficult to assess with CUS may be evaluated.[11]

DVT of the leg

The two most applied US approaches are two-point or whole-leg CUS.[3] With the former, only the proximal veins in the groin and in the popliteal fossa are investigated. Main advantages of this strategy are its simplicity, reproducibility and broad availability. Its major limitation is the need to repeat the test within 1 week in patients with normal findings at presentation, in order to detect extension of non-visualized distal thrombosis to the proximal veins.[3] The advantage of a single whole-leg CUS of the entire deep venous system is the ability to exclude or diagnose DVT in one single examination. The disadvantages of this technique are that it is time consuming and needs experienced operators.[13] Importantly, more patients are subjected to treatment after whole-leg CUS than after two-point CUS because up to 50% of DVTs diagnosed with whole-leg CUS are isolated calf vein thrombi, of which the relevance is uncertain.[1415]

The two strategies were proved to have equal safety in two studies. The first was a trial in 2098 patients with suspected DVT, of whom 1045 patients were randomized to a repeated two-point CUS and 1053 to a single whole-leg CUS. The 3-month incidences of symptomatic VTE in patients with a normal initial test were comparable: 0.9% (95% confidence interval [CI] 0.3-1.8%) vs 1.2% (95% CI 0.5-2.2%).[16] In another study, 1002 patients with suspected DVT were randomized to two-point CUS or whole-leg CUS after application of a clinical decision rule (CDR) and D-dimer test.[17] The 521 patients (52%) with likely probability or abnormal D-dimer were referred for CUS. During 3-month follow-up, the VTE incidence in patients with normal two-point or whole-leg CUS was comparable: 2.0% vs 1.2% (P=0.69). The accuracy of use of color-coded Doppler US only for the diagnosis of DVT has been evaluated in a meta-analysis by Goodacre *et al*., showing a sensitivity of 81.7% (95% CI 77.4-85.5%) and a specificity of 92.7% (95% CI 89.7-95.1%).[3]

Recurrent DVT of the leg

Ultrasound for the detection of suspected contralateral recurrent DVT has comparable sensitivity (89-100%) and specificity (87-100%) compared with first suspicion of DVT, because of the very low risk of chronic non-symptomatic thrombus remains in the contralateral leg.[8,18] The diagnostic management in patients with suspected ipsilateral recurrent DVT is more challenging because of the high prevalence of residual thrombi, which has been estimated to be 50% at 1 year after the index diagnosis despite anti-

coagulation treatment.[19] Accurate distinguishing US features of acute and chronic DVT are lacking. Consequently, CUS is frequently inconclusive in patients with a suspected recurrent ipsilateral DVT.[20] One of the solutions for this diagnostic problem is performing a reference CUS at the end of treatment for the first DVT, to map the location and extent of the thrombotic remains.[21] Ipsilateral recurrent DVT may be diagnosed with some certainty in case of a new non-compressible venous segment, or a pronounced increase in vein diameter (≥2-4 mm) of a previously uncompressible vein compared with the reference CUS.[21,22] In clinical practice, however, this reference CUS is frequently unavailable and interobserver agreement on measurement of residual vein diameter has been reported to be moderate.[23]

Pulmonary embolism

A frequently asked question is whether it is useful to perform CUS among patients presenting with symptoms of PE to eliminate the need for CTPA when DVT can be objectivised. It has been shown that residual DVT is lacking in the majority of PE patients, suggesting that the entire thrombus has already been embolized to the lungs.[24] A prospective management study in 511 patients with suspected PE demonstrated that the sensitivity of CUS of the lower extremities for the presence of PE on CTPA was only 39% (95% CI 32-46%) with a specificity of 99% (95% CI 97-100%).[25] In another study, it has been shown that distal US has an even lower accuracy for predicting PE with a sensitivity of 22% (95% CI 17-29%) and a specificity of 94% (95% CI 91-96%).[26]

It has been suggested that US examination of the lung may also be used in the diagnosis of acute PE. The surface of the lung can be examined on standardized longitudinal sections along the intercostal spaces for the presence of subpleural infarcts, which consist of pleural-based, well-demarcated echo-poor triangular or rounded consolidations.[27] Transthoracic ultrasonography (TUS) has been suggested to have a sensitivity of 74% and a specificity of 95% for PE.[28] Also, TUS may be applied in a diagnostic strategy including lower extremity CUS and echocardiography which may improve its sensitivity.[27,29]

The main drawbacks of TUS are the small amount of accessible lung areas (about 66%), inability to well-visualize aerated lungs, and limited approach because of overlying bony structures. Also, outcome studies are currently lacking, although the results of a prospective study using multi-organ US as part of the diagnostic algorithm of PE are pending(NCT02190110).

Upper extremity deep vein thrombosis

The term Upper Extremity Deep Vein Thrombosis (UEDVT) covers thrombosis in the veins of the upper extremity (brachial, axillary and subclavian), neck (jugular) or central thoracic veins (brachiocephalic and superior caval). UEDVT is relatively uncommon and

comprises 4% of all VTE diagnoses.[30] The primary limitation of CUS for UEDVT is that veins may be inaccessible for compression due to overlying anatomical structures. Colour-coded Doppler US may then be used to visualize intraluminal thrombi or abnormal flow patterns. A systematic review summarized 17 studies using US for UEDVT, although the total number of patients was limited and the methodological quality of the studies was low because venography was not used as a reference test in all patients. The summary estimates of sensitivity and specificity of (C)US were 97% (95% CI 90-100%) and 96% (95% CI 87-100%) and for CUS combined with Doppler were 91% (95% CI 85-97%) and 93% (95% CI 80-100%).[31] The most recent study in this systematic review included the largest patient population (126 patients) and compared CUS combined with Doppler to reference standard invasive contrast venography. Compared with the reference standard, the sensitivity and specificity of (C)US were 82% (95% CI 70-93%) and 82% (95% CI 72-92%) respectively. Venous incompressibility correlated well with thrombosis (100%), but only 50% of isolated flow abnormalities were thrombosis related.[32] The use of CUS in a diagnostic algorithm starting with a CDR and D-dimer testing was recently evaluated in a prospective management study, for an overall failure rate of 0.4% (95% CI 0.0-2.2%). Seven of 406 patients (1.7%) had indeterminate US-results. In six of these seven patients, the diagnosis could be completed with repeated US after 3-5 days and one patient required contrast venography. This algorithm can be used in standard clinical practice, although external validation is needed for a higher level of evidence.[33]

Splanchnic vein thrombosis

Splanchic vein thrombosis (SVT) includes portal vein thrombosis (PVT), mesenterial vein thrombosis (MVT), splenic vein thrombosis, and the Budd-Chiari syndrome (BCS). The incidence of SVT varies from 0.5-1/million (BCS) to 0.7-2.7/100.000 (PVT, MVT).[34,35]

For suspected MVT, Doppler US is not accurate due to overlying bowel gas and CTA and CE-MRV should preferably be performed. Although no thorough accuracy studies have been performed in patients with clinically suspected SVT, according to an older study, sensitivity and specificity of Doppler US for suspected PVT was 89% and 92% respectively.[36]

Computed tomography

Technique

Computed tomography involves computer-processed imaging acquired from combinations of consecutive X-ray projections taken from different angles to produce cross-sectional slices of specific areas of the scanned part of the body.

Pulmonary embolism

CTPA is regarded the primary imaging test for diagnosing patients with suspected PE. After the application of iodinated intravenous contrast material, CTPA enables direct visualisation of endovascular abnormalities including luminal clots. Diagnostic criteria for acute PE by CTPA are: (i) failure of contrast material to fill the entire lumen of an artery (central filling defect), (ii) partial filling defect surrounded by contrast material on a cross-sectional image, (iii) contrast material between the central filling defect and the artery wall on an in-plane, longitudinal image, and (iv) a peripheral intraluminal filling defect that forms an acute angle with the artery wall (**Fig 2.**).[37]

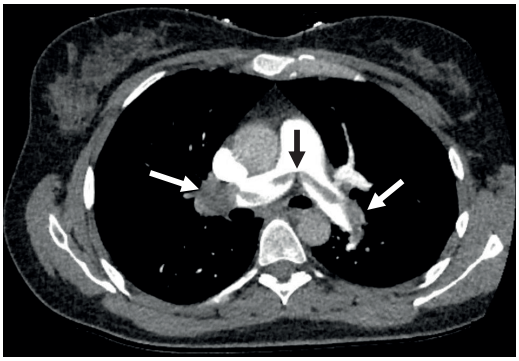

Figure 2. A 39-year-old female patient presenting with dyspnoea, chest pain, and tendency to collapse, leading to suspicion of pulmonary embolism. The computed tomography pulmonary angiography in axial orientation shows a 'saddle' pulmonary embolus at the pulmonary artery bifurcation (black arrow) and large central emboli in the left and right main pulmonary arteries (white arrows).

First generation single-detector-row helical CT scanners had a specificity of 90% but a low sensitivity (70%) for acute PE.[38] The introduction of multidetector-row CT scanners has improved the visualization of segmental and subsegmental pulmonary arteries.[39] CTPA studies using multidetector-row CT scanners have showed excellent sensitivity of 96 to 100% and specificity of 97 to 98%.[37,40,41] A normal CTPA result alone can safely exclude PE in all patients in whom CTPA is required to rule out this disease without the need for additional US to rule out DVT.[5,42] The main advantage of multidetector-row CT scanners is that they are widely available. Scan times have been reduced to 4-5 seconds with 64-slice scanners.[43] Another advantage of CTPA is the possibility to detect an alternative diagnosis that may explain the patient's complaints.[44,45] A prospective study in 203 consecutive patients reported an alternative diagnosis in 88 patients (43%); however, only with therapeutic consequences in 10 (4.9%).[46] Limitations of CTPA include the use of iodinated contrast agent, which is a relative contraindication in patients with previous moderate-to-severe allergic reaction to iodinated contrast agents (occurring in 0.7% of patients). Also, the use of iodinated contrast is associated with a risk of (temporary) contrast-induced nephropathy (occurring in 8.9-12% of patients).[6,47] Second, the radiation dose of a single CTPA ranges from 3 to 5 mSv, with an estimated 150 excess cancer deaths/ 1 million.[41] In the last decades, the proportion of detected

subsegmental PE with multidetector CTPA increased from 4.7% to 9.4% compared to single- detector CT. This increased incidence of subsegmental PE with CTPA has been associated with a lower severity of illness and lower mortality in the CTPA era.[48,49] These peripheral intraluminal filling defects may not represent true thrombus but could be imaging artefacts with uncertain clinical significance. Indeed, small observational studies have suggested that these subsegmental PEs may not need anticoagulant treatment.[50] An ongoing study in which patients with symptomatic subsegmental PE and no DVT or cancer are left untreated and followed for 3 months will provide more clarity on this matter (NCT01455818).

CTEPH

For reasons still unknown, in some patients acute PE does not resolve completely despite adequate anticoagulation treatment. These unresolved, chronic emboli may ultimately lead to small-vessel arteriopathy, high pulmonary vascular resistance, pulmonary hypertension and right heart failure, a rare condition called chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a severe disease with a poor prognosis unless detected in an early stage and anatomic favourable (proximal) location, allowing for successful surgical removal of the chronic clots. Combined with right heart catheterization which is necessary for accurate confirmation of pulmonary hypertension, selective digital subtraction angiography (DSA) has been the traditional method for diagnosing CTEPH and assessing its operability.[51]

Currently, contrast-enhanced CTPA can be used in the diagnostic work-up of CTEPH. Specific findings of CTEPH are dilatation of the central pulmonary arteries, the detection of organized wall-adherent fibrotic material, intraluminal webs and bands, vessel wall irregularities, abrupt vessel cut-offs, complete vessel occlusions and abnormal proximal-to-distal vessel tapering (**Fig. 3**). Compared with DSA, the sensitivity of CTPA for the detection of CTEPH is reported to be 95% (95% CI 92%-97%) at the level of the main and lobar arteries, and 88% (95% CI 87%-90%) at the segmental level, with associated specificities of 96% (95% CI 94%-97%) and 89% (95% CI 87%-91%) respectively.[52] Contemporary CT techniques (i.e. dual-energy and 320-slice CT machines) may even further increase the sensitivity for the segmental arteries.[53,54] Even so and in contrast to planar ventilation/perfusion V/Q lung scan, operable CTEPH may not be excluded by normal CTPA alone. Therefore, the recommended first-line imaging test in the diagnostic work-up of suspected CTEPH is V/Q scintigraphy.[51]

Single photon emission tomography (SPECT)

Pulmonary embolism

Planar V/Q scintigraphy was the first imaging test to replace invasive pulmonary angiography for the diagnosis of acute PE.[55] Perfusion imaging involves an intravenous

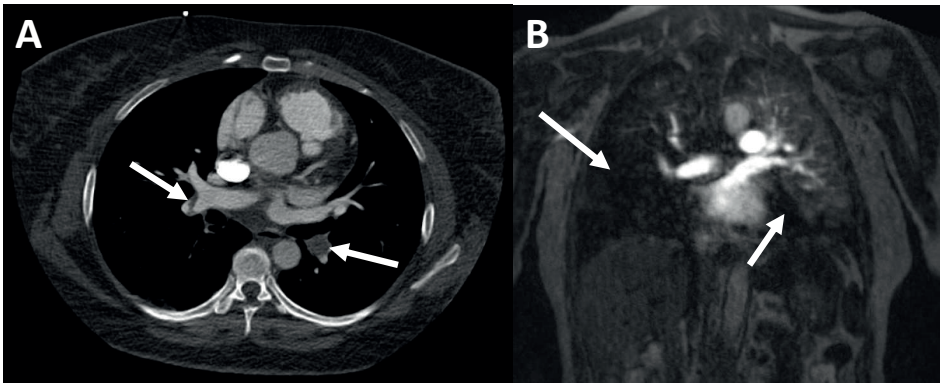

Figure 3. (A) Computed tomography-pulmonary angiography of a patient with chronic thromboembolic pulmonary hypertension (CTEPH). Left white arrow indicates central 'webs' in the lower lobe artery. Right white arrow indicates total occlusion of the left lower lobe artery.
(B) Magnetic resonance pulmonary angiography (twist protocol) of a patient with CTEPH. Left white arrow indicates a total perfusion defect of the right middle and lower lobe, right arrow indicates a perfusion defect of the left lower lobe.

injection of technetium labelled macro-aggregated albumin (^{99m}Tc-MAA). These radioactive particles are small enough to be trapped in the pulmonary capillary bed. The ventilation scan is performed using an inhaled radiopharmaceutical to obtain a pattern of lung ventilation. Acute PE is diagnosed in case of a V/Q mismatch: a thrombus within a pulmonary artery results in reduced perfusion to that lung segment while the alveolar air spaces in the same region remain relatively well aerated. Planar V/Q scintigraphy is a two-dimensional technique: posterior, anterior, oblique and sometimes lateral views are acquired.[56] The main drawback of this technique is the high proportion of non-diagnostic scans in 28-46% of patients.[48] This is because of areas of lung overlap and 'shine through' can occur between segments, which can mask perfusion defects.

SPECT represents a new era in nuclear medicine, which is based on a three-dimensional technique, allowing views in the transverse, coronal and sagittal planes.[56] To date, no large prospective outcome studies evaluating the safety of withholding anticoagulant treatment in patients with normal SPECT have been performed. In a retrospective study the accuracy of SPECT was evaluated in 2328 consecutive patients with suspected PE. SPECT was feasible in 99% of the patients. Based on clinical decision at baseline by expert opinion and 6-month follow-up, sensitivity was quantified as 99% and specificity as 98%. The main drawback of this retrospective study is the lack of reference diagnostic test, which may cause overestimation of the accuracy.[57] A review on 19 studies that comprised 27 data sets including 6393 examinations from 5923 patients concluded that planar V/Q scintigraphy was inferior to both V/Q SPECT and CTPA, with no difference between the latter two. Area under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curves were: 0.85 (95% CI 0.75-0.95), 0.99 (95% CI 0.96-1.0) and 0.98 (95% CI 0.94-1.0)

respectively. Advantages of SPECT are the avoidance of iodinated contrast agent injections and the lower overall radiation burden (1.2-2 vs. 3-5 mSv). CTPA, however takes less time to perform, is more cost-effective, and is more widely available. The application of SPECT may be considered in situations where radiation dose is of concern, such as in young female patients, although future outcome studies should be performed before the technique can be recommended for use in day-to-day clinical practice.[58]

CT venography

DVT of the leg

There are a few situations in which CUS is technically impossible to perform, such as in patients with plaster casts. CT venography (CT-V) has the potential to fill this gap. A meta-analysis pooled the sensitivity and specificity of 13 studies comparing CT-V with US for the diagnosis of lower leg DVT, although most of these studies included patients with suspected PE who -in the majority of cases- had no symptoms or clinical signs of DVT. The summary estimate of sensitivity was 95.9% (95% CI 93.0-97.8%) and of specificity 95.2% (95% CI 93.6-96.5%) indicating comparable diagnostic accuracy.[59] One study compared CT-V directly with invasive contrast venography in 52 patients and showed a sensitivity of 100% (95% CI 92-100%) and a specificity of 96% (95% CI 84-98%).[60] Because CUS and CT-V have comparable diagnostic accuracies, CT-V should be reserved for only those situations in which CUS is impossible to perform.[8]

Upper extremity deep vein thrombosis

CT-V can also be used to detect thrombi within the jugular veins, the brachiocephalic veins and the superior vena cava.[61] Importantly, no large studies with CT-V in patients with arm vein thrombosis have been performed. Only one small study in 18 consecutive patients showed a good correlation of CT-V with digital subtraction venography. All the 24 stenotic sites demonstrated with digital subtraction venography were also identified with CT-V.[62]

Splanchnic vein thrombosis

Using CT, incidental cases of SVT are increasingly found. The prevalence of incidental SVT found in a retrospective review was 1.7%.[63] Signs suggestive of intestinal ischemia, such as thinning or thickening of the intestinal wall, lack of mucosal enhancement after contrast injection, or the presence of intramural gas, may be detected (**Fig. 4**).[64] To our knowledge, accuracy studies using CT-V have not been performed in patients with clinically suspected SVT.

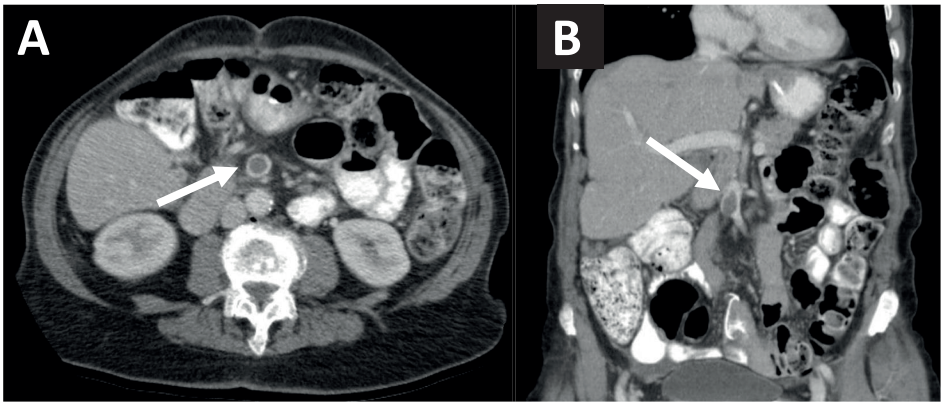

Figure 4. A 79-year-old female patient known with extra-ovarian cancer, presenting with heavy abdominal pain suspected for bowel ischemia. Computed tomography in portal-venous contrast phase showing superior mesenteric vein thrombosis in axial view (arrow in A), and coronal view (arrow in B).

Cerebral vein thrombosis

The cerebral venous system consists of the deep venous system, the dural venous sinuses and the superficial venous system. For the diagnosis of cerebral vein thrombosis (CVT), MRI in combination with contrast enhanced- magnetic resonance venography (CE-MRV) is considered to be the gold standard. CT-V may be a good alternative because of its more widespread availability and shorter imaging time.[65] A further advantage is the possibility to rule out other acute cerebral disorders such as cerebral infarcts or hemorrhages. A non-enhanced CT scan may show the thrombus as a hyperintense signal in one of the cerebral veins ('dense clot sign'). A thrombosed cortical vein can be seen as a linear or cord-like density ('cord sign').[66] The 'empty delta sign' can be detected in 30% of patients with thrombosis of the superior sagittal sinus.[67] This sign consists of a triangular area of enhancement (due to venous collateral circulation surrounding the thrombosed sinus) with a low-attenuating center, which is the thrombosed sinus. More often, in 60-80% of patients with CVT, CT shows only indirect signs of CVT such as brain edema and venous infarction.[68] CT-V has been directly compared to CE-MRV in three small studies. The largest study included 50 patients with suspected CVT and reported a sensitivity of 75-100% and a specificity of 82-100%, depending on thrombus site.[69-71] An example of CVT is shown in **Fig. 5**.

MRI

Technique

With MRI, a magnetic field and pulses of radiowave energy are used to create images of the body.

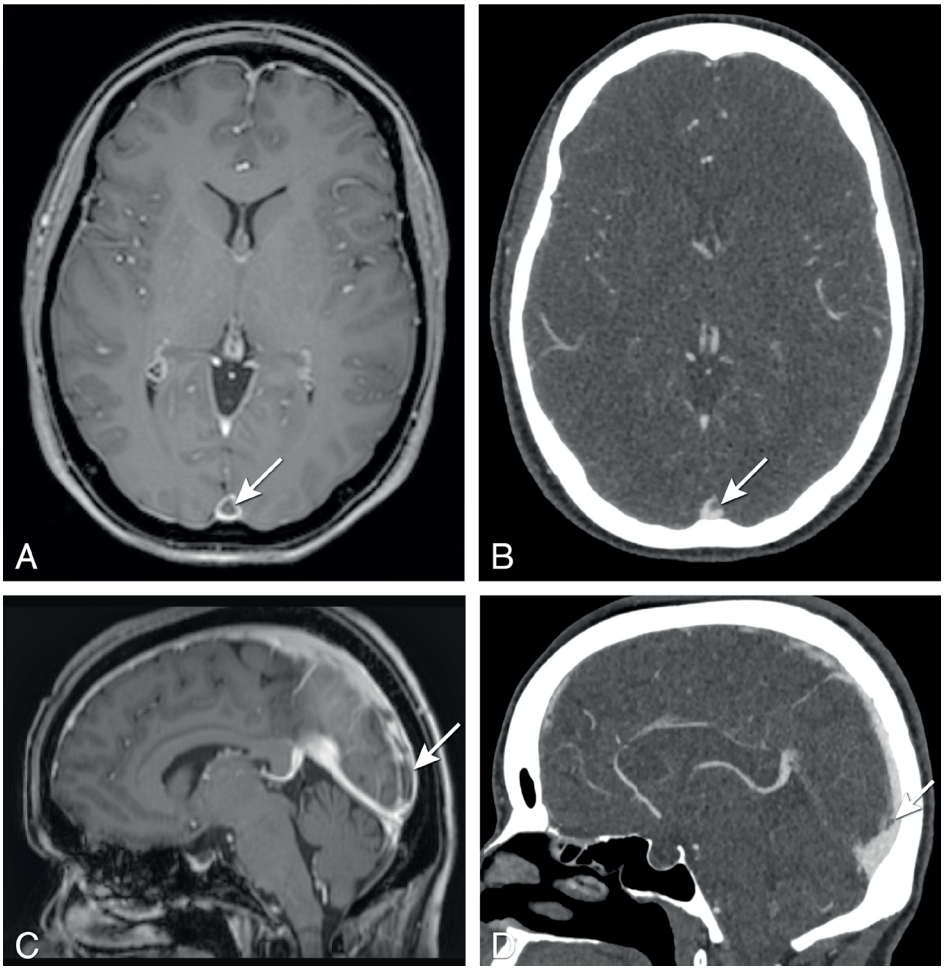

Figure 5. A 32-year-old female with systemic lupus erythematosus and history of pulmonary embolism presenting with 1-week duration of headache. (A,C) Three-dimensional T1-weighted magnetic resonance angiography after gadolinium administration. TE 4.59 ms, TR 9.79 ms, slice thickness 1.2 mm. (B, D) Computed tomography-angiography with iodinated contrast. (B)Axial view. (D) Sagittal view. Filling defect is present in the occipital region of the superior sagittal sinus, representing sagittal sinus thrombosis (arrows) at initial MRI diagnosis (A and C). One week after treatment most of the thrombus has resolved, note residual thrombosis on CT (B and D).

DVT of the leg

Different specific MRI techniques can be used to visualize DVT of the leg. The most described techniques are phase-contrast venography and Time of flight (TOF) venography, which can be used to visualize flow within vessels, without the need of contrast material.[72] Phase-contrast venography is based on using the change in phase shifts of the flowing protons in the region of interest to create an image. Phase-contrast venography

was used to study 100 patients with a suspected upper or lower extremity DVT, with contrast venography as reference standard. The sensitivity was 90% and the specificity 100%.[72] With TOF imaging, a high repetition time is used (high rate of radiofrequency pulses) favouring the inflow effect of blood.[73] This technique was tested in 43 patients with clinical suspicion of DVT. Compared with contrast venography, the sensitivity was 100% and the specificity 94%.[74] Both techniques, however, are rarely used because of the long imaging time.

CE-MRV uses a gadolinium based contrast agent. The use of contrast agents increases the vascular signal by shortening the T1 relaxation time. For the so-called indirect approach, gadolinium-based contrast agent is administered via the antecubital vein and imaging is performed when contrast arrives at the tissue level of interest.[75] Direct CE-MRV uses a diluted contrast agent that is injected upstream on the side of the affected extremity. This technique resembles conventional venography and can visualize the full deep and superficial venous system. The most important pitfalls of CE-MRV are, first, the dark intraluminal filling defect that may be masked by the bright signal of blood surrounding the thrombus and, second, insufficient dilution of contrast agent that can induce a T2 shortening effect that can simulate a thrombus.[76] A meta-analysis of 14 MR diagnostic accuracy studies including TOF, phase contrast and CE-MRV techniques reported a summary estimate sensitivity of 91.5% (95% CI 87.5-94.5%) with an interstudy range of 0 to 100%, and a specificity of 94.8% (95% CI 92.6-96.5%) with an inter-study range of 43 to 100%.[76] The large heterogeneity between the studies was caused by major differences in the applied MRI techniques. Of note, management studies using MR(-venography) as first-line test in the diagnostic management of suspected DVT have not been published so far. Hence, recommendations on its use cannot be made.

Another emerging MRI technique is Magnetic Resonance Direct Thrombus Imaging (MRDTI). MRDTI is based on the oxygenation of haemoglobin when blood clots, which results in the formation of methemoglobin. This acts as an endogenous contrast agent and appears as high signal when imaged using a T1-weighted MRI sequence (**Fig. 6**).[77] The MRDTI scan technique has been tested in several studies. A prospective study performed MRDTI scans in 101 patients with suspected DVT in whom the diagnosis was already proven or rejected by venography results. This resulted in an excellent diagnostic accuracy with a sensitivity of 97-100% and a specificity of 100% with good interobserver variability (κ statistic 0.89-0.98).[78] The high signal disappears completely after six months.[79] This characteristic is valuable in the diagnosis of recurrent ipsilateral DVT since it makes the distinction between residual thrombi and an acute recurrent DVT. In a recent study, it has been shown that MRDTI accurately differentiates patients with CUS-confirmed recurrent ipsilateral DVT and asymptomatic residual intravascular clots.[80] Therefore, MRDTI can likely be used as a single and conclusive diagnostic test in case of suspected recurrent ipsilateral DVT. A prospective, multicenter management

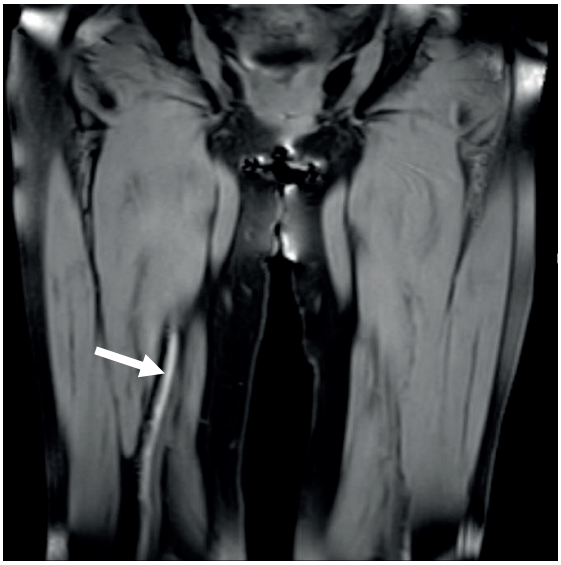

Figure 6. A 76-year-old female patient presenting with suspected ipsilateral recurrent deep vein thrombosis. Magnetic resonance direct thrombus imaging (MRDTI) showing high-signal intensity in the superficial femoral vein and popliteal vein of the right leg, indicating recurrent DVT (arrow).

study aiming to study 305 patients with suspected ipsilateral recurrent DVT managed based on the result of MRDTI only is under way(NCT02262052).

In the last years, new target specific contrast agents have been developed allowing for the use of selective molecular MRI. Targets examined for contrast imaging are fibrin and α2-antiplasmin. Animal models have been developed for fibrin-binding gadolinium-labelled peptides.[81,82] These have been tested in a phase 2 trial and were been shown to be applicable in humans without any adverse effects.[83] Larger prospective studies in humans are however needed.

Pulmonary embolism

Magnetic Resonance Pulmonary Angiography (MR-PA) is an attractive method for the diagnosis of PE because it avoids the use of ionizing radiation. With MR-PA, intravenous gadolinium is used, which can shorten the T1 signal of blood producing bright images of blood. A partially occlusive intraluminal filling defect or complete arterial occlusion with termination of the column of contrast material is diagnostic for PE.

Two large accuracy studies have been performed with MR-PA. The PIOPED III study was a prospective multicentre study that applied MR-PA in 371 patients with suspected PE.[84] The percentage of technically inadequate images was high with a mean of 25%. With CTPA as reference method, the sensitivity and specificity of the remaining technically adequate scans was 78% and 99% respectively. When technically adequate venography was included (52% had technically inadequate results), the sensitivity and specificity increased to 92% and 96%, respectively.[84] The second study was the IRM-EP study, in which 274 patients underwent both CTPA and MR-PA. A total of 30% had inconclusive

MRI results due to artefacts, poor opacification on angiographic sequences or the presence of isolated perfusion abnormalities. Sensitivity and specificity in the remaining patients varied between 79- 85% and 99-100% between the two readers.[85] In an attempt to improve the sensitivity of MR-PA, a study is currently investigating the accuracy of MRI in combination with lower extremity CUS(NCT02059551).

CTEPH

Because of its better safety profile compared with invasive digital subtraction angiography (DSA) and CTPA, the accuracy MR-PA has been investigated in patients with suspected CTEPH. As with acute PE, small studies have shown that MR-PA of the pulmonary vasculature is still inferior to DSA and CTPA from the level of the segmental arteries, with a sensitivity of 83% and a specificity of 99% compared with CTPA.[86] The current role of MR-PA in the work-up of CTEPH patients can be complimentary to DSA and/or CTPA, and used according to local experience in the CTEPH referral centers.[51]

Upper extremity deep vein thrombosis

The different MRI techniques that are used in the diagnosis of DVT can also be used for imaging of the upper extremity veins. In one study including 44 patients with suspected UE-DVT, TOF and CE-MRV were compared to contrast venography. The sensitivity of TOF was 71% (95% CI 29-96%) with a specificity of 89% (95% CI 52-100%). For CE-MRV, the sensitivity was 50% (95% CI 12-88%) with a specificity of 80% (95% CI 44-97%).[87] Both tests, thus, lack the accuracy to be of value in clinical practice.

Splanchnic vein thrombosis

For the diagnosis of SVT, CE-MRV is not the imaging test of choice because motion artefacts limit its accuracy. Even so, in a small case series of 36 patients with portal hypertension, CE-MRV was as accurate as DSA for the diagnosis of thrombosis of the portal, splenic or superior mesenteric veins, with the definite diagnosis confirmed in 22 patients by surgical validation or by means of consensus with the combined reading of the CE-MRV and DSA images in the remaining 14 patients. This resulted in a sensitivity and specificity of 100% and 98% respectively.[88] CE-MRV may, therefore, be a valuable diagnostic alternative in the (near) future in case of suspected abdominal or pelvic vein thrombosis, if these findings are confirmed in external cohorts.

Cerebral vein thrombosis

For thrombosis of the cerebral veins and sinuses, the diagnostic test of first choice is MRI in combination with magnetic resonance venography, although never reliably compared with angiography.[65] The thrombosed veins will appear isointense on T1-weighted images in the first five days, while the T2-weighted images are hypointense. After this

period both T1 and T2 weighted images show increased signals at the thrombosis site. The combination with absence flow on flow magnetic resonance venography is diagnostic for thrombosis, although false-positive results due to artefacts may occur.[65,89,90] A recent study investigated the use of Magnetic Resonance Black-Blood Thrombus Imaging (MRBTI). This technique has similarities with the MRDTI technique, because it can assess the thrombus directly instead of visualization of the reduction of venous flow as result of the thrombus. MRBTI uses a T1 variable flip angle turbo spin-echo technique to nullify the intrinsic blood, leading to a hyperintense signal of the thrombus. MRBTI was performed in 23 patients with proven CVT and 24 patients with negative CVT according to conventional imaging techniques (MRI and CT-V). The sensitivity was 97.4% with a specificity of 99.3%.[91]

No studies have evaluated MRDTI in the diagnostic management of unusual vein thrombosis. Only one study reported that when applying total-body MRDTI for detecting the origin of acute PE in 99 patients, thrombi in superficial and abdominal veins were detected in five and three patients respectively.[24]

Positron Emission Tomography

Technique

The principle of PET with F-18 fluoro-2- desoxy-D-glucose (FDG) is based on accumulation of FDG, which occurs among other in activated leukocytes. Inflammation is linked with thrombus formation, due to accumulation of inflammatory cells within the thrombus and surrounding area.[92] This inflammation mechanism with associated FDG accumulation optionally enables imaging of VT with PET.

Deep vein thrombosis

In a study of 12 patients with proximal DVT, FDG PET/CT was accurate in detecting the thrombus, with a sensitivity and specificity of 87.5% and 100% respectively.[93] Although a recent published study including 62 patients with CUS-proved DVT confirmed the detectable higher metabolic activity in DVT, the optimal diagnostic cut-off is unknown and the reported sensitivity and specificity was much lower with values of 31% (95 % CI 24-39%) and 88% (81-92%) respectively.[94] As with MRDTI, the positive signal of FDG PET decreases over time after initiation of anticoagulant treatment. The proposed ability to differentiate acute from chronic clots in the leg veins may suggest a potential role of FDG-PET in the diagnostic workup of patients with suspected recurrent ipsilateral DVT.[95] Of note, its feasibility in clinical practice has to be evaluated, taking into account the necessary fasting period of 6 hours and the >1 hour waiting time after isotope administration before scanning.[96]

Pulmonary embolism

Several case-reports and retrospective studies have described incidental PE on FDG PET/CT images, mostly observed in cancer patients.[97,98] Preliminary results of a prospective observational study indicated disappointing accuracy of FDG/PET: only two of six PE patients showed notable FDG accumulation.[99] The study is recently completed, but results are not published yet (NCT01466426).

CONCLUSIONS

Today's main used thrombus imaging techniques -CUS and CTPA- are highly accurate and widely applied. Disadvantages of these two techniques nonetheless remain, leaving room for development of new imaging techniques for tomorrow's use. Currently, most of the emerging imaging modalities lack full validation and thus cannot (yet) be recommended for standard use in daily practice.

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3

Disease prevalence dependent failure rate in diagnostic management studies in suspected deep vein thrombosis: communication from the SSC of the ISTH

C.E.A. Dronkers, Y.M. Ende-Verhaar, P.A. Kyrle, M. Righini, S.C. Cannegieter, M.V. Huisman, F. A. Klok FOR THE SUBCOMMITTEE ON PREDICTIVE AND DIAGNOSTIC VARIABLES IN THROMBOTIC DISEASE

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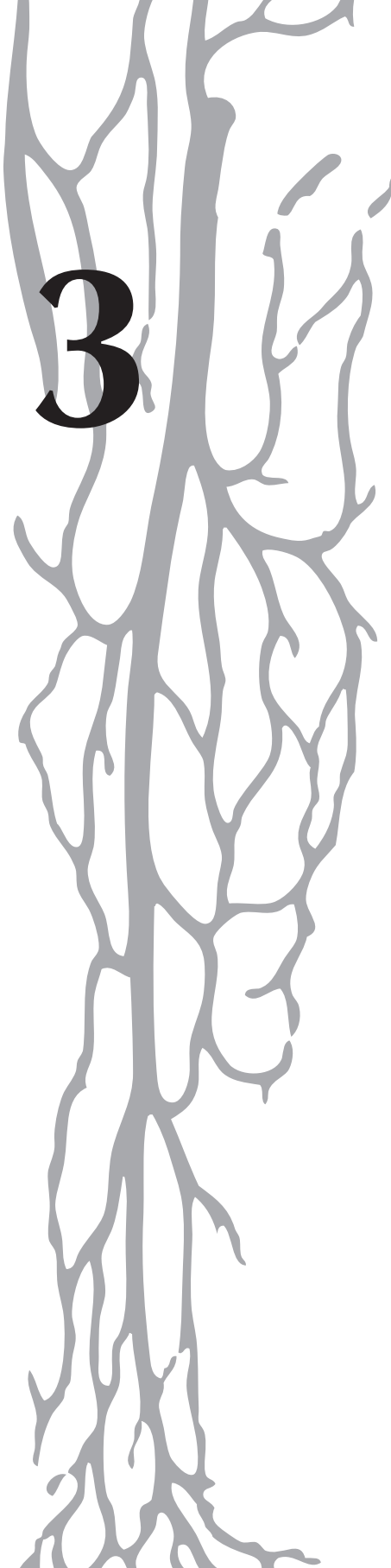

INTRODUCTION

Objective diagnosis of deep vein thrombosis (DVT) is important, because untreated DVT is associated with a high risk of acute pulmonary embolism and post-thrombotic syndrome. As it is impossible to diagnose DVT on the basis of clinical symptoms or laboratory tests alone, objective imaging testing is needed to confirm or refute the diagnosis. The favoured strategy for the diagnostic management of suspected first DVT is the combination of pre-test probability assessment, D-dimer testing and (serial) compression ultrasound (CUS).[1] Recently, several new diagnostic tests have been suggested, such as a higher D-dimer threshold of <1.0 µg/ml if there is a low clinical probability, computed tomography-venography if it is impossible to perform CUS, and magnetic resonance direct thrombus imaging (MRDTI) for the diagnosis of ipsilateral recurrent DVT.[2]

Notably, because contrast venography is still the reference for diagnosing DVT, current guidelines state that the standard against which all DVT diagnostic management studies should be evaluated is the percentage of patients with a venous thromboembolism (VTE) during 3 months of follow-up despite a normal venography finding, to ensure that new diagnostic tests or algorithms are tested against the reference standard.[1] This failure rate has been shown to be 1.3% (upper limit 95% confidence interval [CI] 4.4%) in a study evaluating 160 consecutive patients with suspected acute DVT and a negative venography finding.[3] Importantly, the threshold for doctors to suspect DVT and initiate diagnostic testing has lowered over the past few years. This trend is probably attributable to better awareness of the disease, and the availability of non-invasive CUS as an alternative to venography. This trend has been shown for suspected PE as well.[4] This lower diagnostic threshold has led to a sharp decrease in DVT prevalence in examined patients in recent studies, to even below 10%.[5] Bayes' theorem states that disease prevalence (the pre-test probability of having the disease) and failure rate (the post-test probability of having the disease) are related. This implies that, because the disease prevalence has decreased over the past few years, the diagnostic standard of diagnostic management studies should be changed accordingly.[6] In analogy to the SSC communication entitled: 'Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH,[4] the purpose of this ISTH SSC communication was to evaluate the association of DVT prevalence and diagnostic failure rate in published studies on diagnosis of DVT, in order to propose a new diagnostic safety threshold for future studies on the diagnostic management of suspected DVT.

METHODS

This systematic review and meta-analysis was performed in accordance with the PRISMA criteria.[7] All parts of the systematic review were performed by two independent reviewers (C.D. and Y.E.), disagreements were resolved by an additional reviewer (F.K.). A literature search of Pubmed, Embase, Web of Science, Cochrane and Cohchrane central register of controlled trials (central) was performed on 29 February 2016 with the aim to find all high-quality diagnostic studies in acute DVT from 1990 on. First, all references were screened by title and abstract. After exclusion of non-relevant studies, full-text articles were analysed for eligibility before final study selection. Study selection criteria were: 1) prospective study design, 2) pre-specified study protocol, 3) clear description of inclusion and exclusion criteria, 4) inclusion of >100 consecutive patients, 5) at least 3 months of follow-up, 6) <5% lost to follow-up, and 7) use of an appropriate diagnostic standard. The last of these was defined as: (an algorithm consisting of) a validated clinical decision rule combined with a highly sensitive D-dimer test, venography, and whole leg CUS or serial proximal CUS. In both CUS strategies, the lack of compressibility of a venous segment under the ultrasound probe was diagnostic for DVT. In case of suspected recurrent DVT, a non-compressible previously normalized vein or the enlargement of a residual thrombus diameter of ≥2 mm as compared with the previous CUS assessment was diagnostic for recurrent DVT.[8] To avoid risk of bias, only studies meeting all criteria were included in this meta-analysis. From each selected study, the following information was extracted: 1) year of publication, 2) total number of included patients, 3) diagnostic test or algorithm, 4) focus on proximal DVT only or also distal DVT 5) DVT prevalence at baseline and 6) failure rate defined by the incidence of patients with VTE despite a negative test during 3-month follow-up. Two graphs were plotted: one with year of publication versus DVT prevalence, the second with DVT prevalence versus failure rate. Reference lines with 95% confidence intervals, adjusted for number of patients included in the studies were calculated by the use of least squares linear regression analysis. The formula of this reference line was predefined as being the most accurate safety threshold for future studies. Primary analysis was based on studies with a 3-month follow-up period. A sensitivity analysis was performed that included studies with longer follow-up periods and studies restricted to proximal DVT. Statistical analyses were performed using SPSS version 23 (IBM, Armonk, NY, USA) and Stata 14.0 (Stata Corp., college Station, TX, USA).

FINDINGS

After the literature search, 1034 potentially relevant studies were identified and screened for eligibility. Seven hundred and nineteen studies were excluded after title and abstract screening, leaving 315 studies for full text evaluation. Finally, 51 studies were included, of which 46 had a follow-up period of exactly 3 months and were selected for the primary analysis. Study selection flowchart and reasons for exclusion are shown in **Appendix I**. Study characteristics and extracted information is summarized in **Appendix II**. The selected studies included a total of 28.145 patients, with a mean baseline DVT prevalence of 20% (95%CI 19.9-20.1, range 5.7-47%) and a failure rate of 0.80% (95%CI 0.79-0.81, range 0-2.8%). The reference line of the graph plotting DVT prevalence versus year of publication showed a decrease in DVT prevalence over the years, with a 2.65% decrease per 5 years, according to the formula: Y=27.95-0.53*x (R^2 0.066, p<0.001; **Fig.1a**). The second graph demonstrates that the mean failure rate increased with higher disease prevalence in individual studies with an absolute 1.0% higher DVT prevalence leading to a mean 0.026 percentage points increase in failure rate per 1% increase in prevalence, according to the formula 0.28 + 0.026*x (R^2 0.195, p<0.001; **Fig.1b**). The number 0.28 in this formula indicates the 3-month VTE incidence in a virtual, extrapolated study with 0% DVT prevalence at baseline (which is the cross-point of the reference line with the y-axis). The upper limit of the 95% CI of this regression line resulted in the formula: 1.25 + 0.026*x. The sensitivity analysis, including five additional studies with follow-up beyond the first 3 months and the one limited to studies analysing proximal DVT only, indicated comparable study outcomes (formulas 0.45 +0.02*x and 0.46+0.02*x respectively).

RECOMMENDATIONS

A DVT prevalence-dependent, diagnostic safety threshold should be considered for future diagnostic studies. Our systematic review and meta-analysis of high-quality DVT diagnostic management studies shows that the failure rate increases with 0.03 points per percentage point higher disease prevalence. We suggest that the formula with this regression coefficient of 0.03 combined with a baseline DVT prevalence of 1.25% should be used as diagnostic standard, based on the upper limit of the 95% confidence interval of our pooled analysis. We suggest that all future studies incorporate this formula in their power-analysis to prevent new diagnostic tests being evaluated in underpowered studies that do not allow for sufficient validation. For a power calculation example, we refer to our previous SSC communication.[4]

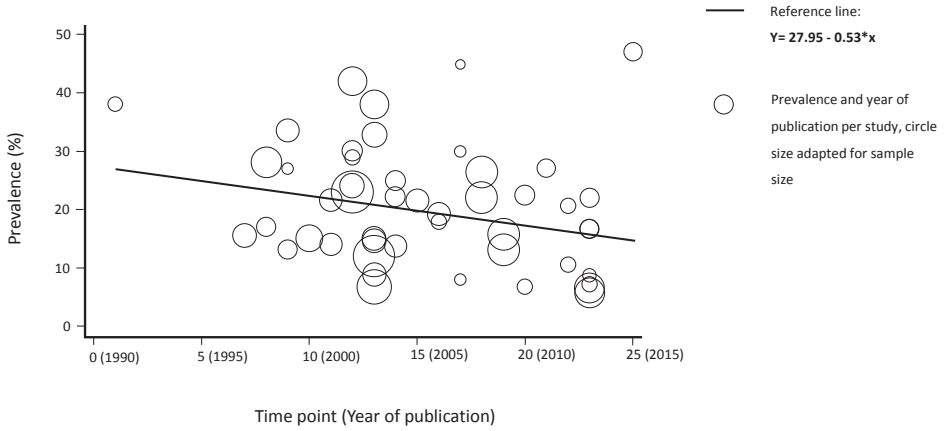

Figure 1a. Decrease of disease prevalence over the last years

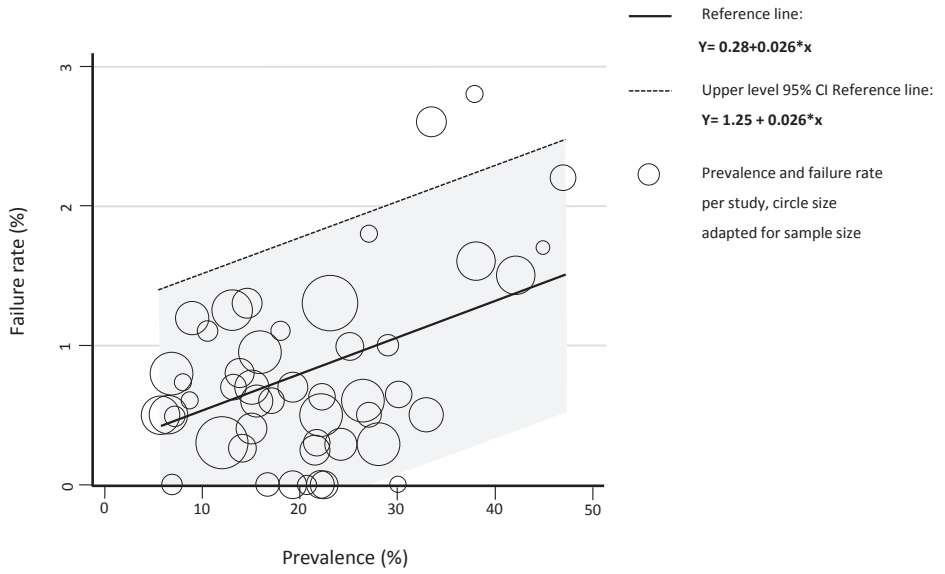

Figure 1b. Prevalence versus failure rate in high quality deep vein thrombosis diagnostic management studies. Grey area depicts the 95% confidence interval of the reference line.

DISCUSSION

This study confirms the decreasing baseline disease prevalence of DVT diagnostic management studies over the last years. We suggest incorporation of the DVT prevalence-dependent diagnostic safety threshold in all future diagnostic studies. The formula is, for example, also applicable to studies including patients with a higher a-priori risk of VTE, such as patients with cancer or previous VTE, mainly due to the fact that these patients

were well represented in the studies included in the meta-analysis and the adaptation of the accepted failure rate to this higher a-priori risk. Of note, the proposed diagnostic safety threshold in this study is not meant to be used in clinical practice, but merely as guidance for planning of future diagnostic studies. Notably, when using diagnostic tests in clinical practice, it is important to keep in mind that the diagnostic indices of tests may differ in specific patient groups. It was, for instance, shown that both sensitivity and specificity of the Wells rule variables differ in patients with cancer, which can lead to a higher rate of false negative test results in such patients.[9] Ideally, this phenomenon should be acknowledged in the design and reporting of (future) diagnostic studies by investigating diagnostic accuracy across different subgroups, where appropriate. Besides a proper safety threshold, it is also important to take the lower costs and/or lower risk of potential harms of a new test into account before its implementation. Even so, a relevant loss of sensitivity of a new diagnostic test does not easily weigh up against potential economic benefits. In conclusion, we propose a new diagnostic safety threshold for future DVT diagnostic management studies, in which the threshold is adjusted for the expected disease prevalence of the study population.

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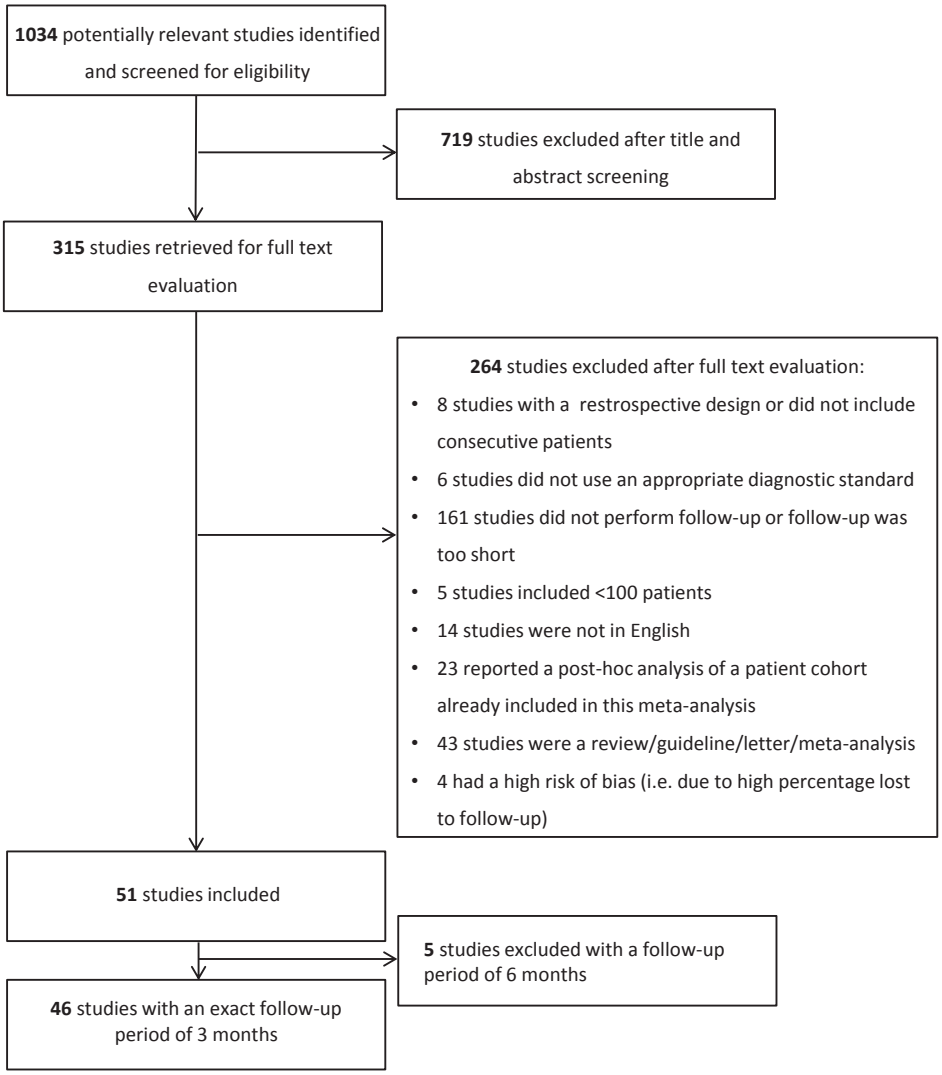

Appendix I. Flowchart of study selection

Appendix II.

Author	Year of publication	Diagnostic tests/ algorithm	Only proximal thrombosis	Follow-up (months)	Number of patients	Disease prevalence at baseline (%)	Failure rate (%)
Aguilar[1]	2007	Wells rule, D-dimer, (serial) proximal CUS	yes	3	105	44.8	1.7
Anderson[2]	1999	CDR, (serial)proximal CUS, venography	no	3	344	13.1	0.7
Anderson[3]	2003	CDR, (serial) proximal CUS, venography	no	3	1109	17.9	0.79
Bates[4]	2003	Wells rule, D-dimer, (serial) proximal CUS	yes	3	556	8.9	1.2
Bernardi[5]	1998	CUS, D-dimer test=> positive: serial proximal CUS	yes	3	946	28	0.4
Bernardi[6]	2008	Randomisation between D-dimer + serial proximal CUS and whole leg CUS	no	3	2098 (1045/1053)	22.1/26.4	0.9/1.2
Birdwell [7]	1998	(Serial) proximal CUS + venography to confirm DVT	no	3	405	17	0.6
Birdwell[8]	2000	(Serial) proximal CUS + venography to confirm DVT	no	3	709	15	0.7
Büller[9]	2009	CDR, D-dimer, US	yes	3	1002	13	1.25
Chan[10]	2007	(Serial) CUS	no	3	149	8	0.73
Chan[11]	2010	(Serial)CUS	no	3	249	6.8	0
Chan[12]	2013	(Serial)CUS	no	3	221	7.2	0.49
Cini[13]	2014	Wells rule, D-dimer, (Serial) proximal CUS	yes	3	326	16.6	0
Cogo[14]	1998	(Serial) CUS	no	6	1702	24	0.7
Cornuz[15]	2002	Wells rule, D-dimer,	no	3	278	29	1.0
Elias[16]	2003	Whole leg CUS	no	3	623	32.8	0.5
Engelberger[17]	2011	Wells rule, D-dimer, whole leg CUS	no	3	298	27	0.5
Gibson[18]	2009	Wells rule, D-dimer, serial proximal CUS/ whole leg CUS	no	3	1002	15.8	0.95
Heijboer[19]	1993	(Serial) CUS + venography to confirm DVT	no	6	490	19	1.5
Hogg[20]	2012	Wells rule, D-dimer (serial) CUS	no	3	199	20.6	0
Imberti[21]	2006	Wells rule, D-dimer (serial) proximal CUS	yes	3	534	19.2	0.7

Appendix II. (continued)

Author	Year of publication	Diagnostic tests/ algorithm	Only proximal thrombosis	Follow-up (months)	Number of patients	Disease prevalence at baseline (%)	Failure rate (%)
Janes[22]	2001	Wells rule, D-dimer, US	no	3	431	21.6	0.3
Kahn[23]	2001	Contrast venography	no	6	159	32	0.9
Kearon[24]	2001	Wells rule, D-dimer, serial US/impedence plethysmography + venography	no	3	445	14	0.26
Kearon[25]	2005	Randomisation between D-dimer +venography/serial CUS	no	6	408/402	4.7/1.2	2.1/0.75
Kraaijenhagen[26]	2002	CDR, D-dimer, (serial) CUS	no	3	1756	23	1.3
Le Gal[27]	2012	Whole leg CUS	no	3	210	10.5	4
Legnani[28]	2010	Wells rule, D-dimer, serial US	no	3	401	22.4	0
Linkins[29]	2013	Wells rule, Randomisation between testing D-dimer in all patients/ selective testing dependent on Wells rule, CUS	yes	3	863/860	6.5/5.7	0.5/0.5
Noren[30]	2002	Duplex US, venography is patients with equivocal US results	no	3	580	24	0.29
Penaloza[31]	2006	Wells rule, D-dimer, (serial) proximal CUS	yes	3	214	18	1.1
Perrier[32]	1999	Wells rule, D-dimer, CUS, venography	no	3	474	33.5	2.6
Prandoni[33]	2002	(serial)CUS + venography for all patients with positive CUS	yes	6	205	27	1.3
Prandoni[34]	2007	Proximal CUS, serial CUS when D-dimer positive	yes	3	146	30	0
Robinson[35]	2002	D-dimer + CUS	no	3	437	30	0.65
Ruiz-Gimenez[36]	2004	Wells rule, d-dimer (serial) proximal CUS	yes	3	401	25	0.99
Schellong[37]	2003	Whole leg CUS	no	3	1646	12	0.3
Schouten[38]	2015	Oudega rule, d-dimer, CUS	no	3	348	47	2.2

Appendix II. (continued)

Author	Year of publication	Diagnostic tests/ algorithm	Only proximal thrombosis	Follow-up (months)	Number of patients	Disease prevalence at baseline (%)	Failure rate (%)
Schutgens[39]	2003	Wells rule, D-dimer, CUS, serial CUS when D-dimer positive	yes	3	812	38	1.6
Siragusa[40]	2004	Wells rule, D-dimer, serial US	no	3	409	22.2	0.63
Sluzewski[41]	1991	(serial) proximal CUS	yes	3	174	38	2.8
Stevens[42]	2004	CUS	no	3	445	13.7	0.8
Stevens[43]	2013	Wells rule, whole leg CUS	no	3	183	8.7	0.6
Subramaniam[44]	2005	Whole leg CUS	no	3	526	21.5	0.24
Subramaniam[45]	2006	Whole leg CUS	no	3	453	19.2	0
ten Wolde[46]	2002	D-dimer+ (serial) CUS	no	3	1739	23	1.3
Tick[47]	2002	Wells rule, D-dimer, single CUS/(serial)CUS	no	3	811	42	1.5
van der Hulle[48]	2013	Wells rule, D-dimer, (serial) CUS	yes	3	389	22	0
Wells[49]	1997	Wells rule, (serial) CUS, venography	yes	3	593	15.5	0.6
Wells[50]	1999	Wells rule, (serial) CUS	yes	3	150	27	1.8
Wells[51]	2003	Wells rule, unlikely probability group: randomisation between first US or D-dimer	yes	3	566/530	15/14.5	0.4/1.3

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4

Evaluation of the new simple and objective clinical decision rule 'I-DVT' in patients with clinically suspected acute deep vein thrombosis

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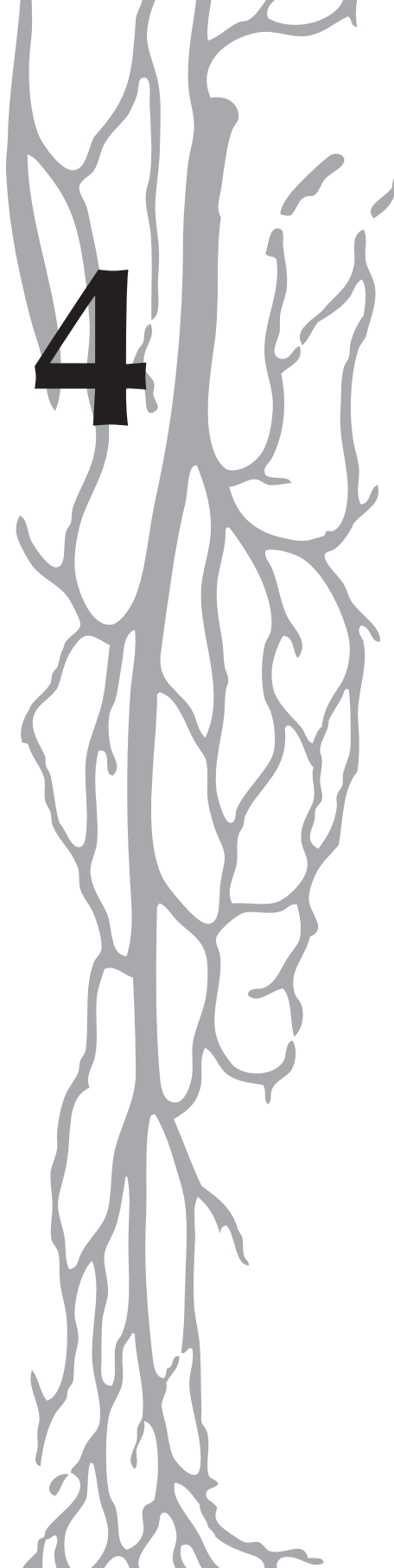

ABSTRACT

Introduction

The Wells rule is the recommended first step in the work-up of suspected deep vein thrombosis (DVT). However, it is often incorrectly used leading to an excessive number of diagnostic tests used in daily practice and diagnostic failures. A simpler objective risk stratification tool may improve adherence to the guidelines. We evaluated the diagnostic performance of the I-DVT score, which consists of four easy assessable variables: Immobilization, >3 cm Difference in calf circumferences, prior Venous thromboembolism (VTE) and active malignant Tumor.

Methods

We performed an observational study in 617 consecutive patients with suspected DVT. All patients were managed according to the recommended algorithm starting with the Wells rule followed by D-dimer test and/or compression ultrasonography (CUS). The I-DVT score was prospectively calculated at baseline and evaluated post-hoc.

Results

The DVT prevalence was 36%. DVT could be excluded in 13% of patients without CUS by the Wells rule and a normal D-dimer test, with a 3-month VTE incidence of 1.2% (95%CI 0.03-6.5%). Using the I-DVT score, DVT would have been excluded in 9.1% of patients without additional CUS, with a 3-month VTE incidence of 0% (95%CI 0.0-6.4%). The area under the ROC curve (AUC) was 0.70 (95%CI 0.66-0.74) and 0.65 (95%CI 0.61-0.70) for the Wells rule and I-DVT score respectively (difference 0.049, 95%CI -0.01-0.11; p=0.13).

Conclusions

The simple I-DVT score and Wells rule have comparable diagnostic accuracy. It's safety, efficiency and associated potential improvement of guideline adherence in clinical practice has to be further evaluated in a prospective management study.

INTRODUCTION

The Wells rule for deep vein thrombosis (DVT) is the most widely studied pre-test probability assessment score for the purpose of pre-test probability assessment in patients with suspected DVT, which is the recommended first step in the diagnostic algorithm for DVT (**Table I**).[1] It has been widely shown that DVT can be ruled out in case of a Wells 'DVT unlikely' score -1 point or less- in combination with a D-dimer concentration <500 µg/L.[2] Patients with either a D-dimer concentration ≥500 µg/L or a 'DVT likely' pre-test probability should be referred for imaging testing since the specificity of the Wells rule of 45-72% does not allow for definite confirmation of DVT.[3] Several other clinical decision rules have been evaluated for the assessment of clinically suspected DVT, but none outperformed the Wells rule nor have been validated in large prospective outcome studies, leaving no alternatives for the Wells rule.[4,5]

Despite its central role in the diagnostic work-up of suspected DVT, the Wells rule has several limitations. First, it consists of 10 items making it less practical to use in a busy emergency ward. Second, it contains one subjective item, i.e. the judgment of the physician whether an alternative diagnosis is less or more likely than DVT, leaving room for inter-observer variability. As a result, the Wells rule is frequently used incorrectly or not at all in day-to-day clinical practice.[6] Recent studies have reported that the implementation of diagnostic algorithms for DVT is poor at best.[7-11] For instance, in response to a standardized questionnaire that was sent out to all 394 physician members of the Italian Society of Thrombosis and Haemostasis, 22% of the physicians claimed never to use a CDR in patients with suspected DVT at all.[12]

Reasons for non-compliance to the validated diagnostic management algorithms are non-attendance to – or miscalculation of – the Clinical Decision Rule (CDR) and/or D-dimer test. This may result in 1) referring patients directly for an imaging test without prior calculation of the CDR score and/or performing a D-dimer test; 2) conducting an imaging test despite a 'DVT unlikely' CDR score and negative D-dimer test result; or 3) refraining from imaging testing in case of a 'DVT likely' CDR score but a negative D-dimer test result. Deviating from any of the validated diagnostic algorithms comes at the cost of the efficiency and safety of the management of patients with suspected venous thromboembolism (VTE) because it has been shown that adhering to a validated algorithm is associated with both a significant decrease in the number of applied diagnostic tests as well as -and more importantly- in the 3-month VTE incidence and perhaps even mortality.[8,13]

The aim of our study was to evaluate a new simple and objective clinical prediction rule, called the I-DVT score, for assessment of pre-test probability in patients with clinically suspected DVT. The goal of deriving a new score was to provide a CDR that can be easily applied, with the potential to improve the adherence to diagnostic algorithms and the related efficiency and safety of the diagnostic management of DVT in the future.

METHODS

Derivation of the I-DVT score

We derived a simple and therefore 'easy to use' clinical prediction score that contains only objective items. In analogy to the derivation of the Wells rule, three experts (MT, FK and MH) independently selected the most relevant predictors of a positive DVT diagnosis based on the clinical relevance, the objectivity of the items and a literature review.[14,15] We predefined, based on the design of the Wells rule, that the selected items would be designated 1 point each, and that an 'unlikely' clinical probability would be defined as a patient who did not score any points at all. The following 4 items were recognized by each individual physician to be associated with a high risk of DVT: Immobilization (minimal 3 days and/or major surgery <4 weeks), Difference in the calve circumferences of at least 3 cm compared to the asymptomatic leg, Venous thromboembolism in the past and active malignant Tumor (treatment ongoing or within previous 6 months or palliative), which were combined in the 'I-DVT' rule (**Table 1**).

Table 1. Original Wells rule, the I-DVT and Adjusted-I-DVT score for clinically suspected DVT.

Item	Wells rule[15]	I-DVT score	Adjusted I-DVT score
Active cancer (treatment ongoing, within previous 6 months, or palliative)	1	1	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1		
Recently bedridden for >3 days and/or major surgery within 4 weeks	1	1	1
Localized tenderness along the distribution of the deep venous system	1		
Thigh and calf swollen (should be measured)	1		
Calf swelling 3 cm> symptomless side (measured 10 cm below tibial tuberosity)	1	1	1
Pitting edema confined to the symptomatic leg	1		
Collateral superficial veins (non varicose)	1		1
Previously documented DVT		1	1
Alternative diagnosis as likely as or greater than that of DVT/ *Adjusted I-DVT score: DVT more likely than alternative diagnosis*	-2		1
Use of oral contraceptive pill			1
Clinical probability categories			
DVT 'unlikely'	0-1	0	0-2
DVT 'likely'	≥2	≥1	≥3

Note: DVT: deep vein thrombosis; I-DVT: Immobilisation (minimal 3 days and/or major surgery<4 weeks), difference in Diameter of the calfs of at least 3 cm, Venous thromboembolism in the past and active malignant Tumor

Exploration of the accuracy of the I-DVT score

The primary aim of this study was to explore the safety and efficiency of the recommended diagnostic algorithm for suspected DVT **(Fig 1)** when applying the I-DVT score versus the Wells rule. The safety of the algorithm is expressed by the rate of symptomatic VTE in patients in whom DVT was ruled-out based on an 'unlikely' clinical probability by the decision rule and a normal D-dimer test with a threshold of <500 µg/L. The efficiency of the algorithm is expressed by the number of patients who can be managed without compression ultrasonography (CUS). The secondary aims of this study were to compare the overall diagnostic accuracy of the Wells rule and I-DVT score and to study whether the items of the Wells rule not included in the I-DVT score still would have additional incremental diagnostic value to the new score.

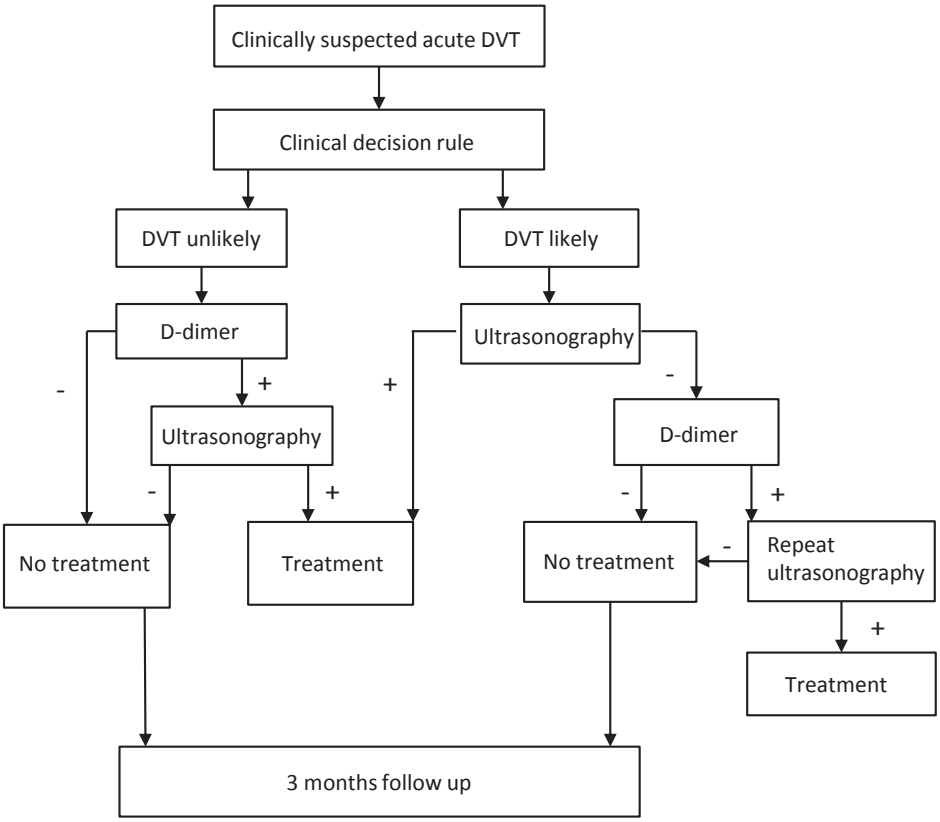

Figure 1. Diagnostic strategy of suspected DVT as applied in this study.
Note: DVT: Deep vein thrombosis

Patients

For the purpose of this study, consecutive patients who presented with a clinically suspected first or recurrent episode of acute DVT during the study period from January 2009 until December 2010 in 1 academic hospital and 2 large teaching clinics in The Netherlands (Leiden University Medical Center (LUMC), Leiden; Diakonessenhuis Hospital, Utrecht; and Rijnland Hospital, Leiderdorp) were eligible for inclusion if they were 18 years or older. Patients were excluded if they were pregnant, had received more than 24 hours of anticoagulant therapy in therapeutic dose before presentation, or in whom pre-test risk stratification had already been performed by the general practitioner.[16] The clinical items of both the Wells rule and I-DVT score were registered on standard clinical registration forms. The probability category of the Wells rule was determined as standard and obligatory first step of the diagnostic assessment. Because of the largely overlapping items, the I-DVT score was calculated at the same moment by the same physician before further laboratory or imaging tests were performed. The I-DVT score result was then extracted from the medical chart on a separate clinical registration form by the researchers. The treating physician was unaware of this score. Follow-up of the patient was performed without knowledge of the I-DVT score. Because this concerned an observational study, the Institutional Review Board (IRB) of the LUMC waived the need for informed consent.

Patients with suspected acute DVT were managed according to current local guidelines **(Fig 1)**, which were based on the Wells rule. D-dimer levels (Tina-Quant Assay (Roche Diagnostica, Mannheim, Germany) or STA Liatest D-Di (Diagnostica Stago, Asnieres-sur-Seine, France)) were only assessed in patients with an 'unlikely' pre-test probability by the Wells rule, defined by 1 point or less. The diagnosis of DVT was established in case of an incompressible venous segment of the proximal deep veins (popliteal vein or higher).[17] Radiologists performing the ultrasound examination were not blinded for the outcome of the Wells rule but unaware of the results of the I-DVT score.

All patients in whom DVT was excluded were followed for three months and instructed to return to the hospital if symptoms of VTE occurred. At the end of the follow-up period, the results from the follow-up visit, that always included mentioning of the occurrence of endpoints: recurrent VTE events and mortality were extracted from the medical charts or assessed by contacting the patients and/or the local Thrombosis Services. These physicians were not blinded for the baseline clinical test results although they were unaware of the results of the I-DVT score. In case of suspected acute DVT during the 3-month follow-up period, a CUS of the symptomatic leg was performed. In case of suspected acute pulmonary embolism (PE), standard contrast enhanced computed tomography pulmonary angiography (CTPA) was performed.

Statistical analysis

We aimed to evaluate the I-DVT score in at least the same amount of patients (N=529) as studied to validate the Wells rule.[18] Based on the numbers of patients that weekly present with a clinical suspicion of DVT in the three participating hospitals, we decided on an inclusion period of two years.

For the primary safety and efficacy endpoint, the 3-month incidence of symptomatic VTE and the number of patients in whom DVT was excluded by the Wells rule and by the I-DVT score, in combination with a normal D-dimer test at baseline, were assessed and expressed with 95% confidence interval (95%CI). A relevant difference was predefined as a point estimate of the safety or efficacy endpoint of one of the two rules lying outside the 95% confidence interval of that of the other rule. For these analyses, only patients in whom the algorithm was (for the Wells rule) or would have been (for the I-DVT) correctly followed were considered.

For the secondary endpoints, the diagnostic accuracy of the Wells rule versus I-DVT score were calculated by the AUC of the ROC curve and compared using the method proposed by Hanley & McNeil.[19] The net reclassification improvement of the I-DVT score over the Wells rule was derived from a reclassification table. Finally, the incremental predictive value of the individual items of the Wells rule who were not included in the I-DVT score, as well as of other relevant baseline characteristics, were assessed using a backward stepwise logistic regression analysis. The independent predictors for DVT were added to the I-DVT score, creating the 'adjusted-I-DVT' score. The optimal threshold of the adjusted-I-DVT score was determined by the highest area under the ROC curve. The AUC of the ROC curves of the I-DVT and the adjusted-I-DVT scores were compared and the net reclassification improvement of the I-DVT score was calculated. All statistical analyses were performed with SPSS software version 17. A p-value <0.05 was considered statistically significant.

RESULTS

Patients

During the 2-year study period, 698 outpatients with suspected acute DVT of the lower extremities were eligible for inclusion. Ten patients were pregnant, 19 patients had received therapeutic anticoagulation for more than 24 hours before they could be included and 52 patients had already been stratified as 'DVT likely' by the general practitioner and had a direct indication for CUS. These patients were excluded leaving a total of 617 patients for analysis (Table 2). Their mean age was 58 years and 43% was male.

Table 2. Baseline characteristics of study patients.

Characteristic	Value (n=617)
Age, mean (SD)	58 (18)
Male, n (%)	262 (43)
Outpatient, n (%)	617 (100)
Immobilization > 3 days or surgery, n (%)	141 (23)
Paralysis, paresis or recent plaster, n (%)	30 (4.9)
Calf swelling 3 cm > symptomless side, n (%)	294 (48)
Localised tenderness along the distribution of the deep venous system, n (%)	324 (53)
Pitting oedema (greater in the symptomatic leg), n (%)	339 (55)
Entire leg swollen, n (%)	136 (22)
Collateral superficial veins (non-varicose), n (%)	57 (9.2)
Malignancy, n (%)	49 (7.9)
Alternative diagnosis as likelyor greater than that of deep-vein thrombosis, n (%)	49 (7.9)
History of venous thromboembolism, n (%)	126 (20)

Note: n: number; SD: standard deviation

Outcome of the algorithm using the Wells rule

Using the Wells rule, 212 patients (34%, 95%CI 31-38) had a 'DVT unlikely' pre-test probability of whom 83 (13%, 95%CI 11-16) had a normal D-dimer result and were left untreated without additional CUS. In 37 patients with an 'unlikely probability' the D-dimer test was not performed due to protocol violations and these patients were directly referred for CUS confirming DVT in 10 patients. In 92 patients of the 'DVT unlikely' group, the D-dimer test was abnormal and DVT was confirmed in 20 of them by CUS. Additionally, 405 patients (405/617; 66%, 95%CI 62-69) had a 'DVT likely' score; these patients underwent CUS, of whom 187 were shown to have DVT. From the remaining 218 patients who had a 'DVT likely' score but normal CUS, D-dimer levels were measured in 165 patients, in 53 patients D-dimer was not tested due to protocol violations. Forty-one patients had a normal D-dimer test and were left untreated (41/617; 6.6%, 95%CI 4.8-8.9). In the other 124 patients D-dimer test was abnormal; repeated CUS after a week showed DVT in 5 additional patients. Repeated CUS was not performed in 40 patients due to protocol violation: all these patients were left untreated.

A total of 11 patients (1.8%) were lost to follow up, of whom three were in the group with 'DVT unlikely' score and were managed without CUS. Two patients had a symptomatic DVT during 3-months follow up (0.3%). One patient originated from the 'DVT unlikely' group and was supposed to be left untreated on the basis of an unlikely probability (Wells rule 1 point) and a negative D-dimer test (460 µg/L). He was however nonetheless referred for CUS at baseline, on which a small partial incompressibility in the femoral vein was objectivated. Notably, this patient had a prior history of DVT in

the venous segment. Based on the symptoms, his treating physician decided to confirm the diagnosis of recurrent ipsilateral DVT and initiate anticoagulant therapy. The other patient originated from the 'DVT likely' group, with no DVT on first ultrasonography but a tissue abnormality that was later confirmed to be an Ewing sarcoma of the leg. Due to this alternative diagnosis, D-dimer test and repeat ultrasonography were not performed. This patient was diagnosed with symptomatic DVT by CUS on day 38 and died on day 58 as a result of the advanced Ewing sarcoma. One additional patient died of post-operative infection at day 83.

The overall prevalence of acute symptomatic DVT was 36% (224/617; 95%CI 33-41): 217 with DVT at baseline, 5 with DVT after repeat ultrasonography and 2 patients with symptomatic DVT during 3-month follow-up. The 3-month incidence of symptomatic VTE during follow-up in patients in whom DVT was excluded by means of a low probability Wells rule in combination with a normal D-dimer test at baseline, was 1.2% (1/83; 95%CI 0.03-6.5%) and for the whole algorithm 0.36% (1/275; 95%CI 0.01-2.0%). The sensitivity of the whole algorithm (Wells rule in combination with d-dimer test and compression ultrasonography) therefore was 99.5% (95%CI 98.1-99.5%) with an associated negative predictive value of 99.6% (95%CI 98.5-99.6%).

Outcome of the algorithm using the I-DVT score

Using the I-DVT score 173 patients (28%, 95%CI 25-32) would have been categorized as 'DVT unlikely' of whom 56 patients (9.1%, 95%CI 6.9-12) had a normal D-dimer result and would be left untreated without additional CUS. D-dimer tests were missing in 38 patients. A total of 79 patients had an abnormal D-dimer test, of whom 16 patients were diagnosed with DVT. Of the 444 patients categorized as a 'DVT likely' (72% 95%CI 68-75), 186 (30%) were diagnosed with DVT by initial CUS, and 5 (0.8%) by repeat CUS.

A total of 8 patients who would have completed the algorithm according to the I-DVT score were lost to follow up. Five would have been in the group with a 'DVT unlikely' pre-test probability and negative D-dimer test. The 3 remaining patients would have been in the group with a 'DVT likely' pre-test probability, of which 2 had a negative D-dimer test and normal ultrasonography and 1 had an abnormal D-dimer test and normal repeat ultrasonography. Both patients who had a symptomatic DVT during 3-month follow-up period would have been categorized as 'likely probability' by the I-DVT score and therefore referred for CUS. This would have resulted in a sensitivity of 100% (95%CI 98.6-100%) and a negative predictive value of 100% (95%CI 98.6-100%) for the diagnostic accuracy of the I-DVT score in combination with a highly sensitive D-dimer test. If the five patients who were lost to follow up in this group, in worst case scenario, all should have had a VTE, the sensitivity and negative predictive value would have been 96.3% (95%CI 94.5-96.3) and 97% (95%CI 95.6-97.0) respectively. **Fig 2 and 3** show the

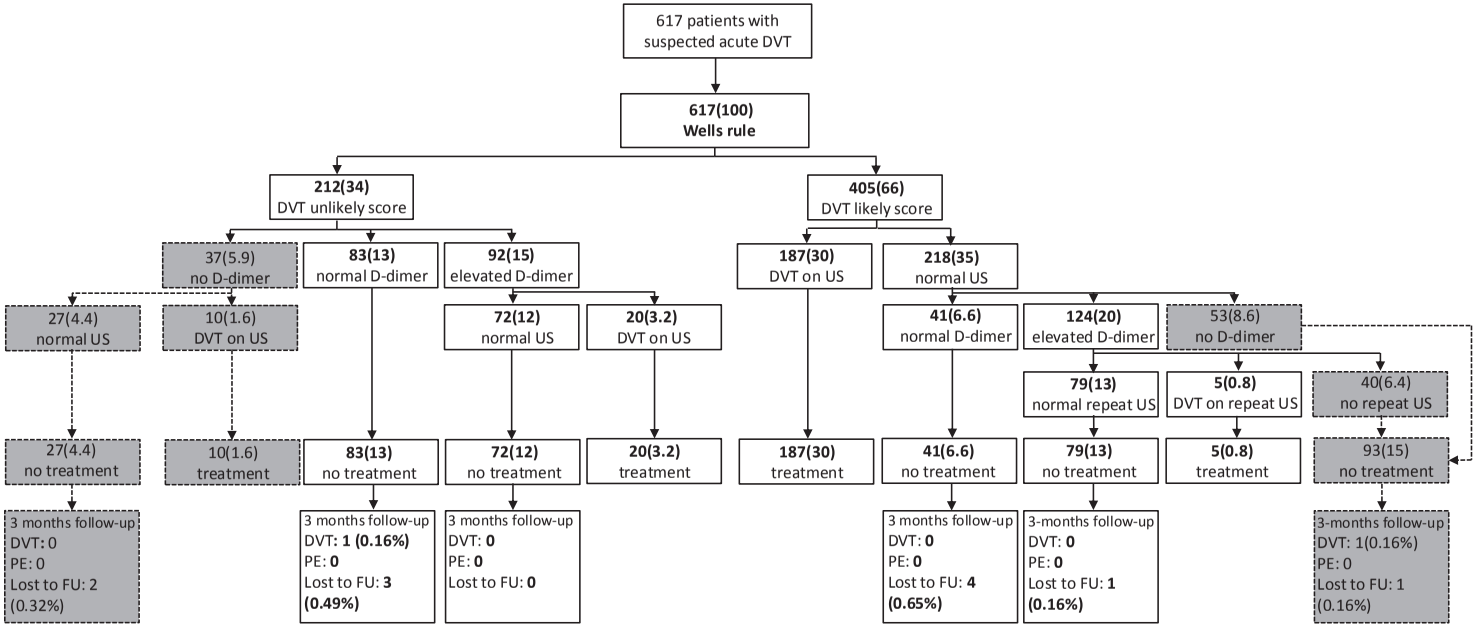

Figure 2. Results of the diagnostic strategy using the Wells rule.
Bold numbers are the number:n(%)of patients in each step of the algorithm managed by the Wells rule. Gray boxes with dashed lines are protocol violations.
Note: DVT: deep vein thrombosis; FU: follow up; PE: pulmonary embolism; US: ultrasonography

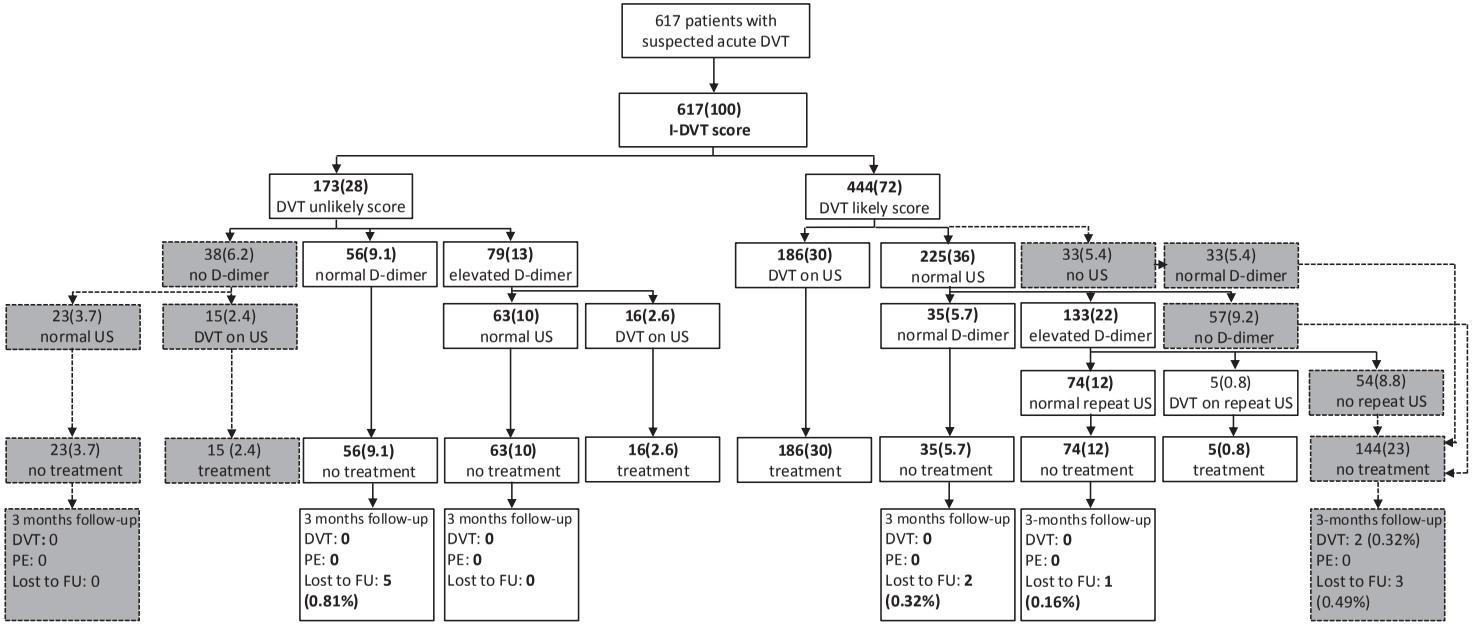

Figure 3. Results of the diagnostic strategy when the I-DVT score would have been used. The bold numbers are the number: n(%) of patients in each step of the algorithm using the I-DVT score. Gray boxes with dashed lines are protocol violation.

Note: DVT: deep vein thrombosis; FU: follow up; PE: pulmonary embolism; US: ultrasonography

flowcharts with an overview of the patient numbers in the different groups according to the Wells rule and I-DVT score.

Comparison of Wells rule and I-DVT score

Using the Wells rule, 86% (95%CI 83-88%) of patients needed examination with CUS. Using the I-DVT score, this percentage increased to 90% (95%CI 88-93%), for an absolute difference of 4% (95%CI 2.9-7.8). The area under the ROC curve (AUC) was 0.70 (95%CI 0.66-0.74) for the Wells Rule and 0.65 (95%CI 0.61-0.70) for the I-DVT score for a difference of 0.049 (95%CI -0.01-0.11, p=0.13; **Fig 4**). The net reclassification improvement of the I-DVT score compared with the Wells rule was -0.956, roughly indicating that 10% of patients were incorrect reclassified in another probability group by the I-DVT score compared to the Wells score.

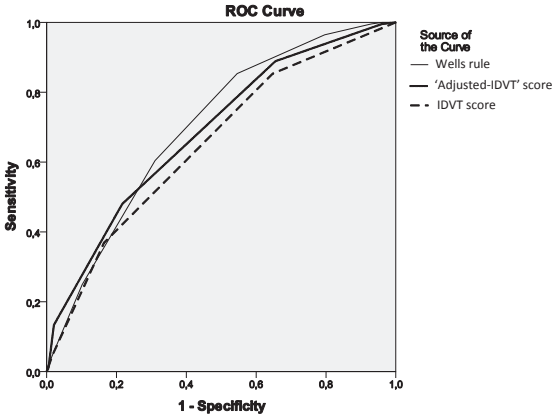

Figure 4. Receiver operating characteristic curves for the Wells rule and I-DVT score

Optimisation of the I-DVT score

The logistic regression analysis identified the following independent predictors of DVT: presence of collaterals, DVT more likely than alternative diagnosis, use of the oral contraceptive pill and the I-DVT score itself (**Table 3**). In the so called 'adjusted-I-DVT' score these additional three variables were included for a weight of 1 point each in addition to the I-DVT score. The AUC of this new score was 0.69 (95%CI 0.65-0.73), which was not significantly better than that of the I-DVT score for a difference of -0.035 (95%CI -0.99-0.028; p=0.29; Fig 4). With an optimal threshold of ≥3 points, the adjusted-I-DVT score was associated with a net reclassification improvement of 0.038 compared to the I-DVT score, roughly indicating that less than 4% of patients would be reclassified correctly by the adjusted-I-DVT score compared to the I-DVT score. Using the adjusted-IDVT score 79% (95%CI 75-82) needed examination with CUS with an absolute difference of 12% (95%CI 7-16).

Table 3. Logistic regression analysis: independent predictors of DVT.

Item	Regression Coefficient (SE)	OR (95%CI)	P-value
Presence of collaterals	1.5 (0.6)	4.7 (1.5-15.0)	0.01
Alternative diagnosis more likely than deep-vein thrombosis	2.5 (1.1)	12.6 (1.5-100)	0.02
Use of the oral contraceptive pill	0.96 (0.4)	2.6 (1.1-5.9)	0.02
I-DVT score	1.4 (0.44)	4.0 (1.7-9.4)	0.002

Note: DVT: deep vein thrombosis; SE: standard estimate; OR: odds ratio

DISCUSSION

In this analysis, the short and objective I-DVT score seemed to have a comparable overall diagnostic accuracy to the Wells rule. In addition, this study implies that a prospective study to evaluate the safety of ruling out DVT by an I-DVT of 0 points, in combination with a normal highly sensitive D-dimer test is feasible. The efficiency of the I-DVT score seems to be slightly lower than that of the Wells rule with an absolute 4% increase in the number of required ultrasound examinations by the algorithm. Extending the I-DVT score with all items from the Wells rule that proved independently associated with a DVT diagnosis by logistic regression analysis on top of the I-DVT score only marginally changed its overall diagnostic performance but significantly lowered the number of required number of ultrasound examinations.

Although the safety and efficiency of diagnostic management algorithms for patients with clinically suspected VTE have been validated in several high-quality trials, adherence to these guidelines is poor which is partly due to the limitations of the Wells rule.[14] The earlier observation that non-adherence to the recommended diagnostic algorithm is associated with diagnostic failures and excessive diagnostic testing was confirmed in our observational study, with both symptomatic VTE diagnosis during follow-up in patients in whom the algorithm was not applied correctly. Therefore, improving adherence to the diagnostic algorithm remains highly relevant. The current study provides arguments that the I-DVT score may be a promising alternative for the Wells rule. We anticipate better adherence to the recommended diagnostic algorithm due to its simplicity and objectivity, although this was not the subject of the current study. The potential benefit of better adherence may largely compensate for the decrease in the number of patients that may be managed without imaging tests.

Despite the fact that the 'adjusted-I-DVT score' may be associated with even a decrease in the number of required radiological examinations, it is debatable whether this compensates for the loss of simplicity (3 additional items) and objectivity (inclusion of the subjective item) with regard to expected adherence in clinical practice. The adjusted I-DVT score may be regarded as a simplification of the Wells rule as was published for

the Wells rule for PE and the revised Geneva score for PE, in which all variables were awarded one single point.[20,21] For these latter scores, it was shown that both the overall accuracy as well as the safety of ruling out PE based on an unlikely clinical probability in combination with a normal D-dimer test were unaffected by the simplification.[22] As for the subjective item, the associated moderate reproducibility resulting from interobserver variability and lack of standardization have been the major reported points of criticism to the Wells rule throughout the years. It has for instance been suggested that the diagnosis of DVT could have been missed in patients who were only assessed by physicians in training alone without supervising physician advice, based on different judgment of the likelihood of DVT or an alternative diagnosis leading to significant differences in the rates of DVT among pre-test probability groups.[23] Since the overall performance of the adjusted I-DVT rule was only marginally better with only a small net reclassification benefit, we consider the simple 4-component I-DVT score to have the most clinical potential.

Strengths of our exploratory study are its prospective design, the large sample size and the DVT prevalence of 36% which is representative for European clinical practice. Our study has limitations as well. First, the I-DVT score was not derived using the recommended logistic regression analysis.[24] Even so, Wells applied an identical approach by including items assembled from information obtained by a literature review and from the collective experience of the participating investigators in his new clinical model.[18] Second, the study patients were managed on the basis of the Wells rule, which resulted in missing D-dimer tests in a relevant number of patients who would have been categorized as 'unlikely' clinical probability by the I-DVT score. This may have caused bias in the estimation of the diagnostic accuracy of the I-DVT score, since patients with missing D-dimer tests were excluded from further analysis. Besides, not all key metrics of quality in accuracy studies could be met because as patients were managed by local guidelines, different persons doing the successive tests could not be blinded to the results of the initial tests. Third, 20.7% of patients included in the study were not managed by the study protocol and were excluded from our final analysis. This resulted in a low number of patients in the group of patients with a 'DVT unlikely' Wells score and a negative d-dimer test (n=83), leading to a high upper level of the confidence interval of the failure rate of this particular group. Nonetheless, the low point estimate of this failure rate was actually in line with that reported by Wells.[25] Lastly, it would have been interesting to compare the I-DVT score to other previously suggested but never validated simplified CDRs for assessing the pre-test probability of DVT.[4]

In summary, we have derived and evaluated a new, simple and objective diagnostic tool for suspected DVT, which has similar overall diagnostic accuracy compared to the widely recommended Wells rule for DVT. Because of its simple character, the I-DVT score may be a promising alternative for the Wells rule, since the adherence to the guidelines

– and with that the safety and efficacy of our clinical practice – may improve. The safety and efficiency of the I-DVT score and its associated effect on guideline adherence in clinical practice have to be further evaluated in a prospective management study before the new diagnostic score may be used in daily practice.

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5

Accurate diagnosis of iliac vein thrombosis in pregnancy with Magnetic Resonance Direct Thrombus Imaging (MRDTI)

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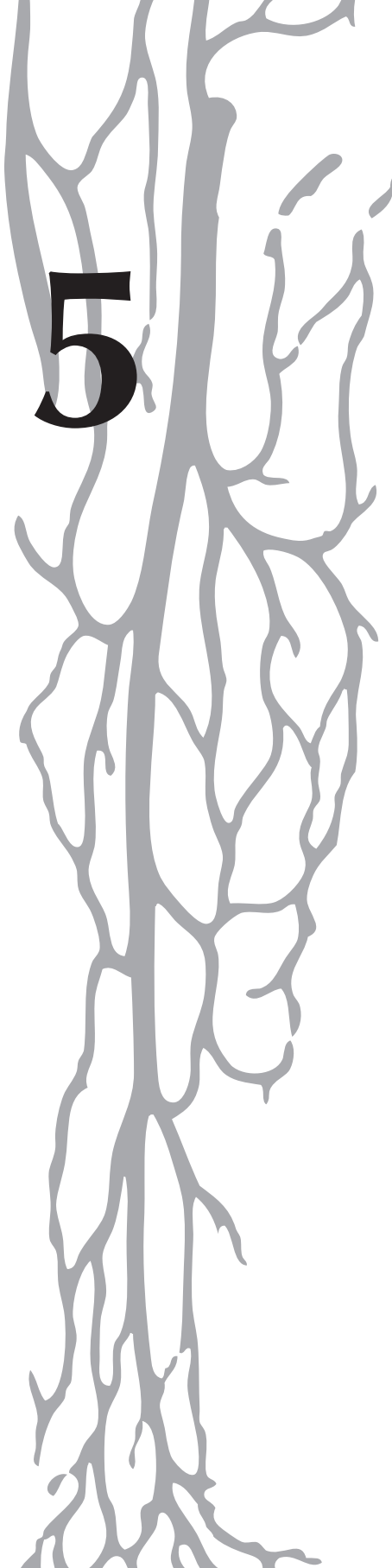

ABSTRACT

A pregnant woman aged 29 years, G1P0 at 21 weeks of gestation of a dichorionic diamniotic twin, presented with suspected deep vein thrombosis (DVT) of the left leg. Repeated (compression) ultrasonography was not diagnostic for DVT but showed reduced flow over the left external iliac vein, common femoral vein and superficial femoral vein. In pursue of a definite diagnosis, Magnetic Resonance Direct Thrombus Imaging (MRDTI) was performed showing a clear high signal in the left common iliac vein which is diagnostic for acute thrombosis in this venous segment. Phase contrast venography supported this diagnosis, showing no flow in the left common iliac vein. Treatment with anticoagulants was started. Six months after the diagnosis, the patient is doing well and does not report signs of post-thrombotic syndrome.

BACKGROUND

Pregnancy is a well-known and strong risk factor for venous thromboembolism (VTE), with pregnant women having a 4-fold increased risk of VTE compared to non-pregnant women.[1] Considering that up to 13.9% of the maternal deaths in the UK are due to VTE,[2] accurate diagnosis and adequate treatment are still of utmost clinical importance, although due to anatomical changes and the contraindication for ionizing radiation, the diagnostic management of suspected VTE remains challenging today.[3] We report the case of a pregnant patient with difficult to diagnose iliac vein thrombosis, in whom we applied the non-invasive Magnetic Resonance Direct Thrombus Imaging (MRDTI) technique after conventional imaging tests were non-diagnostic.

CASE PRESENTATION

A pregnant woman aged 29 years, G1P0 at 21 weeks of gestation of a dichorionic diamniotic twin, was referred by her general practitioner to the emergency department because of suspected deep vein thrombosis (DVT) of the left leg. She had no relevant medical history and was only taking folic acid and multivitamins as medication. Her whole left leg was swollen since one day. She reported no local tenderness but instead a deep pain in the left loin that had started several days before current presentation. She had not experienced respiratory symptoms or chest pain. Her family history was negative for thromboembolic events. On physical examination, her entire left leg was swollen, with a 3 cm difference in calf circumference compared to the right leg. The left leg was slightly more red coloured compared to the right leg. Peripheral pulsations were present in both legs.

INVESTIGATIONS

Laboratory examination showed a C-reactive Protein of 54 mg/L. A D-dimer test was not performed. Based on her presentation, the attending physician confirmed the suspicion of a DVT and ordered compression ultrasonography, showing full compressibility of the common femoral vein, superficial femoral vein and popliteal vein. However, additional Doppler ultrasonography revealed reduced flow over the left external iliac vein, common femoral vein and superficial femoral vein, although it was not possible to visualize a thrombus to explain this phenomenon. Because of the remaining high suspicion of iliac vein or more proximal DVT, treatment with nadroparin 15.200 U once daily was initiated and the patient was kept under close outpatient surveillance. The next day,

repeated ultrasonography showed similar results. In pursue of a definite diagnosis, we subsequently performed MRDTI.[4] The MRDTI sequence showed a clear high signal in the common iliac vein, distal from the crossing with the right common iliac artery, up to the bifurcation into the external iliac vein and left internal iliac vein (**Figure 1**), confirming the presence of a fresh blood clot. MRI-venography was subsequently performed. Phase contrast venography showed flow in the left external iliac vein and internal iliac vein but no flow in the left common iliac vein, which supported the diagnosis made by the MRDTI-sequence.

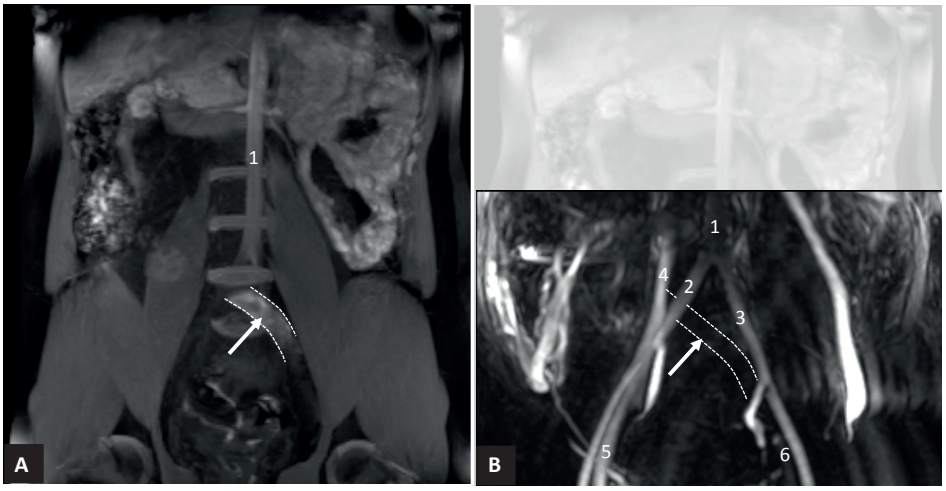

Figure 1. Two different MRI sequences, diagnostic for thrombosis in the left common iliac vein. (A) Magnetic resonance direct thrombus imaging, coronal view: white arrow between dashed lines indicates high-signal intensity in the left common iliac vein, indicating deep vein thrombosis directly. 1: aorta. (B) Phase contrast venography, coronal view, showing flow in the vena cava inferior (4) and right common iliac vein (5) but no flow in the left common iliac vein: should have been visible between the white dashed lines indicated by the white arrow. 1, aorta; 2: right common iliac artery; 3: left common iliac artery; 4: vena cava inferior; 5: right common iliac vein; 6: left external iliac vein.

TREATMENT

Consequently, anticoagulation therapy was continued and compression stockings were prescribed. Within days, her symptoms resolved completely.

OUTCOME AND FOLLOW-UP

Six weeks later, at 26 weeks plus 5 days of gestation, she presented with unexplained vaginal blood loss, CTG (cardiotocography) showed some contractions and transvagi-

nal ultrasonography showed a lightly shortened cervix. Because of imminent preterm birth Nifidepine and Betamethasone were started, and treatment with nadroparin was temporally discontinued. The next day vaginal ultrasound showed a fully effaced cervix with 14 mm dilatation and she gave birth to a premature male twin after uncomplicated vaginal delivery. The day following delivery treatment with nadroparin was restarted and continued for a period of 3 months. Both children developed an Escherichia coli sepsis with meningitis in the first week after birth, complicated by cerebral hemorrhages of which they recovered well. Currently, 6 months after the diagnosis, the patient does not report signs of post-thrombotic syndrome and the twins are doing well.

DISCUSSION

The standard diagnostic algorithm of suspected DVT consisting of a combination of the Wells rule, D-dimer test and compression ultrasonography (CUS),[5] has several limitations in pregnant women. First, because leg swelling and leg pain are common in pregnancy and often indistinguishable from symptoms of DVT, questioning and physical examination are less sensitive and cannot be relied on. Second, the Wells rule -nor any other clinical decision rule- has not been validated in pregnant patients.[1] Third, the diagnostic accuracy of D-dimer tests in the diagnosis of VTE in pregnancy is hampered because of the substantial increase of D-dimer throughout gestational age.[3]

Fourth and most notably, 12% of all DVTs in pregnant woman are isolated pelvic vein thrombosis, compared with <1% in a non-pregnant population.[6] This is caused by the compression of the left iliac vein by the gravid uterus at the point where it crosses the right iliac artery, also known as the 'functional' May Turner syndrome. Owing to obvious anatomical reasons, CUS examination of the pelvic veins is not possible and colour Doppler imaging of the pelvic veins may be unreliable. The latter was demonstrated in two small prospective studies in which non-pregnant patients with acute pulmonary embolism (PE) and normal bilateral CUS examination including Doppler imaging of the iliac veins up to the inferior vena cava, were subjected to MR-venography. Isolated pelvic vein thrombosis was demonstrated in 7.1% and 29% of the study subjects respectively, despite the normal ultrasound examination.[7,8]A third study that applied MR-imaging in pregnant woman with CUS proven DVT showed that the CUS examination had not picked-up the concurrent presence of pelvic vein thrombosis in 11% of patients.[9] The largest diagnostic study in pregnant patients with suspected DVT to date applying a single whole-leg CUS examination, reported a 3-month failure rate of up to 4.0%, which underlines the poor accuracy of current diagnostic imaging tests in this setting.[10] Other established imaging modalities such as conventional venography or CT-venography

expose mother and foetus to ionizing radiation and are therefore not recommended nor acceptable.[11]

An alternative MR imaging technique for the detection of acute DVT is MRDTI. This technique has reached an advanced stage of development and is close to implementation in clinical practice. The method is based on the formation of methaemoglobin in a fresh thrombus which leads to shortening of the T1 signal.[4,12] It does not require contrast dye and takes about 10 minutes to perform. The diagnostic accuracy (sensitivity 97-100%, specificity 100%) as well as the inter-observer agreement of MRDTI for DVT were reported to be excellent (kappa 0.89-0.98).[4] MDRTI was additionally shown to accurately and reproducibly differentiate between patients with confirmed recurrent ipsilateral DVT and those with asymptomatic residual intravascular clots,[13] and is now being tested in an prospective outcome study as first-line imaging test in suspected ipsilateral DVT (ClinicalTrials.gov Identifier: NCT02262052).[14] MRDTI is not contraindicated in pregnancy and may potentially be a useful test in pregnant patients with a high clinical suspicion of DVT, but normal CUS examination, as was the case in our patient. A future outcome study in pregnant patients should investigate the incremental diagnostic value of MRDTI in this clinical setting.

Because of the associated morbidity and mortality of pregnancy-associated thrombosis, more accurate diagnosis of DVT remains an important priority of future research. We present the case of a patient with suspected DVT in whom conventional diagnostic tests failed to establish a definite diagnosis. MRDTI, a non-invasive and reproducible technique with high accuracy for acute thrombosis that currently is undergoing the final steps of validation, was able to establish the diagnosis and potentially is a valuable addition to the diagnostic arsenal of imaging tests for DVT in pregnant patients.

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6

Diagnosing recurrent DVT of the leg by two different non-contrast enhanced Magnetic Resonance Direct Thrombus Imaging techniques.

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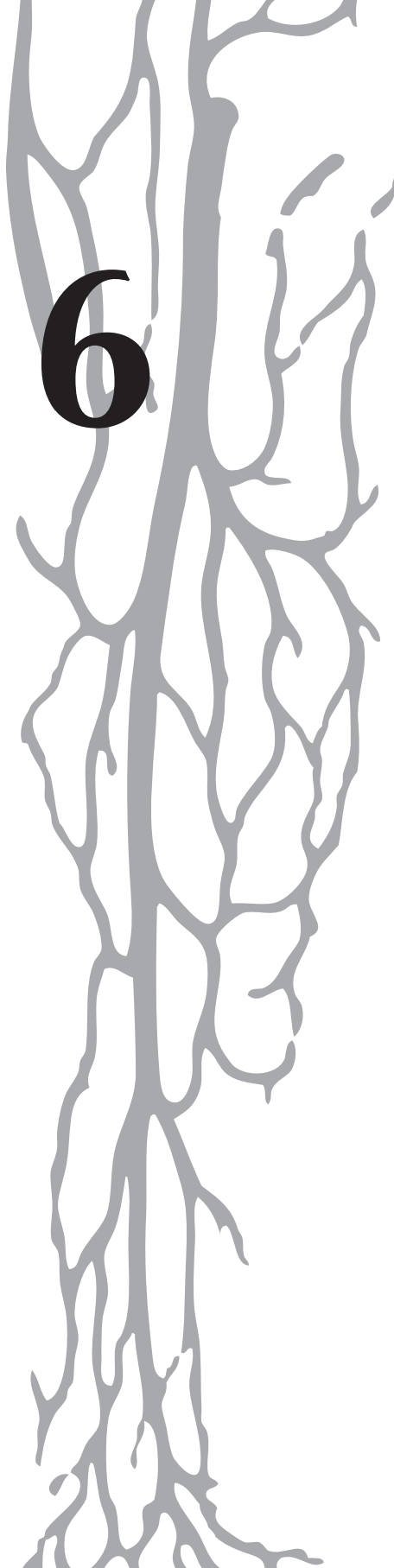
Submitted



ABSTRACT

Objectives

Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a promising technique to improve the diagnostic management of patients with a suspected ipsilateral recurrent DVT by direct visualisation of a thrombus. Another MRI technique, T1 weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery(TSE-SPAIR), has the potential to image a thrombus directly with a high spatial resolution as well. The main aim of this study was to investigate if adding the TSE-SPAIR sequence to a MRDTI sequence performed in patients with suspected recurrent DVT may increase the diagnostic confidence of expert MRDTI readers.

Methods

Fifteen patients with suspected acute recurrent DVT were included in this study. The TSE-SPAIR sequence was scanned directly after the MRDTI scan but not used to guide clinical decision making, and both scans were adjudicated post-hoc two times separately by 3 independent expert MRDTI readers. Diagnostic confidence was scored on a 4 point Likert scale: 1) poor(definite diagnosis impossible), 2) fair (evaluation of major findings possible), 3) good (definite diagnosis possible), 4) excellent (exact diagnosis possible).

Results

The diagnostic confidence of expert readers increased when adding the TSE-SPAIR sequence on top of the MRDTI sequence from 'good' (median 3.0 [IQR 2.66-3.0]) to 'excellent' (median 3.67 [IQR 3.33-3.67]) p=0.001. Evaluation of the scans in the reversed order 5 months after initial reading showed similar results. Diagnostic accuracy for proximal DVT of both scan techniques was good.

Conclusion

The extra TSE-SPAIR sequence may help to increase diagnostic confidence of radiologists in case of uncertain diagnosis in patients with suspected ipsilateral recurrent DVT.

INTRODUCTION

The diagnostic management of suspected ipsilateral recurrent proximal deep vein thrombosis (DVT) is complicated, mainly because of persistent intravascular abnormalities after a first DVT.[1,2]

With the current imaging technique of first choice, i.e. compression ultrasonography (CUS), it is not always possible to make a distinction between residual vein thrombosis and acute recurrent DVT. CUS can only diagnose recurrent DVT with certainty in case of a new non- compressible venous segment or an increase in vein diameter of a previously non-compressible vein when compared to a reference CUS assessed after a prior DVT.[3,4] In clinical practice however, a reference CUS is often not available, making it impossible to diagnose an ipsilateral recurrent DVT with CUS.[5]

Magnetic Resonance Imaging (MRI) is a non-invasive imaging technique. Several sequences have been evaluated for diagnosing DVT. Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a T1 weighted gradient-echo sequence, that is based on a shortened T1 signal after formation of methaemoglobin in a fresh thrombus.[6] MRDTI has been shown to accurately diagnose a first DVT and can make a distinction between chronic residual thrombotic scars and an acute recurrent DVT.[7-9] MRDTI could therefore potentially be used in the diagnostic management of clinically suspected recurrent ipsilateral DVT.[2,10]

In a pilot study, the T1 weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery (TSE-SPAIR) sequence has been tested successfully in three patients with upper extremity DVT.[11] With this sequence, an acute thrombus can be directly visualised by the formation of methaemoglobin in a fresh blood clot as well. Moreover, this sequence results in high resolution images with a particular clear resolution of the vessel wall. This latter quality has the potential to increase the accuracy of the diagnosis of ipsilateral recurrent DVT.

We hypothesized that this TSE-SPAIR sequence may have additional diagnostic value on top of the MRDTI sequence in diagnosing acute recurrent ipsilateral DVT.

METHODS

Objectives

The objective of this study was to assess the additional value of a TSE-SPAIR sequence on top of the standard MRDTI sequence with regard to diagnostic confidence, image quality and diagnostic accuracy in the setting of suspected ipsilateral recurrent DVT. Diagnostic confidence was defined as the number of points on a 4 point Likert scale, specified as: 1) poor: definite diagnosis impossible, 2) fair: evaluation of major findings possible, 3)

good: definite diagnosis possible and 4) excellent: exact diagnosis possible. Image quality was scored on a 4 point Likert scale as well, specified as 1) insufficient: insufficient for diagnosis, 2) adequate: adequate for diagnosis, 3) good: minimal inhomogeneity, 4) excellent: no relevant artefacts. The reference standard against which diagnostic accuracy (number of false positive or false negative tests) was tested were the results of the standard MRDTI sequence in combination with a three month follow-up period. Our secondary objective was to explore the diagnostic accuracy of the TSE-SPAIR sequence as single diagnostic test.

Patients

Patients included in the Theia study at the Leiden University Medical Center (LUMC) between March and December 2016 were selected to participate in this study. The Theia study is a prospective, multicentre, single-arm management (cohort) study.[10] The primary objective of this study is to assess the safety of a negative MRDTI scan to rule out acute, recurrent ipsilateral DVT. Inclusion criteria for this study are: 1) suspected acute recurrent ipsilateral DVT as defined by a documented prior objectivated episode of DVT in the same leg as where the current symptoms originate from, 2) Age ≥ 18 years 3) ability of subject to understand the character and individual consequences of this study, 4) signed and dated informed consent. Exclusion criteria are: 1) General contraindications for MRI, 2) CUS- proven acute symptomatic DVT within 6 months before current presentation, 3) onset of symptoms suggestive of acute recurrent DVT more than 10 days prior to presentation, 4) suspected acute PE, 5) hemodynamic instability at presentation, 6) medical or psychological condition that would not permit completion of the study or signing of informed consent, 7) non-compliance or inability to adhere to treatment or follow-up visits. The study protocol was approved by the local Institutional Review Board (P4.295, NL50663.058.14) and all patients provided written informed consent.

MRDTI

In the context of the Theia study, patients underwent MRI within 24 hours after presentation with a suspected ipsilateral DVT with a 1.5-Tesla unit (Philips Ingenia 1.5T, release 5, Philips Medical Systems, Best, the Netherlands) with maximum gradient amplitude of 45 mT/m, slew rate of 200 T/m/s, using an integrated 16-channel posterior coil and an 16-channel anterior body coil for signal reception. For the MRDTI sequence a T1-weighted magnetization prepared three-dimensional gradient-echo sequence was used. The sequence includes a water-only excitation radiofrequency pulse (PROSET 121) to eliminate the fat signal, and the effective inversion time is chosen to nullify the blood signal. Scan parameters were: Echo time (TE) 5.2 ms, Repetition time (TR) 10 ms, TFE prepulse inversion time 1200 ms, flip angle 15 degrees, field of view 400 x 362, acquisition resolution 1.56 x 2.24 x 4 mm, 60 slices, slice thickness 4 mm (acq)/2mm (rec), slice gap 0

mm. Imaging was performed on both legs simultaneously, from the ankle to the inferior vena cava in two or three imaging blocks, dependent on the length of the patient, using a 55-cm body coil. Scan time was 1.59 minutes for the MRDTI sequence per imaging block. In case of a positive MRDTI signal, anticoagulant treatment was started.

Patients with a negative MRDTI were subjected to a standardized compression ultrasonography (CUS) within 48 hours after initial presentation. This CUS served as reference test in case the patient returned with symptoms of ipsilateral recurrent DVT during follow-up, however it was not used for management decisions at baseline. All patients were followed for three months for the occurrence of recurrent VTE.

TSE-SPAIR sequence

The TSE-SPAIR sequence was performed after the MRDTI sequence in the same session, without motion of the patient between the two scans. 3D TSE SPAIR is a T1 weighted 3D sequence using a spectral, adiabatic presaturation (inversion) pulse to achieve fat suppression. Scan parameters were: Echo time (TE) 24 ms, Repetition time (TR) 400 ms, SPAIR inversion delay 110 ms, flip angle 90 degrees, field of view 400 x 350, acquisition resolution 1 x 1 x 1mm, 200 slices, slice thickness 1 mm, slice gap 0 mm. With this sequence the affected leg was scanned from the calve to the hip in two imaging blocks, with an extra imaging time of 4.15 minutes per block, leading to a total imaging time of 20 minutes. This extra TSE-SPAIR sequence was not shown to the radiologist who evaluated the MRI scan for the Theia study. This way, the TSE-SPAIR sequence did not influence the final diagnosis and treatment of the patients.

Image Analysis

After the follow-up period of the Theia study was completed for all patients included in the current analysis, the MRDTI and TSE-SPAIR sequences were evaluated separately by three independent readers with experience in MRDTI reading: KL (radiology resident with 5 years of experience) AR (radiologist with >20 years of experience) and AS (radiologist with 10 years of experience) who were blinded to the final clinical diagnosis and follow-up of the study subjects and had not seen the MRDTI images of the patients before the current reading. All scans were evaluated twice in two phases. First, the MRDTI scan was read and scored for diagnosis, diagnostic confidence and image quality (**Table 1**). Proximal DVT was defined as thrombus present in the external iliac, common femoral, deep femoral, superficial femoral or popliteal vein and distal DVT as thrombus located below the knee in the posterior or anterior tibial, peroneal or muscular veins. Secondly, the TSE-SPAIR sequence was shown to the readers, and the combination of the MRDTI and TSE-SPAIR scan was again scored for diagnosis, diagnostic confidence and image quality. To be able to explore the diagnostic accuracy of the TSE-SPAIR sequence alone, all scans were scored for the second time by all reviewers, in the reversed order

Table 1. Scoring Form Diagnostic Confidence and Image Quality: 4 point Likert scale [21]

Diagnostic confidence MRDTI		**Image Quality MRDTI**		**Diagnostic confidence MRDTI + TSE-SPAIR/ TSE SPAIR + MRDTI**		**Image Quality TSE-SPAIR**	
1) Poor	Definite diagnosis impossible	1) Insufficient	Insufficient for diagnosis	1) Poor	Definite diagnosis impossible	1) Insufficient	Insufficient for diagnosis
2) Fair	Evaluation of major findings possible	2) Adequate	Adequate for diagnosis	2) Fair	Evaluation of major findings possible	2) Adequate	Adequate for diagnosis
3) Good	Definite diagnosis possible	3) Good	Minimal inhomogeneity	3) Good	Definite diagnosis possible	3) Good	Minimal inhomogeneity
4)Excellent	Exact diagnosis possible	4) Excellent	No relevant artifacts	4) Excellent	Exact diagnosis possible	4) Excellent	No relevant artifacts

with a minimum period of 5 months in between the adjudications: first, the TSE-SPAIR sequence was scored for diagnosis, diagnostic confidence and image quality, and thereafter, the MRDTI sequence was shown, and the combination of the TSE-SPAIR and MRDTI sequence was scored for the same variables.

Statistics

It was predefined to include 15 patients in this study based on the number of patients included in comparable diagnostic studies.[12,13] The Wilcoxon signed rank test was used to evaluate the difference in diagnostic confidence and image quality between the MRDTI and TSE-SPAIR sequence. To analyse overall differences, the Likert scale scores of the three independent readers were first combined and divided by 3. A p-value <0.05 was considered statistically significant. The number of false positive and false negative tests based on the MRDTI sequence alone and MRDTI plus TSE-SPAIR sequences together, as well as the TSE-SPAIR alone and combined with MRDTI, were calculated based on the results of the majority; i.e. two out of three reviewers, with the clinical diagnosis based on MRDTI and events occurring during 3-month FU as reference. Exact diagnostic accuracy numbers, i.e. sensitivity and specificity were not calculated since the sample size was too small. All statistics were performed using SPSS version 23 (IBM Corp, Armonk, NY).

RESULTS

Patients

Of the 15 included patients, 8 were female and 7 male, and their mean age was 49 years (range 24-71). The duration of complaints ranged from 1-10 days (median 3, IQR 2-8.5). With MRDTI 1 patient was diagnosed with proximal ipsilateral recurrent DVT (**Figure 1**) and anticoagulant therapy was started. Two patients were diagnosed with limited distal DVT, for which anticoagulant therapy was started as well. Twelve patients had a negative MRDTI scan, of which reference CUS was normal in seven. In the five remaining patients with a negative MRDTI scan CUS indicated thrombus material in the femoral vein (1 patient) or popliteal vein (4 patients). For none of these five patients it was possible to make a distinction between acute DVT and residual DVT with CUS. None of the 12 patients with a negative MRDTI were treated with anticoagulants and none developed clinical symptoms of a recurrent VTE during a 3-month follow-up period.

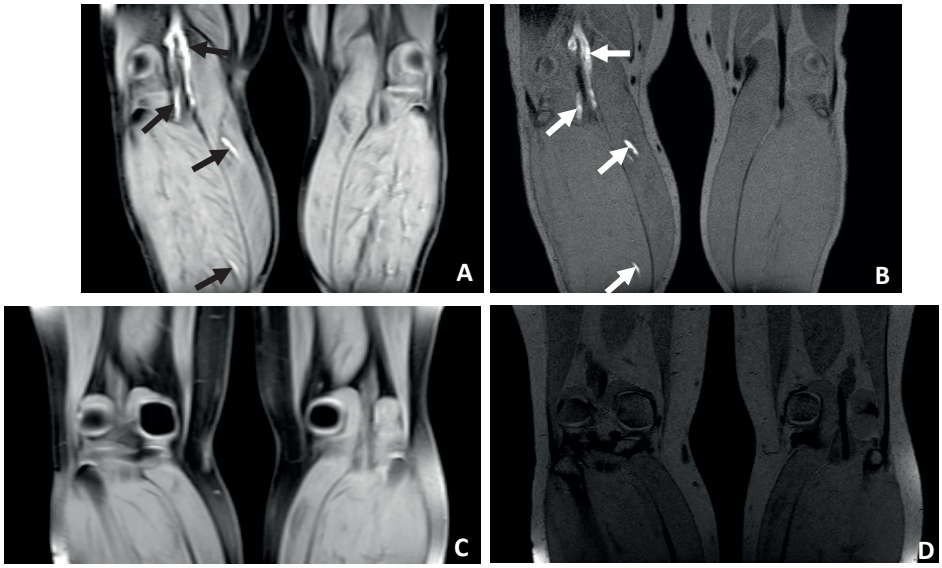


Figure 1. Panel A and B: 51 year old male patient (patient 1, table 2) with a recurrent DVT of the left leg, shown on the MRDTI sequence (panel A, black arrows) and TSE-SPAIR sequence (panel B, white arrows) Panel C and D: 42 year old female patient with a suspected recurrent DVT of the right leg (patient 11, table 2), ruled out based on the results of the MRDTI (panel C) and TSE-SPAIR (panel D) sequence

Diagnosis and accuracy of MRDTI and MRDTI + TSE-SPAIR

Table 2 shows the diagnosis of the individual scans of each reviewer and the number of false-positive and false negative tests of the 3 reviewers together based on the majority rule when comparing the MRDTI and MRDTI + TSE-SPAIR sequences against the results

of the MRDTI sequence at baseline. The evaluation of the MRDTI sequences by the three independent readers corresponded overall for 93% with the original MRDTI reading. After adding the TSE-SPAIR sequence on top of the MRDTI sequence for evaluation, the consensus diagnosis changed for one patient who 2 of 3 radiologists judged to have a normal MRDTI, to distal DVT based on the TSE-SPAIR. Notably, this patient was diagnosed with distal DVT and treated with anticoagulants based on the results of the MRDTI scan reading at baseline.

Table 2. Diagnosis and number of false positive or negative cases for the majority of the 3 reviewers

Patient	Clinical diagnosis: based on MRDTI and events occurring during 3-month FU		MRDTI						MRDTI+TSE-SPAIR						TSE-SPAIR						TSE-SPAIR +MRDTI					
			Proximal			Distal			Proximal			Distal			Proximal			Distal			Proximal			Distal		
	Proximal DVT	Distal DVT	Reviewer			Reviewer			Reviewer			Reviewer			Reviewer			Reviewer			Reviewer			Reviewer		
			1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-
3	-	+	-	-	-	+	-	-	-	-	-	+	-	+	-	-	-	+	+	+	-	+	-	+	+	+
4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	-	+	-	-	-	+	+	+	-	-	-	+	+	+	-	-	-	+	-	+	-	-	-	+	+	+
8	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	+	-	-	-	-	+	-
9	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	+
Number of false positive and false negative interpretations counted for the majority of the 3 reviewers.						1 false negative												2 false positive								

Note: += positive for DVT -=negative for DVT

MRDTI and TSE-SPAIR analysis: diagnostic confidence

The diagnostic confidence of MRDTI was scored overall, after pooling the results from the reviewers, as 'good' for a Likert scale score 3.0 (IQR 2.66-3.0). After adding the TSE-SPAIR sequence, the overall median diagnostic confidence increased significantly to 'excellent' for a Likert scale of 3.67 (IQR 3.33-3.67; p=0.001) (**table 3**).

Table 3. Overall diagnostic confidence MRDTI and MRDTI + TSE-SPAIR sequences and vice versa

	Overall
Diagnostic confidence MRDTI	Median: 3.0 (IQR 2.66-3.0)
Diagnostic confidence MRDTI+TSE-SPAIR	Median: 3.67 (IQR 3.33-3.67)
Wilcoxon signed rank test	p=0.001
Diagnostic confidence TSE-SPAIR	Median: 3.33 (IQR 3.0-3.67)
Diagnostic confidence TSE-SPAIR + MRDTI	Median: 3.67 (IQR 3.0-3.67)
Wilcoxon signed rank test	p=0.176

Note: IQR: interquartile range

MRDTI and TSE-SPAIR analysis: image quality

Overall, the image quality of the TSE-SPAIR sequence was judged to be slightly better than the MRDTI sequence with a median increase from 2.67 (IQR 2.67-3.00) to 3.00 (IQR 3.00-3.33; p=0.018) (**table 4**). There was no correlation between image quality and diagnostic confidence.

Table 4. Overall Image quality MRDTI and TSE-SPAIR

	Overall
Image quality MRDTI	Median: 2.67 (IQR 2.67-3.00)
Image quality TSE-SPAIR	Median: 3.00 (IQR 3.00-3.33)
Wilcoxon signed rank test	p=0.018
Image quality TSE-SPAIR	Median: 3.33 (IQR 3.0-3.33)
Image quality MRDTI	Median 3.0 (IQR 3.0-3.33)
Wilcoxon signed rank test	p= 0.35

IQR= interquartile range

Evaluation in reversed order: TSE-SPAIR alone and TSE-SPAIR + MRDTI

The evaluation of the TSE-SPAIR sequences alone corresponded overall for 82% with the original MRDTI reading (**table 2**). Based on the TSE-SPAIR sequence alone, 2 additional patients were diagnosed with distal DVT, on top of the 3 patients diagnosed with proximal or distal DVT on the aggregate reading of MRDTI. Indeed, after adding the MRDTI sequence, these two patients were adjudicated as not having DVT, which corresponded with the results of the MRDTI scan reading and management decision at baseline. Overall, the median diagnostic confidence increased after evaluation of the MRDTI sequence on top of the TSE-SPAIR sequence from a median of 3.33 (IQR 3.0-3.67) to 3.67 (IQR 3.0-3.67), although this change was not significant (p= 0.176). Image quality of the TSE-SPAIR sequence was scored slightly better (table 4).

DISCUSSION

This study shows that after adding the TSE-SPAIR sequence on top of the MRDTI sequence for diagnosing proximal ipsilateral recurrent DVT, diagnostic confidence increased overall from 'good' (median 3.0, IQR 2.66-3.0) to 'excellent' (median 3.67, IQR 3.33-3.67). When the scans were evaluated in the reversed order, the diagnostic confidence did also increase but to a lesser extent. The image quality of the TSE-SPAIR sequence was scored higher than the MRDTI sequence for the first and second evaluation. The diagnostic accuracy of both imaging tests for proximal DVT was good, although the small sample size does not allow calculation and comparison of sensitivity.

With the MRDTI sequence, a thrombus can be visualized directly as a hyperintense signal based on the shorter T1 relaxation time in comparison with blood. The change in the T1 relaxation time is caused by change in paramagnetic properties by accumulation of methemoglobin in fresh thrombus, which is formed from haemoglobin by the oxidation of Fe2+ into Fe3+ during the acute phase of DVT.[14,15] Previous studies have shown that this high signal appears within 3 hours after thrombus formation and resolves completely after 6 months.[15] The same bright signal intensity can be visualized with the TSE-SPAIR sequence. Additionally, this sequence has a better spatial resolution, leading to improved visualization of the vessel-wall.[13] The better visualisation of the vessel wall may help to (double) confirm that increased signal intensity is indeed present in one of the deep veins, and is not an artifact. In the MRDTI sequence the signal in arteries may appear high due to inflow effect, even when using a saturation slab. This may explain the overall increase in diagnostic confidence for the reviewers when the TSE-SPAIR sequence was evaluated on top of the MRDTI sequence in this study. This raises the question whether TSE-SPAIR may be standardly combined to MRDTI scanning, and/or has the potential to be used as a single test, instead of MRDTI. Importantly, for

the TSE-SPAIR sequence, the timing of development and disappearance of high signal intensity in thrombus is not validated yet. This was also noticed during evaluation of the TSE-SPAIR sequences alone: some venous segments were detected with an intermediate/ 'grey' signal and considered positive for DVT in two patients, although they were considered negative for DVT on the initial MRDTI evaluation. Of note and in contrast to MRDTI, TSE-SPAIR has to be tested against the gold standard in a larger patient group before it can be used as single test. An advantage of using the MRDTI and TSE-SPAIR sequences is that these are both non-contrast enhanced MRI sequences. Disadvantages of using Gadolinium-based contrast agents are costs of the contrast agent itself, application materials, and more importantly the extra time needed for contrast administration. Potential risks are adverse events (contrast allergy, and nephrogenic systemic sclerosis in patients with severe renal insufficiency).[16] Also, recent research has suggested the potential risk of gadolinium retention in the human body.[17]

A disadvantage of using the TSE-SPAIR sequence on top of the MRDTI sequence is the significant increase in MRI scan time, approximately 8 minutes per investigation. With the high costs and low availability of MRI time, this may be an important issue.

Similar non-contrast enhanced direct thrombus imaging MRI techniques have been investigated for the visualization of the intracranial arteries, the carotid artery and the superficial femoral arteries.[18-20] To our knowledge there is only one other study that investigated a MRI technique that is comparable with TSE-SPAIR for diagnosing DVT.[13] That was a small pilot study including thirteen patients with a CUS proven first DVT and using a 3.0 Tesla scanner with a volumetric isotropic turbo spin-echo acquisition technique (VISTA). Accuracy was calculated compared with contrast-enhanced MRI and ultrasonography as a reference standard. This resulted in a sensitivity of 77.8%, specificity of 94.8%, a negative predictive value of 91.6% and a positive predictive value of 85.4%. Image quality and diagnostic confidence level of VISTA were 3.54 and 3.80 respectively, both scored on a 4 point Likert scale. Compared with our study, that study included patients with a suspected first DVT, instead of recurrent DVT in our study, and they used a contrast-enhanced MRI and ultrasonography as reference to the VISTA technique instead of another T1 weighted MRI technique. Additionally, the diagnostic confidence was based on the VISTA technique alone instead of MRDTI +TSE-SPAIR together in our study so therefore direct comparison of the results of the two studies is not possible. However, the diagnostic confidence of VISTA and MRDTI+TSE-SPAIR was comparable with Likert scale scores of 3.80 and 3.67 respectively.

A limitation of our study was that we have no reference test to identify false-positive patients since it is not possible to differentiate residual thrombosis from acute recurrent thrombosis neither with ultrasound nor with venography. A second limitation was that the three independent readers were experienced in reading the MRDTI sequences, but had no experience in reading TSE-SPAIR sequences, which may have influenced our

findings. Thirdly, our sample size was small, most of them were negative cases and the study was not powered nor designed to compare the diagnostic accuracy of both scan sequences accurately.

In conclusion, this study shows that the diagnostic confidence improved when adding the TSE-SPAIR sequence to the MRDTI sequence for diagnosing acute recurrent proximal DVT. The extra (TSE-SPAIR) sequence may help to increase diagnostic confidence in case of uncertain diagnosis.

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Diagnosing upper extremity deep vein thrombosis with non-contrast-enhanced magnetic resonance direct thrombus imaging: a pilot study

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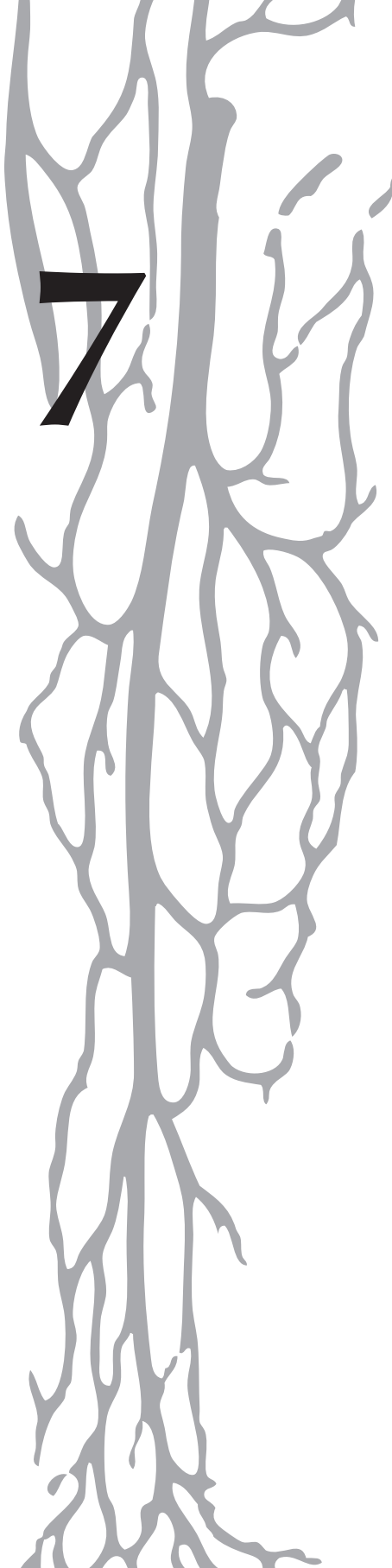

ABSTRACT

Diagnosing upper extremity deep vein thrombosis (UEDVT) can be challenging. Compression ultrasonography is often inconclusive because of overlying anatomic structures that hamper compressing veins. Contrast venography is invasive and has a risk of contrast allergy. Magnetic Resonance Direct Thrombus Imaging (MRDTI) and Three Dimensional Turbo Spin-echo Spectral Attenuated Inversion Recovery (3D TSE-SPAIR) are both non-contrast-enhanced Magnetic Resonance Imaging (MRI) sequences that can visualize a thrombus directly by the visualization of methemoglobin, which is formed in a fresh blood clot. MRDTI has been proven to be accurate in diagnosing deep venous thrombosis (DVT) of the leg. The primary aim of this pilot study was to test the feasibility of diagnosing UEDVT with these MRI techniques. MRDTI and 3D TSE-SPAIR were performed in 3 pilot patients who were already diagnosed with UEDVT by ultrasonography or contrast venography. In all patients, UEDVT diagnosis could be confirmed by MRDTI and 3D TSE-SPAIR in all vein segments. In conclusion, this study showed that non-contrast MRDTI and 3D TSE-SPAIR sequences may be feasible tests to diagnose UEDVT. However, diagnostic accuracy and management studies have to be performed before these techniques can be routinely used in clinical practice.

INTRODUCTION

Upper extremity deep vein thrombosis (UEDVT) accounts for 4-11% of all thromboses in the deep veins.[1,2] UEDVT is defined as a thrombus localized in the internal jugular, subclavian, axillary, brachial or brachiocephalic vein. Prompt and accurate diagnosis of UEDVT is important to prevent pulmonary embolism (PE) and long-term complications including the post-thrombotic syndrome.[3]

Compression ultrasonography has as major limitation when the thromboses are located more centrally in the subclavian region, compression is impeded due to overlying anatomical structures. Therefore, contrast venography is the reference standard in these cases, but this poses risks to the patient due to its invasive nature, radiation exposure and the potential for allergic reactions to contrast media.[4] CT-Venography (CT-V) can also be used to detect thrombi, but large studies with CT-V in patients with suspected UEDVT are lacking.[5] Moreover, CT-V is associated with exposure to contrast media and ionizing radiation as well. Magnetic Resonance Venography (MRV) has also been evaluated for diagnosing UEDVT. This MRI technique uses a gadolinium-based contrast agent, and has shown low accuracy in a feasibility study of 44 patients with a sensitivity of 50% and a specificity of 80%.[6] Time of Flight (TOF) MR venography is a non-contrast based technique, however has a long imaging time and showed low accuracy also.[6] Magnetic Resonance Direct Thrombus Imaging (MRDTI) and Three Dimensional Turbo Spin-echo Spectral Attenuated Inversion Recovery (3D TSE-SPAIR) are both MRI sequences that can visualize a thrombus directly without need of venous contrast by the visualization of methemoglobin, which is formed in a fresh blood clot. MRDTI has already been shown highly accurate in diagnosing a first DVT of the leg.[7] In a pilot study a three-dimensional black blood T1-weighted turbo spin-echo technique (VISTA), another direct thrombus imaging technique, has been compared to contrast-enhanced MRI for the diagnosis of DVT.[8] This technique is comparable with the T1 weighted 3D TSE-SPAIR sequence. To date, there are no published reports on the use of MRDTI or 3D TSE-SPAIR in patients with a suspected UEDVT. Since formation of methemoglobin in a thrombus is common in DVT within both the lower and the upper extremities, we hypothesize that MRDTI and 3D TSE-SPAIR may also be accurate diagnostic tests for UEDVT. In this pilot study we assess the feasibility of MRDTI and 3D TSE-SPAIR sequences to visualize UEDVT in 3 patients who were already diagnosed with UEDVT by ultrasonography and/or venography.

METHODS

This pilot study was performed in the context of the MAGNITUDE/Selene study (NTR5738), a prospective proof of concept study to explore the diagnostic accuracy of MRDTI and

3D TSE-SPAIR in the diagnostic management of UEDVT. It was pre-defined to first include 3 pilot patients with confirmed UEDVT, as to optimize the MRI scan techniques before including 60 additional patients. The study was approved by the institutional review board and all patients provided written consent.

Patients

We included three adult patients who were referred to the Radiology department of our hospital between December 2016 and March 2017 with a clinically suspected acute UEDVT, after symptom onset <10 days before presentation, who were diagnosed with UEDVT by ultrasonography and/or by venography and had no contra-indications for MRI.

MRI

MRI was performed using a 1.5-Tesla unit (Philips Ingenia 1.5T, release 5, Philips Medical Systems, Best, the Netherlands) to image the subclavian, axillary, brachial and brachio-cephalic vein. Image assessment involved acquiring images in the coronal plane with standard image reconstruction techniques. First, a MRDTI sequence was performed; directly followed by a 3D TSE-SPAIR sequence. Scan parameters of both sequences were optimized from imaging DVT of the legs to imaging UEDVT. MRDTI is based on visualization of methemoglobin which is formed in a fresh thrombus by the oxidation of haemoglobin. Methemoglobin has other paramagnetic properties which causes shortening of the T1- relaxation time and consequently appears as a high signal on a T1 weighted MRI scan.[9,10] This signal disappears completely after 6 months.[11] Therefore, this technique can also differentiate between acute recurrent thrombosis and asymptomatic residual thrombosis.[12,13] 3D TSE-SPAIR is based on the visualization of methemoglobin as well, but results in a higher spatial resolution of the vessel wall than MRDTI.[8] The time course of the methemoglobin signal is not known for this sequence.

Image analysis

Results of the MRDTI and 3D TSE-SPAIR images were evaluated by an expert panel (L.K. , C.D. and G. v. H.). Acute UEDVT was confirmed by high MRI signal against suppressed background.

RESULTS

Optimization of MRI sequences

MRDTI and 3D TSE-SPAIR sequences were used with an integrated 16-channel posterior coil and a 16-channel anterior body coil (scan parameters, **table 1**). MRDTI includes a

Table 1. MRDTI and 3D TSE-SPAIR scan parameters

	MRDTI	3D TSE-SPAIR
Technique	T1TFE	TSE
Orientation	Coronal	Coronal
FOV	400x405	350x400
Slices	60	180
Thickness	4.0	1.1
Voxelsize	1.6 x 2.24 acq. 1.6 x 1.6 recon	1.09 x 1.1acq. 0,5 x 0,5 recon
Scantime	5:53	5:33
Echo time	5.4	23
Repetition Time	11	400
Flip Angle	15	90
TFE prepulse Inversion Time	1200	-
SPAIR Inversion delay	-	110

Note: all times in ms

water-only excitation radiofrequency pulse to abolish the fat signal; the effective inversion time is chosen to nullify the blood signal. 3D TSE SPAIR is a T1 weighted 3D sequence using a spectral, adiabatic presaturation (inversion) pulse to achieve fat suppression. To optimise the MRDTI sequence for visualization of UEDVT, a saturation slab was placed obliquely over the heart for suppression of possible and potentially confusing high signal in the arteries due to inflow effects.

The anatomy of interest was placed as close as possible to the isocenter of the magnet for optimal image quality and fat suppression.

Patients and MRI results

The first patient was a 48-year-old woman, known with diabetes mellitus type II and hypertension. She presented with pain and swelling of her left arm three days after exercising with repetitive arm movements above her head. On examination, her left arm was swollen, red and painful and showed collateral superficial veins. Compression ultrasonography (CUS) revealed a thrombus in the brachial, axillary and subclavian vein up to the jugular vein. MRDTI and 3D TSE-SPAIR MRI was performed 11 days after initial CUS diagnosis. For both sequences a high signal, corresponding with DVT in the left subclavian and axillary vein was reported (**Figure 1A, 1B**).

The second patient was a 38-year-old male, without relevant medical history, who had progressive swelling of the left arm and hand for two days. Besides a brother who had experienced idiopathic pulmonary embolism at the age of 35, he had no other risk factors for thrombosis. On physical examination the left arm was edematous, warm, with red/purple colouring of the hand but without any pain. The left upper arm circumference

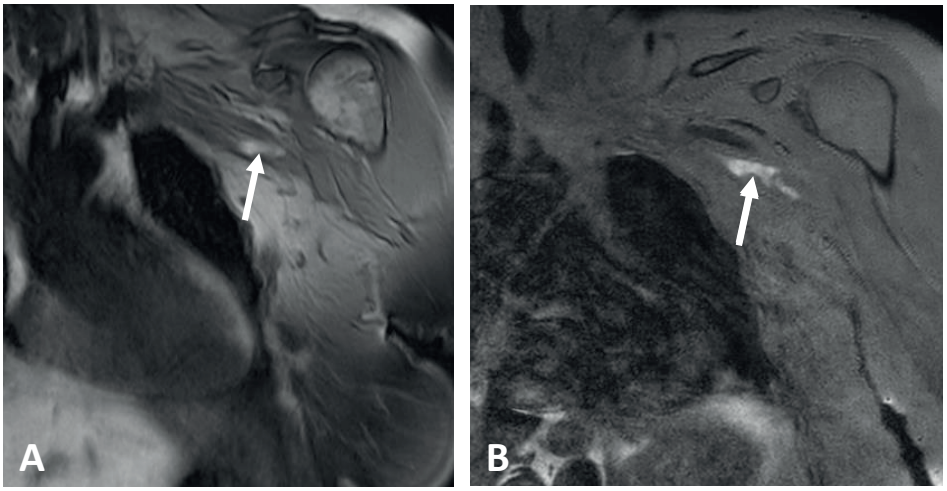

Figure 1A, 1B – Unenhanced MRI sequences: MRDTI (A) and 3D TSE-SPAIR (B) acquisitions of the upper extremities, coronal view.

48-year-old woman diagnosed with thrombosis in the left brachial-, axillary- and subclavian veins by compression ultrasonography. MRI: high signal intensity in the left subclavian vein, diagnostic for recent DVT (arrow).

was 5 cm larger than the right arm. CUS was performed, which showed no thrombosis but a slow venous return from the superficial and deep veins of the arms. Subsequently, a CT scan with venous contrast was performed, showing a lack of contrast in the left subclavian vein, but without an abrupt stop of contrast. This finding was highly suspected for UEDVT although not conclusive. Therefore, a contrast venography was performed, which finally confirmed a thrombosis in the left subclavian vein. MRI was performed 1 day after the venogram. MRDTI and 3D TSE-SPAIR MRI corresponded with the results of venography and were reported as DVT of the left subclavian vein (**Figure 2A,2B**).

The third patient was a 53-year old female known with Ehlers-Danlos type III in history, who was admitted to the hospital with fever and pain in her left arm. One week before admission, a long intravenous line, which was used for intravenous feeding, was replaced from her left subclavian vein to her right subclavian vein because of infection. On physical examination she had swelling and pain in her left arm. CUS revealed a thrombus in the left subclavian vein. MRDTI was performed 3 days after UEDVT diagnosis. MRDTI and 3D-TSE SPAIR were evaluated as diagnostic for a small thrombus in the subclavian vein based on a small high signal intensity focus that was only identified by following the precise course of the subclavian vein (**Figure 3A, 3B**).

The delay in performing the MRI scans in the first and third patient was due to logistic reasons. In all 3 patients 3D TSE-SPAIR was judged as visualizing the vessel walls with a higher spatial resolution, with improved anatomical distinction between the arteries and veins. The thrombus signal intensity was judged to be higher with 3D TSE-SPAIR

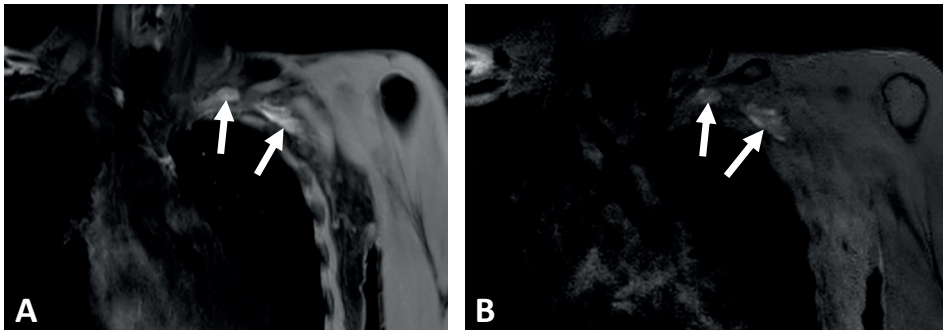

Figure 2A, 2B – Unenhanced MRI sequences: MRDTI (A) and 3D TSE-SPAIR (B) acquisitions of the upper extremities, coronal view.
38-year-old man, diagnosed with thrombosis in the left subclavian vein by contrast venography. MRI: striking high signal intensity in the left subclavian vein, diagnostic for recent DVT.

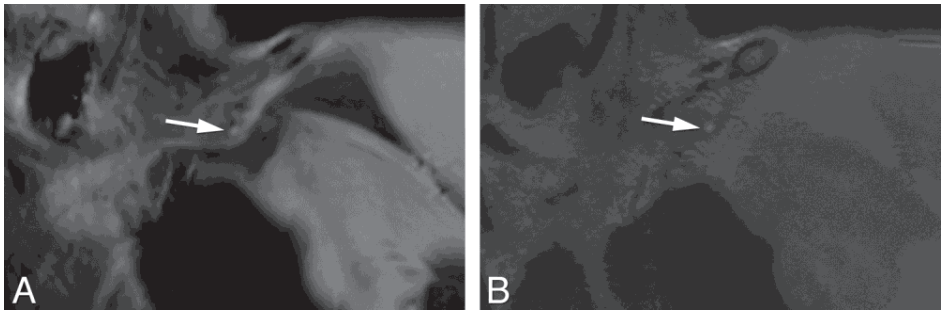

Figure 3A, 3B– Unenhanced MRI sequences: MRDTI (A) and 3D TSE-SPAIR (B) acquisitions of the upper extremities, coronal view.
53-year-old woman, diagnosed with a thrombus in the left subclavian vein by ultrasonography. MRI: Small high signal intensity focus that was only identified by following the precise course of the subclavian vein, diagnostic for recent DVT (arrow).

than MRDTI in patient 1, MRDTI was judged as showing higher signal intensity than 3D TSE-SPAIR in patient 2, and in patient 3 the signal intensity was evaluated as equal between the two sequences.

DISCUSSION

This feasibility study showed that both MRDTI and 3D TSE-SPAIR sequences were able to visualize UEDVT in 3 patients with confirmed UEDVT. The non-invasive diagnostic management of UEDVT is challenging, as illustrated by the case of patient 2. Ultrasonography, CT-venography and contrast venography had to be performed before the diagnosis could be established. MRI is both non-invasive and safe, and has particular

advantages over compression ultrasound for imaging the subclavian vein behind the clavicle. MRI is available in most hospitals, and radiology residents can be trained to independently review MRI investigations within a short training program.[14] Also, MRDTI and 3D TSE-SPAIR sequences together have a short imaging time of only 11 minutes. However, MRI is associated with higher costs than ultrasonography. Moreover, MRI scan time may not be readily available in the acute setting. Therefore MRI, after further validation, could potentially be used as a second test when CUS is not conclusive especially for the subclavian vein, i.e. in patients with a high clinical suspicion but normal CUS, instead of venography and/or in patients with known contrast allergy.

In this study we tested two different non-contrast enhanced MRI sequences, i.e. MRDTI and 3D TSE-SPAIR, which showed similar results in diagnosis, although with varying signal intensity of the thrombus. For the MRDTI sequence it is well established that a fresh thrombus results in a high signal by the visualisation of methemoglobin within 3 hours after thrombus formation and this high signal disappears completely after 6 months.[9,11] This last characteristic allows MRDTI to distinguish acute thrombosis from chronic residual thrombus.[12] However, the time frame for visualizing methemoglobin in thrombus is not known yet for the 3D TSE-SPAIR sequence. An advantage of 3D TSE-SPAIR over MRDTI is the higher spatial resolution of the vessel wall. Also, the signal of normal veins and arteries is low in this sequence whereas in the DTI sequence the signal in arteries may appear high due to inflow effect, even when using saturation slabs. Both sequences have to be tested in more patients to investigate the similarities and differences in thrombus-intensity on both sequences.

To our knowledge these are the first UEDVT cases confirmed by MRI by using MRDTI and 3D TSE-SPAIR sequences without using contrast-agents in patients with UEDVT. Two other MRI techniques have been tested in the past: time of flight vessel imaging and gadolinium contrast-agent enhanced MR-venography, but the first technique had long scan times and both techniques showed low accuracy for DVT.[6] In 2 of the 3 patients presented, MRI could not be performed within 24 hours after diagnosis of UEDVT because of logistical reasons. This could have led to a less high signal of the thrombus on both sequences due to resolution of thrombus after medical therapy over time.

We conclude that this pilot study suggests that both MRDTI and 3D TSE-SPAIR sequences may be feasible non-invasive non-contrast-enhanced tests to diagnose UEDVT. However, the sensitivity and specificity of these sequences have to be further explored and the safety of using these MR sequences to diagnose or rule-out UEDVT confirmed in an outcome study. Based on the presented 3 cases, the Magnitude/Selene study (NTR5738) will be performed to more accurately determine the diagnostic accuracy of MRDTI and 3D TSE-SPAIR in the diagnostic management of UEDVT.

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PART II

Prognostic challenges of deep vein thrombosis

8

Persistence to direct oral anticoagulants for acute venous thromboembolism

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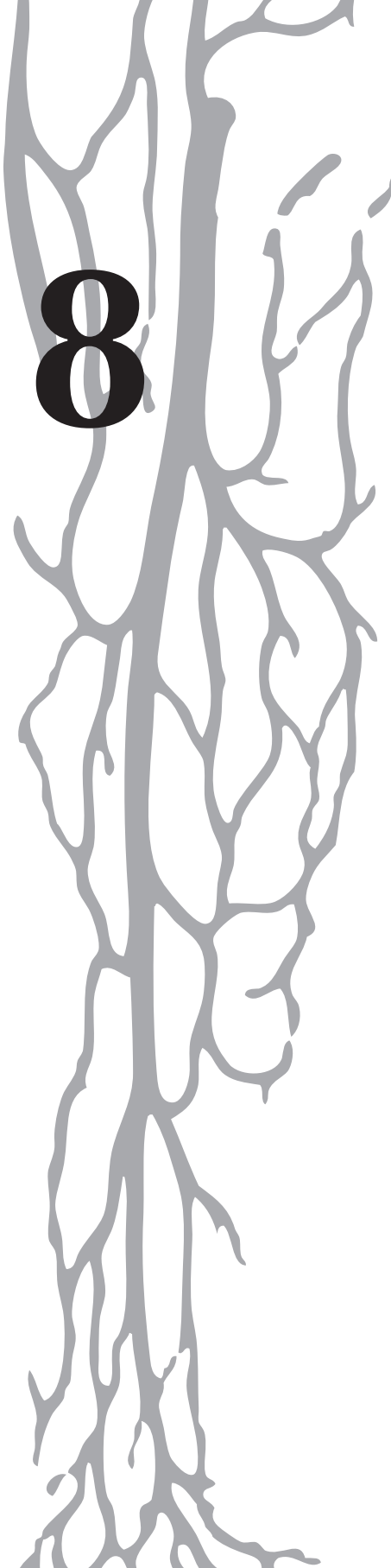

ABSTRACT

Background

Currently, direct oral anticoagulants(DOACs) are the treatment of choice for venous thromboembolism (VTE) in the Netherlands. The main advantages of DOACs over vitamin K antagonists (VKAs) are that they are safer than VKA and that neither monitoring nor dose titrations are needed. A main drawback is a potential risk of lower drug persistence, as compared with VKA treatment, which is strictly controlled by anticoagulation clinics in the Netherlands.

Objectives

The primary aim of this study was to audit the persistence to DOAC treatment for acute VTE during the first 2 months in daily clinical practice.

Methods

Dispensing data from the Dutch Foundation of Pharmaceutical Statistics were used to monitor persistence to DOAC for treatment of VTE from 1 January 2012-1 April 2016. Non-persistence was defined as the cumulative incidence of patients who completely stopped DOAC or VKA treatment. In addition, we estimated the persistence to VKA treatment for VTE in data from the Anticoagulation Clinic Leiden.

Results

1834 patients were selected as DOAC users for the indication VTE. The 2-month cumulative incidence of completely stopping DOAC was 20% (95% confidence interval [CI] 18-24). In the population of 4910 VKA users, 9.1% (95%CI 8.3-9.9) stopped prematurely with VKA.

Conclusion

The stopping rate of 20% we found is in line with other cardiovascular treatments. Further research into the reasons and consequences of prematurely stopping DOAC treatment for acute VTE is urgently needed.

INTRODUCTION

Direct oral anticoagulants (DOACs) are approved for treatment of venous thromboembolism (VTE), thromboembolic prevention in atrial fibrillation (AF) and thromboprophylaxis. Recently, DOACs have been suggested by international and Dutch guidelines as the treatment of choice for acute VTE.[1,2] In two meta-analyses based on randomized controlled trials it has been shown that DOACs are overall non-inferior in terms of efficacy (recurrent VTE) but lead to less major bleeding compared with vitamin K antagonists (VKAs).[3,4] An important practical advantage of DOACs over VKAs is that neither monitoring nor dose titration is needed. However, a lack of monitoring could decrease drug adherence and persistence.[5] Treatment duration for VTE is recommended to be at least three months,[1] as the risk of recurrence is high after prematurely stopping anticoagulation treatment within 1 or 1.5 months after the VTE event compared with longer treatment duration, for a reported Hazard Ratio (HR) of 1.52 (95% confidence interval [CI] 1.1 to 2.0).[6] In the DOAC trials, the percentage of patients who stopped DOAC treatment prematurely within 6 months ranged from 11 to 15%.[7-10] However, these trials might not be representative for the persistence to DOACs in clinical daily practice since less support for patients to continue their DOAC use will be present as compared with the trial settings. Recently, a Danish registry study in patients treated with DOACs for AF showed that out of 50632 patients, 30% discontinued their initial DOAC treatment within one year: 14% completely stopped DOAC treatment, 10% switched to VKA and 5% switched to another DOAC.[11] Other studies in patients with AF also confirmed a higher non-persistence to DOAC in clinical settings than in trials, with discontinuation rates of 20 to 25% within two years of follow-up.[12,13] To our knowledge, there are no published data on DOAC persistence in VTE patients in routine clinical practice. In the Netherlands, the first DOAC approved for treatment of VTE was rivaroxaban in 2012, followed by dabigatran and apixaban in 2014 and edoxaban in 2015. Over the last years, the use of DOACs has increased in the Netherlands.[14] The main purpose of the current study was to explore the persistence to DOACs in Dutch patients with acute VTE. A second aim was to assess for potential predictors for stopping DOAC prematurely. Since, to our knowledge, there is no literature about persistence to VKAs available, this was explored as well. The aim was to compare the two types of treatment, i.e. with monitoring, as provided by anticoagulant clinics in the Netherlands, and without monitoring.

METHODS

Definition of persistence

Drug persistence is defined as: continuing treatment for the prescribed duration.[15] The opposite of drug persistence, non-persistence or lower drug persistence can therefore be defined as: prematurely stopping treatment. Because the minimal treatment duration with DOAC for acute VTE is 3 months (also for distal DVT), and many patients will stop shortly before the exact 3 months date, a cut-off point of 2 months treatment duration was chosen as the period in which discontinuation was defined as definitely premature (**figure 1**).

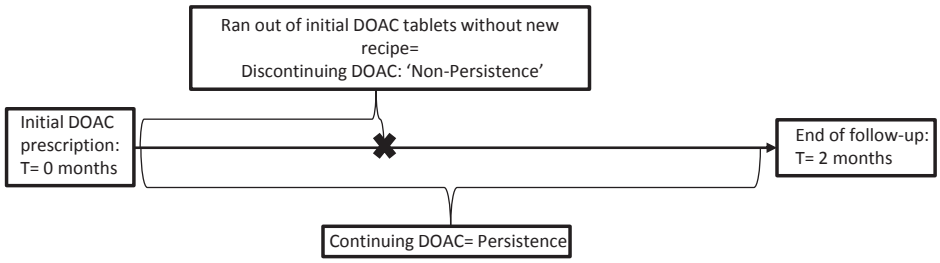

Figure 1. Definition of persistence to DOACs

Data source

Data from the Foundation of Pharmaceutical Statistics (SFK) were used for selection of patients treated with DOACs. SFK collects pharmacy dispensing data from >95% of community pharmacies in the Netherlands, i.e. information on which drugs were dispensed, including the codes from the Anatomic-Therapeutic-Chemical (ATC) system of the World Health Organization, the prescribed dose and the amount dispensed. For the current study, data collected by SFK from 1538 pharmacies in the Netherlands, which comprise 79% of all community pharmacies in the Netherlands, could be used. All data between January 1st 2012 and April 1st 2016 about type of DOAC (by ATC code), DOAC dose and number of tablets dispensed daily (once or twice), date of dispensing, patient sex, age, concomitant medical therapy and the use of a VKA prior to inclusion or during follow-up were provided. Although SFK does not collect information on the clinical indication for which DOACs are used, this could be approximated by differences in first dose of DOAC. The first dose of rivaroxaban and apixaban differs between short term prophylaxis (i.e. after orthopaedic surgery), initial treatment of VTE and thromboembolic prevention in atrial fibrillation. DOACs are not registered for treatment of thrombophlebitis in the Netherlands. In case dabigatran is prescribed for acute VTE treatment, this will be preceded by at least 5 days treatment with low-molecular weight heparin (LMWH).

Selection of patients

First, between 1 January 2012 and 1 April 2016, all patients who received one or more dispensings of one of the DOACs rivaroxaban, apixaban or dabigatran according to the data from SFK, were selected. The DOAC edoxaban was not included since it was rarely used in the Netherlands during the studied time period. The aim of this study was to investigate DOAC use for the indication of acute VTE. Records of patients who received rivaroxaban and apixaban doses corresponding with the initial treatment of VTE, or dabigatran preceded by LMWH were selected. From the selected patient group, only patients who received a first prescription of DOAC were included, for which reason patients who received a DOAC prescription between 1 January 2012 and 1 April 2012 were excluded. Since DOAC data were provided until 1 April 2016, patients who started DOACs after 1 February 2016 were excluded because it was unknown whether these patients stopped or continued treatment after 2 months. Specific DOACs were identified by ATC codes: B01AE07 for dabigatran, B01AF01 for rivaroxaban and B01AF02 for apixaban. Patients were also classified for previous use of VKA (ATC code B01AA) or any other concomitant medication (any ATC code) within 0-180 days prior to baseline as provided by SFK.

Outcomes

The primary outcome of this study was the non-persistence to initial DOAC treatment at two months. Non-persistence to DOAC was defined as the cumulative incidence of 'stoppers' in the DOAC group, so patients who stopped DOAC treatment within 2 months without switching to any other oral anticoagulant treatment. They were selected by counting the number of patients who did not register a new prescription of their initial DOAC within 45 days. A secondary outcome of this study was the number of patients who switched from DOAC treatment to another anticoagulant (DOAC or VKA) within 2 months. The cumulative incidence of patients who stopped or switched DOAC was also calculated, together defined as 'discontinuing DOAC'. The cumulative incidence of stopping or switching DOAC within 3 months was calculated as well.

Statistical analysis

Baseline characteristics of the DOAC users are expressed as numbers and percentages, or as means and standard deviations (SD). Observation time was defined as the time between the dates of first DOAC prescription and the end of follow-up, which was restricted to a maximum of 3 months. For stopping with DOAC, follow-up ended at the date that a patient ran out of DOAC tablets. Kaplan-Meier analyses were used to determine the cumulative incidence for the outcome events.

With univariable and multivariable logistic regression analysis we compared the likelihood of non-persistence between the DOAC groups, adjusting for age, sex, and previous

VKA use, to get an indication which covariates were related with persistence in DOAC users. Since SFK registers data per pharmacy and not per patient, there is a possibility that patients retrieved their medication from different pharmacies, which could lead to an underestimation in persistence. To adjust for this possibility, we performed a sensitivity analysis for the primary outcome excluding all patients who had the same birth year, sex, postal code and who used the same DOAC.

All statistics were performed using SPSS version 23 (IBM Corp, Armonk, NY).

Persistence to VKA therapy

Since for VKA therapy the first doses for thromboembolic prevention in AF and treatment of VTE are the same and LMWH is often prescribed when AF is initially diagnosed, it was not possible to distinguish the two indications based on SFK data. Therefore, another database, i.e., the registry of the Anticoagulation Clinic was used to explore the persistence to VKA. In the Netherlands, all patients who use VKA therapy are monitored by the Anticoagulation clinics, which are organized per geographical area. For this study, data from the Anticoagulation Clinic in Leiden were used. Patients are closely monitored by the Anticoagulation Clinic and visit the clinic for INR monitoring at least once per 6 weeks. Patients who seem non-persistent to VKA (i.e. have low INRs) are called or receive letters from the Anticoagulation Clinic. In this VKA only cohort, date of VKA initiation, age at VKA initiation, sex, indication for which the VKA was prescribed (i.e. VTE) and date of VKA discontinuation were provided. From this VKA cohort all patients who started with VKA treatment between 1 January 2004 and 1 January 2012 were included. Patients with an upper extremity deep vein thrombosis (UEDVT) or thrombosis at another infrequent location were excluded, since DOACs were not prescribed for these indications in the studied period.

We chose for the time period between 2004 and 2012 because in this period only VKA was available as oral anticoagulant drug, since DOACs were not registered for the indication VTE. Therefore, these patients could not discontinue their drug due to a switch to a DOAC (as was possible from 2012 onwards). Using this time period for VKA allowed us to estimate the expected non-persistence rate in an unselected group of patients with VTE who were prescribed oral anticoagulant treatment at an anticoagulation clinic where this treatment is rigorously monitored. Non-persistence to VKA was defined as the cumulative incidence of patients who stopped VKA treatment within 2 months after initiation. For treatment duration the time between the start and discontinuation of VKA according to the data from the Anticoagulation Clinic Leiden was calculated. Kaplan-Meier analyses were used to determine the cumulative incidence for stopping with VKA within 2 months. Cumulative incidence of stopping VKA within 3 months was calculated as well.

Ethical approval

The data from SFK and the Anticoagulation Clinic Leiden were anonymised prior to analysis. For use of retrospective observational registry data for a descriptive study no approval from the medical ethical committee was needed according to Directive 2001/20/EC and Dutch legislation.

RESULTS

Study population

Between January 1st 2012 and April 1st 2016, 92718 patients initiated DOAC therapy. From this cohort, 87352 patients who were identified as incident DOAC users were selected (Flow chart, **figure 2**). A total of 3427 patients were excluded because the DOAC type or dosage was unknown and 12 patients were excluded because they used (according to SFK) more than 1 DOAC at the same time. From the remaining 83913 eligible DOAC users, 2048 were identified as DOAC users for acute VTE treatment, 77333 for AF, and 4532 as DOAC users for thromboprophylaxis. Lastly, from the 2048 patients on DOAC for the indication VTE, 214 patients who started DOAC treatment after 1 February 2016 were excluded, leaving 1834 patients for the primary analysis.

Baseline characteristics from the included DOAC users are shown in **Table 1**. Most patients used rivaroxaban (n=1429), followed by dabigatran (n=311) and apixaban (n=94). A small proportion of DOAC patients (7%) had used VKA previously.

Table 1. Baseline characteristics

	DOAC use	Apixaban use	Rivaroxaban use	Dabigatran use
Venous thrombosis patients				
Any dose, n	1834	94	1429	311
Mean age, years (SD)	60 (16)	68 (12)	58 (16)	67 (13)
Men, n (%)	990 (54)	59 (61)	778 (54)	153 (49)
Concomitant drug use, n (%)	1370 (75)	80 (85)	989 (69)	301 (97)
Previous use of VKA, n (%)	131 (7)	11 (12)	98 (7)	22 (7)

DOAC denotes direct oral anticoagulant; SD, standard deviation; VKA, vitamin K antagonist; NA not available

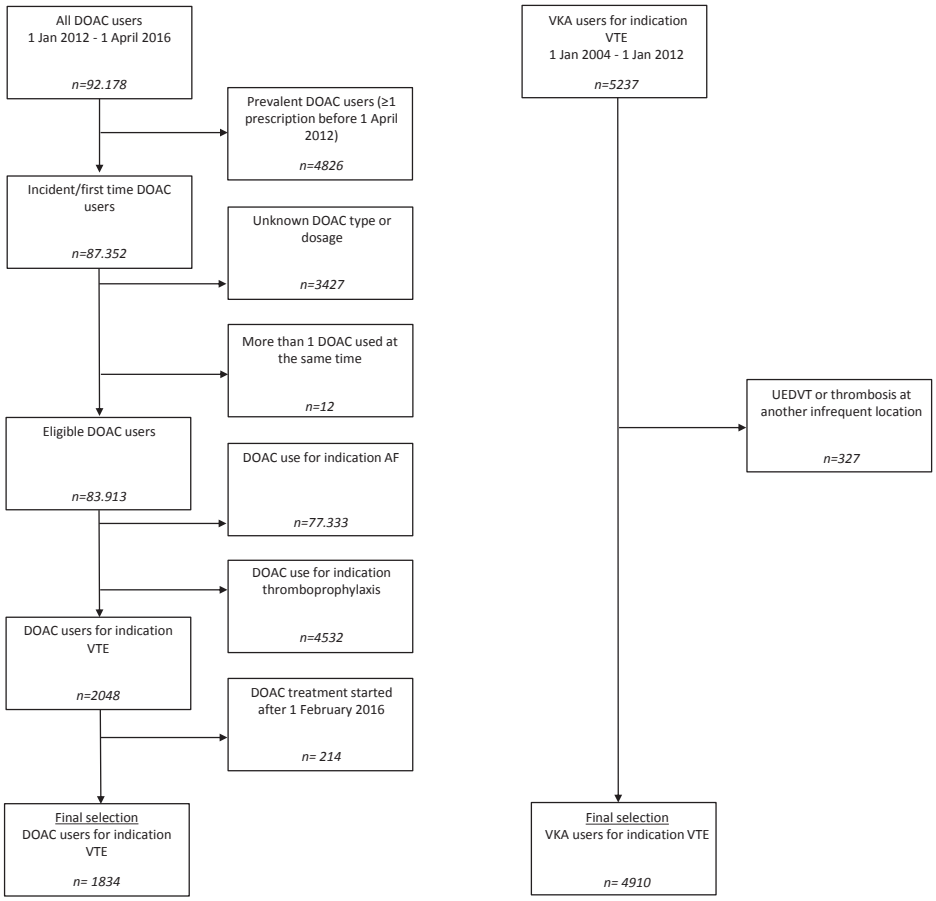

Figure 2. Flow chart selecting DOAC users for the indication VTE

Discontinuation

From 1834 patients, 352 stopped DOAC within 2 months for a cumulative incidence of 20% (95%CI 18 to 24). Additionally, 117 from 1834 patients switched their initial DOAC prescription: 113 to VKA and 4 to another DOAC for a cumulative incidence of 7% (95%CI 5.7 to 8.1). In total, 469 discontinued DOAC (both 'stoppers' and 'switchers') within 2 months, for a cumulative incidence of 26% (95%CI 24 to 28; Kaplan-Meier curves, **figure 3a**). After 3 months the number of patients that stopped DOAC increased to 470, for a cumulative incidence of 27% (95%CI 25-29). In addition, 134 patients (8.1% [95%CI 6.7-9.4]) switched to another anticoagulant. In total, 604 patients discontinued DOAC for a cumulative incidence of 33% (95%CI 31-35). In the sensitivity analysis in which 52 patients who had the same birth year, sex, postal code and DOAC type were excluded, discontinuation patterns were comparable: 444 of 1782 patients discontinued for a cumulative incidence of 26% (95%CI 23 to 27).

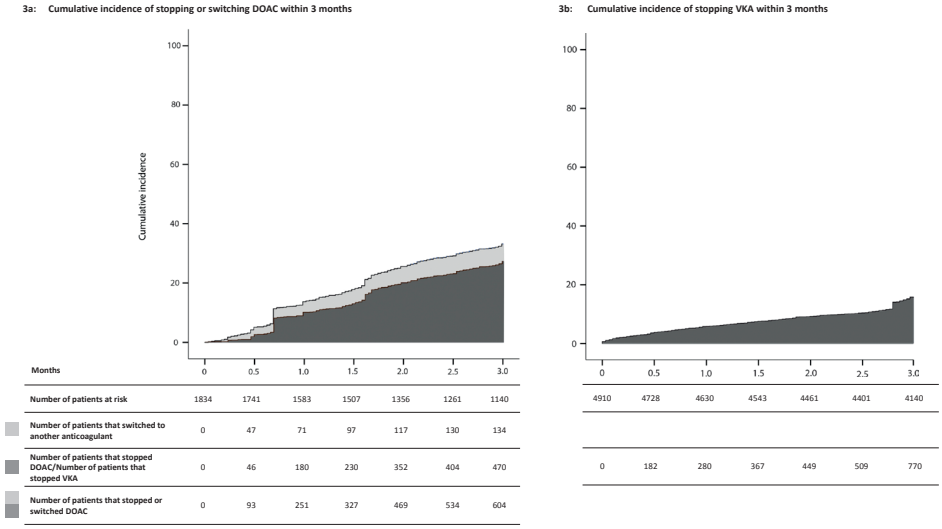

Figure 3. Cumulative incidence of stopping or switching DOAC within 3 months and cumulative incidence of stopping VKA

Predictors for premature discontinuation

In univariable analysis, predictors for discontinuing DOAC (stopping DOAC or switching to alternative treatment) were: no previous use of VKA (OR 1.67; 95%CI 1.05 to 2.65), the use of no other drugs (concomitant drug use) (OR 1.57; 95%CI 1.25 to 1.98) and female sex (OR 1.32; 95%CI 1.07 to 1.63). After multivariable analysis, no concomitant drug use (OR 1.86; 95%CI 1.45 to 2.39), and female sex (OR 1.38; 95%CI 1.11 to 1.72) remained predictors of premature discontinuation of DOAC treatment **(Table 2)**.

Rivaroxaban and dabigatran were associated with higher discontinuation rates than apixaban with odds ratios of 2.45 (95%CI 1.29 to 4.64) and 4.01 (95%CI 2.05 to 7.85; Table 2) compared with apixaban respectively. After multivariable analysis these odds ratios were: 2.19 (95%CI 1.15 to 4.20) and 4.16 (95%CI 2.12 to 8.18) respectively.

Persistence to VKA therapy

5237 patients started VKA between January 1st 2004 and January 1st 2012 for the indication VTE. From this patient group, 327 patients who used VKA for upper extremity DVT (UEDVT) or thrombosis at another infrequent location were excluded, leaving 4910 patients for the analysis. Mean age was 60 years (95% CI 59-60), and 48% of patients were men. Within 2 months 449 of 4910 stopped VKA for a cumulative incidence of 9.1% (95%CI 8.3 to 9.9; **figure 3b**). After 3 months 800 patients stopped with VKA, for a cumulative incidence of 18% (95%CI 17-19).

Table 2. Predictors for discontinuing DOAC treatment within 2 months according to clinical characteristics

	Discontinued	Continued	Odds ratio (95% CI)	Odds ratio (95% CI)*
Apixaban	11	83	1 (reference)	1 (reference)
Rivaroxaban	350	1079	2.45 (1.29-4.64)	2.19 (1.15-4.20)
Dabigatran	108	203	4.01 (2.05-7.85)	4.16 (2.12-8.18)
Previous use of VKA	23	108	1 (reference)	1 (reference)
No previous use of VKA	446	1257	1.67 (1.05-2.65)	1.37 (0.85-2.20)
Concomitant drug use	319	1051	1 (reference)	1 (reference)
No concomitant drug use	150	314	1.57 (1.25-1.98)	1.86 (1.45-2.39)
Age $\leq$ 60 years	205	640	1 (reference)	1 (reference)
Age 60-75 years	179	475	1.18 (0.93-1.49)	1.19 (0.93-1.52)
Age >75 years	85	250	1.06 (0.79-1.42)	1.04 (0.77-1.41)
Men	229	761	1 (reference)	1 (reference)
Women	240	604	1.32 (1.07-1.63)	1.38 (1.11-1.72)

*Multivariable adjusted for each other

DISCUSSION

This study, based on Dutch pharmacy dispensing and anticoagulation clinics registry data, showed that the cumulative incidence of premature discontinuation of DOAC treatment for the indication VTE in daily clinical practice within the first 2 months was 20% (95%CI 18 to 24) and an additional 7% (95%CI 5.7 to 8.1) switched to another anticoagulant treatment. The cumulative incidence of discontinuation (stopping or switching) DOAC was 26% (95%CI 24 to 28). This discontinuation rate is higher than was reported in the phase 3 DOAC trials, i.e., 11 to 15% within 6 months.[7-10] Furthermore, we showed that the cumulative incidence of stopping VKA within the first 2 months was 9.1% (95% CI 8.3-9.9).

To our knowledge, there are only a few observational studies in small numbers of patients on discontinuation rates in DOAC use. One systematic review in patients with acute VTE included 7 VKA studies and 3 conference abstracts about DOAC persistence. Stratifying the results from this systematic review into patients with VTE who used VKA and who used DOAC, discontinuation rates within 3 months ranged between 6% to 28% for VKA (average 18%) and 6% to 36% in patients on DOAC (average 13%).[16] This study therefore shows the opposite from our study: a lower discontinuation rate in DOACs compared with VKA. However, the systematic review only included 203 patients with acute VTE who were treated with DOAC, which is in stark contrast to our large population based registry of patients with acute VTE who were treated with a DOAC (n=1834). Another recent study used the Dresden registry to analyse the persistence to Rivaroxaban

in 418 patients with VTE. After 6 months 58.3% of patients were still taking rivaroxaban, 28.2% had a scheduled end of treatment, 7.2% were switched to other anticoagulants, 1.7% had withdrawn their consent and the remaining 3.6% of patients had unplanned complete discontinuation of anticoagulation. However, in contrast to our study, patients were contacted by phone during follow-up which could have positively altered the persistence rate.[17] Recently, a study based on RIETE registry data also reported that adequate treatment with DOACs for VTE is challenging in clinical practice.[18] This study showed that a high proportion of VTE patients who were prescribed DOACs did not receive the recommended daily dosings, i.e. once daily dosing of apixaban instead of twice daily. For the initial therapy, 50% (22 of 44) of apixaban users and 18% (287 of 1591) of rivaroxaban did not receive the recommended dosing, resulting in a higher VTE recurrence rate (HR 10.5, 95%CI 1.28-85.9); discontinuation rates of DOAC during follow-up were not reported in this study.

We found a high incidence of stopping DOACs within 2 months after initiation. Although we cannot directly compare this finding to previous studies in patients with acute VTE who used DOACs, this non-persistence percentage is in line with other treatment regimens for cardiovascular conditions that are strongly recommended according to clinical guidelines. For example, oral antiplatelet (OAP) treatment after acute coronary syndrome (ACS) is recommended to be used for at least one year. Nevertheless, a study based on prescription register data from Finland showed that only 49% of patients received OAP treatment after hospital discharge and approximately 20% of patients stopped OAP within 90 days.[19] Other studies showed similar results in treatment with antiplatelet therapy after acute coronary syndrome and percutaneous coronary intervention (PCI).[20,21] Also, the percentage of stopping chronic medication after acute myocardial infarction as beta blockers or aspirin is close to 20-30% within one year.[22] This percentage is also described for preventive drugs after hospitalization for stroke. A large American registry study in 2589 patients showed that 25% of patients reported stopping 1 or more of their prescribed regimen of secondary prevention medications within 3 months after acute stroke.[23]

Clearly, the stopping rates that we found for DOACs are in line with those of other cardiovascular medications and therefore seem to be part of a general problem of low persistence to medication.[24] The fact that the stopping rate in VKA users is lower suggests that the strict monitoring by an anticoagulation clinic improves adherence compared to the routine use of other medications. A previous study that focussed on adherence to dabigatran for the indication of AF showed that monitoring by phone calls or follow-up visits performed by pharmacists resulted in higher adherence.[25] Such a strategy is also followed by anticoagulation clinics in the Netherlands for patients who use VKA and this clearly contrasts with the current clinical practice where patients on DOAC are not mandatorily monitored on their drug persistence. In contrast, one study in AF patients

reported a higher persistence to DOACs (79.2) compared with VKA (63.6%) after one year.[13] This was assumed to be the result of the more simple treatment with DOAC, without food interactions and monitoring compared with VKA. In countries where VKA monitoring is not as well organized as in the Netherlands, the difference in persistence to DOAC and VKA may be less pronounced.

Nevertheless, reasons for discontinuing DOAC in particular can be speculated on. Reasons for discontinuing reported in the DOAC trials were diverse and included bleeding events, withdrew of consent, loss to follow-up, death or other non-specified reasons.[7,9,10] A small part of the 20% stopping rate could be explained by death. In addition, cancer could also be a reason to stop DOAC treatment, in a Dutch study, the incidence of cancer diagnosis shortly after VTE was 3.5%.[26]

With respect to adverse events, it may well be that patients could have discontinued DOAC because of bleeding complications. Although it has been shown that DOACs have a lower risk of major bleeding compared with VKA, the percentage of patients with a major or clinically relevant bleeding in the several DOAC trials still ranged from 4-10% within 3 months of follow-up. However, this is no explanation for the discrepancy with the VKA group.[7,9,10] We showed that female sex was a predictor of premature discontinuation of DOAC. This result is in line with a meta-analysis including 8 studies comprising 9417 patients that showed that women suffer from more bleeding complications than men when using DOACs for VTE treatment.[27] Part of this higher bleeding risk in women may be due to increased uterine bleeds when using a DOAC, as suggested by a recent study that showed that the occurrence of uterine bleeds was higher in women treated with rivaroxaban or apixaban compared with warfarin.[28,29] Another study showed that abnormal menstrual bleeding also occurred more frequently with rivaroxaban treatment than with enoxaparin/VKA, for a HR 2.13 (95%CI 1.57-2.89).[29] In a survey among clinicians, 15% replied to consider (temporally) stopping DOAC treatment in patients with abnormal menstrual bleeding.[30]

The main strength of our study is that we investigated the persistence to DOAC for the indication of VTE in a large population of unselected DOAC users. For the interpretation of our study some limitations should be mentioned. First, we do not know why patients were non-persistent. We tested a few predictors by multivariate analysis as concomitant drug use, age and sex, but could not study other potentially relevant predictors as socioeconomic class or level of education. Our results indicate that studies focusing on the reason *why* patients with acute VTE stop using their DOAC should be conducted. A second limitation of this study is that SFK does not provide the exact indication and planned treatment duration for DOAC treatment. However, we could have missed patients who used DOAC for VTE in our study, for example because they received the wrong initial dosing. Another potential limitation is that SFK was only able to provide data of 79% of all pharmacies in the Netherlands. However, reasons for not including

pharmacies were completely at random, so could not have introduced selection bias. The first reason was that pharmacies which went out of business during the study period could not provide follow-up data from the moment that they closed. In addition, merging pharmacies received new pharmacy numbers by SFK, and from that moment onwards it was unclear from which patient follow-up was provided. Furthermore, pharmacies who switched to another computer system during the study period could not be used for a similar reason. A fourth limitation is that we cannot ascertain whether the DOACs dispensed by the pharmacies were actually taken by the patients. Notably, not having taken the medication would have led to an even higher discontinuation rate than we have found. For example, even clinical trials report that the percentage of the prescribed doses of medication actually taken by the patient ranges between 43-78%.[24] A final limitation of our study is that we used different time periods for the DOAC and VKA databases. As mentioned, we did this on purpose in order to investigate the persistence to VKA in a period in which it was not possible to switch to another oral anticoagulant, to create a representative reference population for the persistence to oral anticoagulants in general. However, there was a slight possibility to switch to low molecular weight heparin (LMWH) as therapeutic anticoagulation treatment in that time period. Although the incidence of switching from VKA to LMWH is expected to be low, we have no data about this available. Even so, this could have led to an overestimation of the persistence in the VKA group.

In conclusion, in this study, based on Dutch pharmacy registry data, in patients who were selected as DOAC users for acute VTE, the cumulative incidence of stopping DOAC treatment within 2 months after initiation was 20%, which is in line with use of other cardiovascular medications. Since the primary outcome of this study is based on Dutch registry data with corresponding limitations and may be not representative for other countries, our results should be mainly interpreted as hypothesis generating and as a warning that further investigation on the incidence and consequences of non-persistence in DOAC patients is urgently needed.

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9

Predicting post-thrombotic syndrome with ultrasonographic follow-up after deep vein thrombosis: a systematic review and meta-analysis

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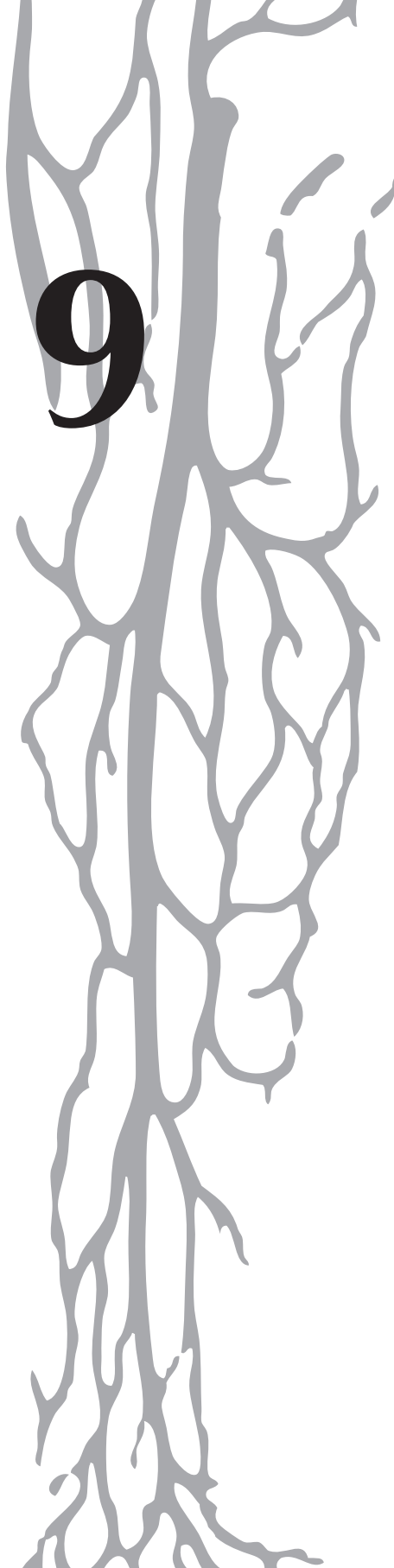

ABSTRACT

Background

Post-thrombotic syndrome (PTS) is a common and potential severe complication of deep venous thrombosis (DVT). Elastic compression stocking therapy may prevent PTS if worn on a daily basis, but stockings are cumbersome to apply and uncomfortable to wear. Hence, identification of predictors of PTS may help physicians to select patients at high risk of PTS.

Aims

To identify ultrasonography (US) parameters assessed during or after treatment of DVT of the leg, that predict post-thrombotic syndrome.

Methods

Systematic review and meta-analysis. Databases were searched for prospective studies including consecutive patients with DVT who received standardized treatment, had an ultrasonography during follow-up assessing findings consistent with vascular damage after DVT, and had a follow-up period of at least 6 months for the occurrence of PTS assessed by a standardized protocol.

Results

The literature search revealed 1156 studies of which 1068 were irrelevant after title and abstract screening by 3 independent reviewers. After full text screening, 12 relevant studies were included, with a total of 2684 analysed patients. Two US parameters proved to be predictive of PTS: residual vein thrombosis, for a pooled Odds Ratio (OR) of 2.17 (95%CI 1.79-2.63) and venous reflux at the popliteal level, for a pooled OR of 1.34(95%CI 1.03-1.75).

Conclusion

The US features reflux and residual thrombosis measured at least 6 weeks after DVT predict post-thrombotic syndrome. Whether these features may be used to identify patients who may benefit from compression therapy remains to be assessed in further studies.

INTRODUCTION

Post-thrombotic syndrome (PTS) is a common complication after deep vein thrombosis (DVT).[1,2] PTS may manifest with several signs and symptoms, ranging from mild pain or itching, to severe and difficult-to-treat venous ulcers.[3] Despite adequate anticoagulation treatment, PTS develops in 20-50% of patients following acute DVT with 5-10% of all PTS cases classified as being severe.[2] Since there are no reference laboratory or imaging tests, PTS is diagnosed only on clinical grounds using one of the available clinical scales.[4] The Villalta scale is the most widely used and is recommended by the International Society on Thrombosis and Haemostasis (ISTH) (**Table 1**).[5] The CEAP classification was originally developed for chronic venous disease, but is also often used for diagnosing PTS (**Table 2**).[6,7]

Table 1. Villalta Scale[33]

	None	Mild	Moderate	Severe
Symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paraesthesia's	0	1	2	3
Pruritus	0	1	2	3
Clinical Signs				
Pretibial oedema	0	1	2	3
Hyperpigmentation	0	1	2	3
Venous ectasia (venules or varicose veins)	0	1	2	3
Redness	0	1	2	3
Skin induration	0	1	2	3
Pain on calf compression	0	1	2	3
Venous Ulcer		Absent		Present
		Total score		
0-4			*No PTS*	
5-9			*Mild PTS*	
10-14			*Moderate PTS*	
≥15/venous ulcer present			*Severe PTS*	

Table 2. Clinical component CEAP Classification[6,7]

Class	Clinical Signs
0	No visible or palpable signs of venous disease
1	Telangiectasies or reticular veins
2	Varicose veins: distinguished from reticular veins by a diameter of ≥3 mm
3	Edema
4	Changes in skin and subcutaneous tissue secondary to CVD:
4a	Pigmentation or eczema
4b	Lipodermatosclerosis or atrophie blanche
5	Healed venous ulcer
6	Active venous ulcer

Note: CEAP indicates clinical, etiological, anatomic, pathophysiological

The pathophysiology of PTS is not completely understood, although chronic venous hypertension by residual venous obstruction and valvular reflux likely plays a major role.[8,9] Because treatment options for PTS are limited, its management relies on the prevention of its occurrence after DVT. It has been shown that elastic compression stocking (ECS) therapy may prevent PTS, provided patients are compliant to wearing the stocking on a daily base for 2 years.[10,11] Recently, a randomised controlled trial showed that stopping ECS after one year in compliant patients was not non-inferior to continuing ECS therapy for two years. In other words, ECS therapy should be ideally continued for two years after DVT.[12] However, stockings are costly, cumbersome to apply, and can be hot, constricting, and itchy. One randomized trial clearly indicated that adherence to prescribed daily ECS therapy in daily clinical practice is poor, which ultimately resulted in ineffective PTS prevention.[13] Hence, identification of predictors of PTS may help physicians to target PTS prevention to those patients with high risk of PTS who are likely to benefit most of the ECS therapy. Several risk factors for PTS at the time of the DVT diagnosis have been identified, such as proximal DVT, older age, obesity and history of ipsilateral recurrent DVT.[1] Whether ultrasound-measured chronic vein obstruction by residual clots and/or valvular reflux may be helpful in better predicting PTS remains controversial. Therefore the primary aim of this systematic review and meta-analysis was to identify ultra-sonographic parameters, assessed during or after treatment of proximal DVT of the leg, that predict post thrombotic syndrome.

METHODS

This systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) criteria.[14] All parts of

this study were performed by 3 independent reviewers (C.E.A.D., G.C.M. and G.M.), any disagreements were resolved by a fourth reviewer (F.A.K.)

Information sources and literature search

A literature search was performed of Pubmed, Embase, Web of Science, Cochrane, CINAHL and ScienceDirect in Oktober 2015. This search was updated in November 2016. The search strategy included (the synonyms of) the terms: 'deep venous thrombosis', 'post-thrombotic syndrome' and 'ultrasonography'. Full articles, abstracts and letters in the English language were eligible for this study.

Study selection

Studies were first screened by title and abstract. After excluding non-relevant studies, full-text articles were analysed for eligibility. All prospective studies including consecutive patients with DVT who received standardized treatment and had an ultrasonography during follow-up assessing findings consistent with vascular damage after DVT were eligible when they had a follow-up period of at least 6 months and assessed the occurrence of PTS. Occurrence of PTS had to be evaluated by a standardized protocol, i.e. the Villalta, Brandjes or CEAP score. Exclusion criteria were impossibility to create two by two tables of ultrasonography abnormalities and PTS, based on the study set-up, or the use of trombolytic therapy and/or thrombectomies. In articles randomizing patients between thrombolytic therapy and oral anticoagulation treatment, only the oral anticoagulation treatment group was included in the study.

Data extraction

From each selected study, all extracted information was completed in pre-defined tables. The following information was extracted: 1) study characteristics: author, year of publication, study design, inclusion and exclusion criteria; 2) patient characteristics: number at baseline, number with complete follow-up, age, gender, history of VTE and presence of malignancy; 3) DVT characteristics: modality of diagnosis at baseline (whole leg/2 point CUS or venography), proximal (femoropopliteal) DVT or distal DVT(calf veins) and unprovoked or provoked VTE; 4) treatment of DVT: therapy, duration, use of compression stockings and percentage of adherence to compression therapy; 5) ultrasound measurements consistent with vascular damage after DVT: modalities, timing after initial thrombosis, 6) Outcome measure: duration of follow-up, PTS scoring system protocol, timing PTS scoring and number of patients with and without PTS combined with ultrasound abnormalities during follow-up (for completing two by two tables). If creating the two by two tables should be possible based on the study set-up but the needed data were not reported in the articles, authors were contacted and asked for additional data.

Quality assessment

Included studies were assessed for risk of bias with the QUIPS (Qualitiy in Prognosis Studies) tool.[15] This tool has been developed to evaluate the risk of bias in studies on prognostic factors based on 6 areas: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. All areas were scored as low risk of bias, moderate risk of bias or high risk of bias. Studies with one area with high risk of bias or with ≥2 areas of moderate risk of bias were overall scored as 'moderate risk of bias'. Studies with low risk of bias in all areas or ≤1 area with moderate risk of bias were overall scored as 'low risk of bias'.

Data synthesis and analysis

Patients who were lost to follow-up were excluded from the analysis. Odds ratio's (OR) were calculated to assess the relationship between the different ultrasound measurements consistent with vascular damage and the occurrence of post-thrombotic syndrome during follow-up. Data from the 2 by 2 tables were entered in Review Manager (RevMan), Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. To assess study heterogeneity Cochran's chi-square test and the I^2 test for heterogeneity were used. The chi-square test is used to assess if the differences in results are by chance alone. I^2 calculates the percentage of the variability in the effect estimates that is due to heterogeneity rather than sampling error.[16] Statistically heterogeneity was considered present for a chi-square of $P<0.10$ and $I^2>50\%$. The presence of publication bias was evaluated using funnel plot analysis. Several sensitivity analysis were performed: for studies with a low risk of bias versus moderate risk of bias; studies with ultrasound assessment < 12 months after DVT versus ≥ 12 months after DVT and studies including only patients with proximal DVT

RESULTS

Study selection

With the literature search, 1156 potentially relevant studies were identified and screened for eligibility. Reasons of exclusion of 1068 studies after title and abstract screening are shown in **Figure 1**. Eighty-eight studies were retrieved for full text evaluation. After reading full text, 77 studies were excluded: 4 studies with a retrospective design, 6 studies with a follow-up less than 6 months, 2 studies in which DVT was not adequately diagnosed at baseline, 3 studies based on post-hoc analysis of a patient cohort already included in the meta-analysis, 19 were congress abstracts showing insufficient data on study design and outcome, 10 studies did not perform ultrasonography during follow-up, 24 studies did not have a standardized assessment of PTS and 9 studies did not

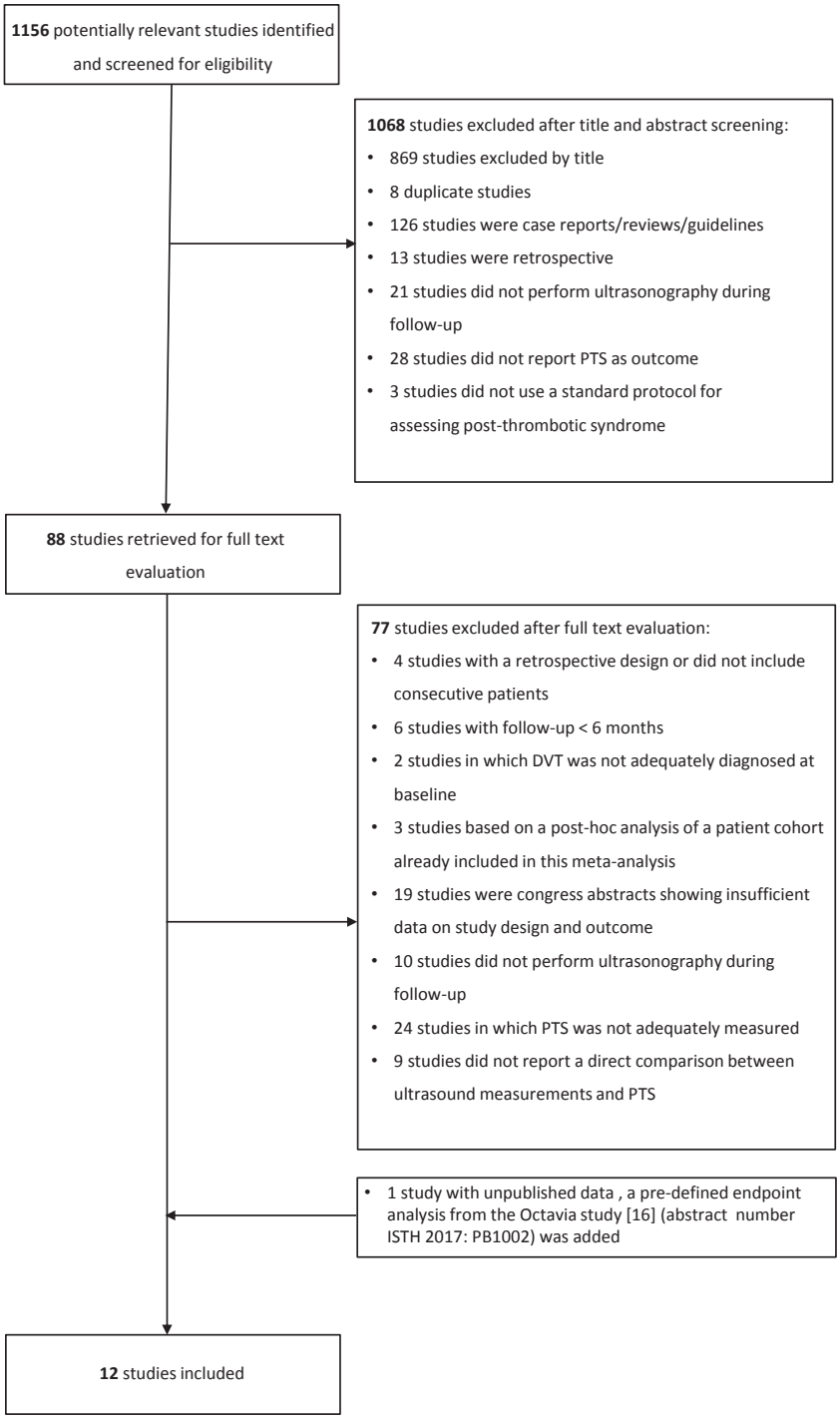

Figure 1. Flow-chart of study selection

report a direct comparison between ultrasound measurements and PTS. One study with unpublished data, a pre-defined endpoint analysis from the Octavia study (abstract number ISTH 2017: PB1002) was added to the list of included articles.[17] Finally, a total of 12 studies fulfilled all inclusion criteria and none of the exclusion criteria.[17-28] For 4 of these 12 studies, additional data was requested from the authors to complete the 2 by 2 tables, which was provided by two,[18,23] leaving 10 studies for the final meta-analysis.

Quality and patient characteristics of included studies

All included studies were prospective cohort studies including consecutive patients, diagnosed with DVT at baseline by compression ultrasonography. The quality of each selected study assessed by the QUIPS tool is presented in **Table 3**. The patient characteristics of the studies included in the meta-analysis are shown in **Table 4**. A total of 2684 patients were included with a mean age varying between 48 and 68 years. The percentage of male gender varied between 36% and 64%. Four [17,19,20,27] of the 10 studies included 8-19% of patients with a history of VTE. The percentage of patients with malignancy ranged between 0% and 12%.[17,19,25-28] Eight studies reported the number of patients with idiopathic DVT, which ranged between 16% and 55%.[17-21,23,25,28] Five studies included only patients with a proximal DVT.[17,18,20,23,26] Overall, 2374 patients (88%) had a proximal DVT, and 310 patients (12%) had a distal DVT. The duration of anticoagulation therapy ranged between 3 and 18 months. Nine out of 10 studies reported prescription of elastic compression stockings.[17-19,21,23,25-28] Three studies reported the percentage of adherence to the stockings, ranging from 52.2% to 88.4% (details table 4).[17,19,25]

Assessment of ultrasound abnormalities

During follow-up, compression ultrasound was performed in 2510 (94%) of the patients. The time between DVT diagnosis at baseline and follow-up ultrasound varied between 6 weeks,[25] 3 months,[20] 6 months[26-28]) and 12 months[17,19] (**Table 5**). In one study the timing of ultrasound was dependent on the treatment duration: ultrasound was performed 6 weeks after stopping anticoagulation treatment with variable total treatment duration.[21] Different ultrasound measurements were performed including reflux, patency, residual vein thrombosis and 'the thrombosis score'. Reflux was defined as a valve closure time >0.5 seconds,[18,26-28] > 1second[17,19,25] or >1.5 seconds[21] after calf or thigh compression. Compression was accomplished by a Valsalva manoeuvre,[19] or performed by manual compression of the calf for at least 10 seconds followed by sudden release[17,19,21] or by using a compression unit.[18,25-28] Patency was defined as flow in the pelvic and femoral vein and complete compressibility of the femoral vein.[18] Residual vein thrombosis was defined as the persistence of thrombotic material resulting in a diameter of 4 mm or more,[20,26] or when a previously thrombosed deep venous segment was incompletely compressible.[21] The thrombosis score was based on the number of veins with throm-

bosis and the degree of occlusion, measured as diameter of the clot during maximal compression, giving 1 point when the diameter was 2-3 mm, 2 points for 4-5 mm and 3 points when ≥ 6 mm.[23,25] Since the measurements of patency and the thrombosis score are comparable with that of residual vein thrombosis, these 2 terms were combined in the 'residual thrombosis' group for the purpose of this meta-analysis, with 'absence of patency' or a thrombosis score ≥1 defined as presence of residual thrombosis. The incidence of residual vein thrombosis in the included studies ranged between 10% and 75%. The reported incidence of reflux ranged between 12% and 78%. Two studies reported on the combination of residual thrombosis and reflux, with an incidence of 14% and 22% respectively.[26,28]

Table 3. Study quality assessment (QUIPS Tool)

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall
Haig *et al.*[18]	🟢	🟡	🟢	🟢	🟢	🟢	🟢
Latella *et al.*[19]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Mol *et al., unpublished data*[17]	🟢	🟡	🟢	🟢	🟢	🟢	🟢
Prandoni *et al.*[20]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Roberts *et al.*[21]	🟡	🔴	🟡	🟢	🟢	🟢	🟡
Roumen-Klappe *et al.**[22]	🟡	🔴	🟡	🟢	🟢	🟢	🟡
Sartori *et al.*[23]	🟢	🟢	🟡	🟢	🟢	🟢	🟢
Ten Cate-Hoek*[24]	🟢	🟡	🔴	🔴	🟢	🟢	🟡
Tick *et al.*[25]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Vedovetto *et al*[26]	🟡	🟡	🟢	🟢	🟢	🟢	🟡
Yamaki *et al. (2011)*[27]	🟡	🟡	🟢	🟢	🟢	🟢	🟡
Yamaki *et al.* (2016)[28]	🟢	🟡	🟢	🟢	🟢	🟢	🟢

🟢: low risk of bias; 🟡: moderate risk of bias; 🔴: high risk of bias. * not included in final meta-analysis because data for two by two tables could not be extracted from the manuscript and could not be provided by the authors.

Table 4. Patient characteristics of the included studies

Study	Total study population	Mean age (years)	Percentage of men	Percentage VTE in history	Percentage Malignancy	Idiopathic/ risk factor (n/n)	Distal/ proximal DVT (n/n)	Mean duration of anticoagulation therapy	Compression stocking use	Percentage adherent to stockings
Haig *et* al.[18]	99 (standard therapy group)	50	62	Exclusion criterion	NR	26/73	0/99	6 months	Yes	NR
Latella *et al.*[19]	387	56.3	51	19	12.4	211/176	154/233	34.1 weeks	Yes	52.2% (not further specified)
Mol *et al* [17]	518	57	59	14	9.6	215/303	0/518	6 months	Yes	88.4% (7 days/week in the first year)
Prandoni *et al*[20].	869	63	58	12	Exclusion criterion	444/425	0/869	At least 3 months	NR	NR
Roberts *et al*[21].	114	47.8	52.6	Exclusion criterion	Exclusion criterion	47/67	57/57	3 months (distal DVT)/6 monhts (proximal DVT)	Yes	NR
Sartori *et al.*[23]	59	62.8	56	Exlusion criterion	Exclusion criterion	22/36	0/59	3 months	Yes	NR
Tick *et al.*[25]	111	48	53	Exclusion criterion	5.0	34/77	18/93	6 months	Yes	67% (≥ 6 days/week)
Vedovetto *et al.*[26]	290	67.7	49	Exclusion criterion	14	Not reported	0/290	6 months	Yes	NR
Yamaki *et al.* (2011)[27]	121	65.8	42.1	5	15	Not reported	29/92	at least 3 months	Yes	NR
Yamaki *et al.* (2016)[28]	116	61.3	36	Exclusion criterion	13	19/97	52/64	18 months	Yes	NR

Note: NR: not reported

Table 5. Outcome of included studies

Study	Total study population (n)	CUS performed (n)	Time between DVT and follow-up ultrasound	Collected ultrasound abnormalities	CUS positive for residual thrombosis (n (%))	CUS positive for reflux (n (%))	CUS positive for residual thrombosis and reflux (n(%))	Time between DVT and PTS scoring	PTS score	PTS diagnosed (n (%))
Haig *et al.*[18]	99	95	6 months	Reflux, patency	45 (47)	74 (78)	NR	24 months	Villalta	53 (55)
Latella *et al.*[19]	387	233	12 months	Reflux		109 (47)	NR	24 months	Villalta	116 (50)
Mol *et al* [17]	518	516	12 months	Residual vein thrombosis, reflux	220 (43)	354 (69)	NR	24 months	Villalta	84 (16)
Prandoni *et al.*[20]	869	869	3 months	Residual vein thrombosis	429 (49)		NR	36 months	Villalta	343 (39)
Roberts *et al.*[21]	114	114	6 weeks after stopping anticoagulation therapy	Reflux, residual vein thrombosis	56 (49)	19 (17)	NR	Median: 11 months	Villalta	61 (54)
Sartori *et al.*[23]	59	59	90 days after DVT	Thrombosis score	44 (75)		NR	Day 180	Villalta	13 (22)
Tick *et al.*[25]	111	97	6 weeks	Reflux and thrombosis score	64 (66)	29 (30)	NR	1 year	CEAP	49 (51)
Vedovetto *et al.*[26]	290	290	6 months	Residual vein thrombosis and popliteal valve incompetence	75 (26)	36 (12)	42 (14)	3 years	Villalta	119 (41)
Yamaki *et al. (2011)*[27]	121	121	6 months	Reflux, residual thrombosis	12 (10)	31 (26)	NR	Mean 66.4 months	CEAP	25 (21)
Yamaki *et al.* (2016)[28]	116	116	6 months	Reflux, residual thrombosis	21 (18)	16 (14)	26 (22)	6 years	Villalta	19 (16)

Note: NR: not reported

Assessment of PTS

The time between DVT at baseline and scoring of PTS differed between the studies, ranging from 6 months,[23] 11 months[21] and 12 months[17-19,25] to 3[26] and 6 years,[27,28] respectively. Most (8 out of 10) studies used the Villalta score for diagnosing PTS. The diagnosis PTS was established when the Villalta score was ≥5 points at 1 visit[17,18,21,28] or 2 consecutive visits.[19,20,23,26] The symptoms were scored by the patient and the signs by the treating physician. In one study a full colour visual guide was used to score the clinical signs.[17] In another study, the doctors who scored the clinical signs of the Villalta score were blinded to the symptoms reported by the patient and the ultrasound abnormalities.[19] Two studies used the CEAP score to diagnose PTS. The first study defined a CEAP score ≥3 as diagnostic for PTS;[25] the second used a cut-off of ≥4.[27] The incidence of PTS in the included studies ranged between 16% and 55%. Overall, 882 out of all 2510 patients (35%) with a complete follow-up developed PTS.

Outcome of the meta-analysis

The results of 9 studies measuring residual thrombosis were pooled, as were 8 studies measuring reflux as predictive value of PTS and the results of 2 studies measuring the combination of residual thrombosis and reflux. The meta-analysis showed that residual vein thrombosis measured 6 weeks to 12 months after DVT was predictive for PTS with an OR of 2.2 (95%CI 1.8-2.6) (**Figure 2a**). From 966 patients with residual thrombosis, a total of 421 (44%) developed PTS, compared with 343 (26%) of 1311 patients without residual thrombosis for a positive likelihood ratio (LR+) of 1.53 (95%CI 1.4-1.7) and negative likelihood ratio of (LR-) of 0.70 (95%CI 0.6-0.8). The heterogeneity between these studies was high as indicated by an I^2 of 65% and a Chi^2 of P=0.004. Funnel plot analysis showed no indication for publication bias.

Sensitivity analyses including studies with measurement of residual thrombosis <12 months after DVT showed an even higher predictive value with an OR of 2.5 (95%CI 2.0-3.1), with an I^2 of 49% and Chi^2 of P=0.06. Sensitivity analysis of studies with a low risk of bias, moderate risk of bias and studies including only patients with proximal DVT showed similar predictive values.

Reflux was predictive for PTS as well, with an OR of 1.3 (95%CI 1.03-1.7) (**Figure 2b**). From a total of 668 patients with reflux, 218 (33%) developed PTS. From 909 patients without reflux, 306 (34%) developed PTS, for a LR+ of 0.97 (95% CI 0.9-1.1) and LR- of 1.02 (0.9-1.1). These studies showed less heterogeneity with an I^2 of 33% and a Chi^2 of p=0.17. Funnel plot analysis was not indicative for publication bias (Appendix II). Sensitivity analyses of studies that assessed reflux at 12 months after DVT, studies with low risk of bias and studies including only patients with proximal DVT showed similar results, but with less heterogeneity.

The meta-analysis on the combination of residual thrombosis and reflux showed an OR of 2.35 (95%CI 1.35-4.11), with an I^2 of 37% and Chi^2 of p=0.21 (**Figure 2c)**. From the patients with both residual thrombosis and reflux, 32 (47%) of 68 developed PTS. Of the patients without residual thrombosis or reflux, 106 of 338 (31%) developed PTS, for a NNT of 6.3, LR+ of 1.73 (95%CI 1.1-2.7) and LR- of 0.89 (95%CI 0.8-1.0).

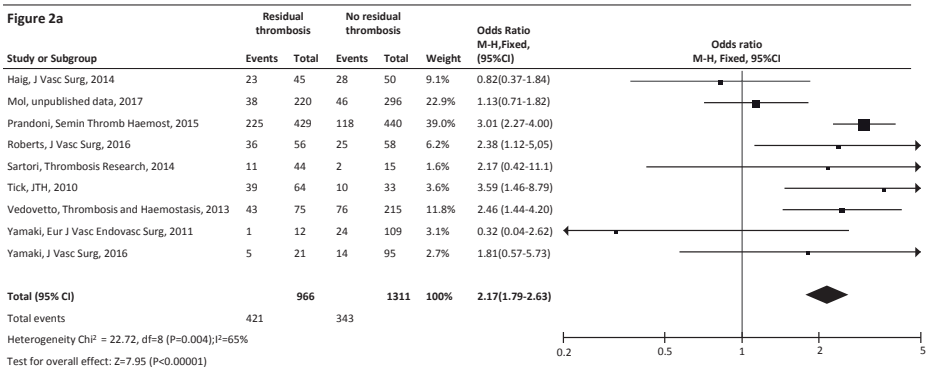

Figure 2a. Forrest plot of meta-analysis of residual thrombosis measured during or after treatment of acute DVT as predictive factor for PTS

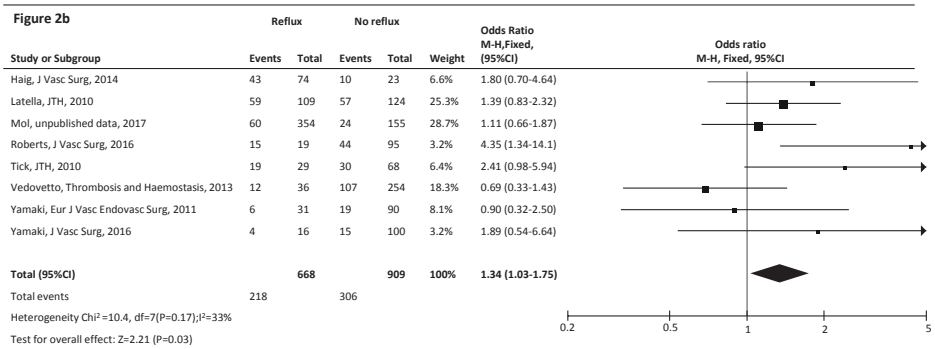

Figure 2b. Forrest plot of meta-analysis of reflux measured during or after treatment of acute DVT as predictive factor for PTS

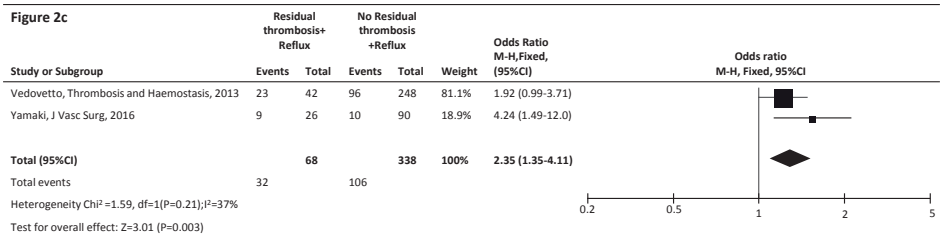

Figure 2c. Forrest plot of meta-analysis of the combination of residual thrombosis and reflux during or after treatment of acute DVT as predictive factor for PTS.

DISCUSSION

Despite heterogeneity between the selected studies, this systematic review and meta-analysis showed that both residual thrombosis and reflux, measured by ultrasonography during or after treatment of acute DVT, is predictive of PTS. The combination of residual thrombosis and reflux showed the largest predictive value (OR 2.35 [95%CI 1.3-4.1]), although this was based on only 2 studies with a total of 406 patients. Moreover, residual thrombosis showed a good predictive value with an OR of 2.17 (95% CI 1.8-2.6) based on meta-analysis of 2307 patients, and reflux showed a predictive value to a lesser extent with an OR of 1.34 (95%CI 1.0-1.7) based on 1577 patients.

Our findings are biologically plausible. After DVT, recanalization of the thrombosed veins occurs by a combination of fibrinolysis, thrombus organization and neovascularization.[9] Inflammation plays a major role in case of incomplete recanalization, leading to residual vein thrombosis. This remaining thrombus causes damage to the venous valves,[29] resulting in incompetent valves and reflux. Both reflux and residual thrombosis are associated with a higher risk of venous hypertension.[8] Although the pathophysiology of PTS is not fully understood yet, venous hypertension, causing an absence of pressure decrease in the venous system of the legs during walking, which plays a major role in the cause of PTS development.[30]

What are the potential implications of our findings? Our meta-analysis supports the practice of using ultrasonography to identify patients at higher risk of PTS. These patients could thus be counselled with regard to PTS prevention. One cohort study investigated a tailored stocking therapy in 125 patients after acute DVT based on ultrasound findings. Ultrasound was performed one week before planned cessation of anticoagulation therapy.[24] If ultrasound showed no reflux and the Villalta score was ≤4, patients were allowed to discontinue their elastic compression therapy. In case of reflux or a Villalta score ≥5 points, patients were advised to continue this therapy for a total of 2 years. This study showed an overall incidence of PTS of 21% (95%CI 14-29), which is very much comparable to the reported incidence in another randomized controlled trial, suggesting that this strategy was safe.[11] An additional outcome study however, randomizing patients between stopping ECS therapy in case of absence of reflux and/or residual thrombosis and continuing ECS for two years is needed to confirm this hypothesis.

Some limitations should be considered for the interpretation of the results of this meta-analysis. Firstly, the heterogeneity between these studies was large, especially for the studies measuring residual vein thrombosis ($I^2$of 65% and Chi^2 of P=0.004). Therefore, this meta-analysis is not conclusive. The heterogeneity can be explained by the differences in study design and study populations. Especially treatment duration and timing of ultrasound examinations as well as the criteria for a PTS diagnosis were different between all studies. Moreover, the ultrasound measurement techniques and

PTS score thresholds varied among the studies. Sensitivity analyses of studies which assessed residual vein thrombosis <12 months after DVT showed a slightly lower heterogeneity: I^2 49%, Chi^2 p=0.06. However other sensitivity analyses did not result in a lower heterogeneity. Secondly, we found in our meta-analysis an absolute small predictive value of reflux for PTS, leading to a high NNT of 100. Although there were only two studies which assessed the combination of the presence of both residual thrombosis and reflux as predictive factors, these showed the largest predictive value (OR: 2.35 (95%CI 1.35-4.11)) but a relatively low LR+ of 1.73 (95%CI 1.1-2.7). Whereas our findings may encourage patients with residual thrombosis and reflux to be adherent to ECS therapy, it remains unclear whether ECS therapy can be safely stopped in patients without both residual thrombosis and reflux.

Further studies are needed to establish the role of residual vein thrombosis and reflux after acute DVT in predicting PTS, in conjunction with other known risk factors for PTS being proximal DVT, older age, obesity and history of ipsilateral recurrent DVT.[1] Ideally, these risk factors should be investigated in a large study and summarized in a clinical prediction score. Two of such scores, consisting of readily accessible baseline characteristics have recently been suggested, but both lack adequate external validation.[31,32]

In conclusion, our systematic review and meta-analysis showed that residual vein thrombosis and reflux, assessed by ultrasound during or after treatment of acute DVT are predictive for PTS. Even with the heterogeneity between the included studies, the shown associations may be helpful in the identification of patients at high risk for PTS.

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10

Elastic compression stockings one year after DVT diagnosis: who might discontinue?

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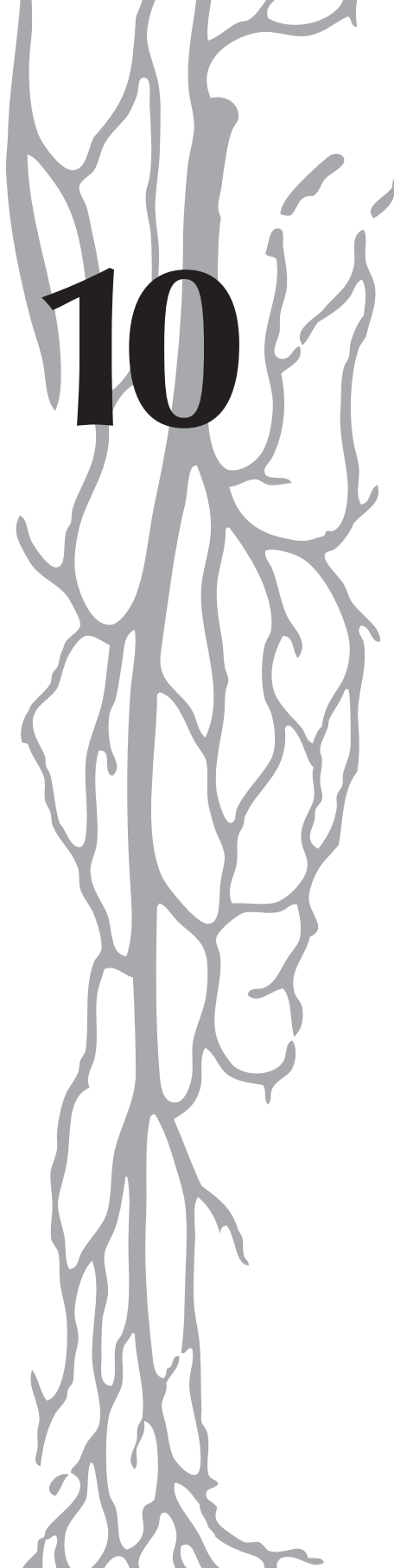

ABSTRACT

Background

Elastic compression stockings (ECS) are uncomfortable to wear but may prevent post-thrombotic syndrome (PTS). The ability to predict PTS may help clinical decision making regarding the optimal duration of ECS after deep vein thrombosis (DVT).

Aims

Predefined endpoint analysis of the Octavia study that randomized patients who compliantly used ECS up to one year after DVT to continue or discontinue ECS treatment. Primary aim was to identify predictors of PTS.

Methods

Patient characteristics were collected and ultrasonography was performed to assess reflux, residual thrombosis and persistent thrombus load 12 months after DVT. Multivariable analyses were performed to identify factors related to PTS.

Results

Thrombus score ≥3, BMI ≥26, duration of symptoms before DVT diagnosis ≥8 days and a Villalta score of 2-4 points were statistically significant predictors of PTS. The predictive value for PTS for the assessed variables was not different between the 2 treatment groups. In the stop ECS group, 3.2% (95%CI 0.08-18) of patients without any predictors for PTS were diagnosed with mild PTS during follow-up, and none with severe PTS, for a sensitivity of 98% (95% CI 89-100), a specificity of 14% (95% CI 10-20), a positive predictive value of 20% (95% CI 19-22), and a negative predictive value of 97% (95% CI 81-100).

Conclusion

We identified 4 predictors of PTS occurring in the 2nd year after DVT. Our findings may be used to decide on whether to continue ECS treatment for an additional year after one year of compliant ECS use, keeping in mind that patients with none of the predictors will have the lowest PTS incidence.

INTRODUCTION

Despite adequate anticoagulation therapy, 20-50% of patients develop post-thrombotic syndrome (PTS) after deep vein thrombosis (DVT).[1] The clinical presentation of PTS ranges from mild skin changes to severe venous ulcers.[2] The signs and symptoms of PTS are assessed and quantified in clinical scales such as the Villalta score, which are used to diagnose PTS.[3] To prevent PTS, elastic compression stockings (ECS) have been suggested to be helpful when patients wear them on a daily basis for 2 years.[4,5] Even so, stockings are constricting, can be itchy and difficult to apply, which can lead to a low adherence in many patients, leading to an absence of efficacy as shown in the SOX trial.[6] Therefore recently, two studies were performed to investigate if a shorter duration of ECS therapy is non-inferior to continuing ECS therapy for two years. The Octavia study showed that stopping ECS therapy in patients who did not develop PTS after a one-year period of compliant use of ECS was **not** non-inferior to continuing ECS therapy, indicating that ECS therapy should be generally continued for at least 2 years after DVT.[7] In contrast, the IDEAL DVT study showed that individualised therapy with compression therapy, i.e. stopping ECS therapy after a minimal duration of 6 months in case of a Villalta score ≤4 on two consecutive visits, was non-inferior to continuing ECS therapy for two years.[8]

The ability to predict PTS may help clinical decision making with regard to the optimal duration of ECS therapy after DVT. Extensive proximal DVT, ipsilateral recurrent DVT and insufficient anticoagulation treatment have been previously described as strong risk factors for PTS.[1] Obesity, primary venous insufficiency and residual venous obstruction have been widely shown as being associated with PTS as well.[9-11] Recently, three clinical prediction scores to predict PTS after DVT were derived, consisting of these easily accessible patients characteristics assessed at time of diagnosis of DVT.[12-14] With a substantial proportion of patients diagnosed with PTS after the first year of DVT diagnosis, the existing scores are not suitable for making long-term decisions on ECS therapy.[1,7]

The primary aim of this predefined secondary analysis of the Octavia study was to find independent predictors for long-term PTS development, i.e. beyond the first year of ECS therapy, to select patients who may stop ECS therapy after an initial treatment period of one year.

METHODS

Patients

Data from the multicentre single blind non-inferiority randomized controlled Octavia study were used to perform a pre-defined endpoint analysis. In the Octavia study, adequately anticoagulated (with VKA) patients from eight teaching hospitals in the

Netherlands who were compliant to compression therapy (knee length, ECS class III) for 12 months after a symptomatic, ultrasound proven proximal DVT (popliteal or more proximal vein) and were not diagnosed with PTS in these 12 months were randomized between continuation (continue-ECS group) and cessation (stop-ECS group) of ECS therapy. Patients were followed for 12 months. The primary endpoint was the incidence of PTS at the end of follow-up period. The diagnosis of PTS was assessed with a full colour visual guide and defined as a Villalta score of 5 points or more and/or the presence of a venous ulcer.[15]

Assessment of predictive values

At baseline, one year after DVT diagnosis patient characteristics at time of DVT diagnosis were collected including age, sex, BMI, smoking status, history of VTE, trauma or surgery <8 weeks or immobilisation >3 days before DVT, number of days of symptoms before DVT diagnosis, cancer, thrombophilia and oral anticonception use. Information about anticoagulant use and compliance to ECS therapy in the first year after DVT was collected. Physical examination was performed to assess the Villalta score one year after the index DVT diagnosis, at study entry. In the statistical analysis patients were divided in two groups: those with 0-1 points of the Villalta score and those with 2-4 points. In addition, in three of the study sites (Diakonessenhuis Utrecht, St Antonius Hospital Nieuwegein and University Medical Center Utrecht), 20 millilitres of blood was taken from each patient and stored in a -80 degrees fridge to assess for D-dimer, high sensitive CRP and fibrinogen levels in one batch at the end of the study.

Ultrasound assessments

At baseline, 12 months after initial DVT diagnosis, a duplex and colour Doppler ultrasound was performed to assess for presence of reflux, 'the reflux score', residual thrombosis and 'the thrombus score'. The deep venous system, i.e. the common femoral vein, superficial femoral vein, profunda femoris, and popliteal veins, as well as the superficial venous system, i.e. proximal and distal saphenous veins, were evaluated for the presence of reflux and residual thrombosis. To assess reflux, patients were examined in supine position; a compression unit (100 mmHg) was placed distal from the examined venous segment. Flow and reflux of the valves were assessed in the longitudinal plane; pathologic reflux was defined as reversed flow duration of more than 1 second in the proximal veins and more than 0.5 seconds in the distal veins. This method has been shown to be highly reproducible.[16] The reflux score was defined as the total number of veins with pathologic reflux.[17] To assess residual thrombosis, vein segments were examined in the transverse plane. Residual thrombosis was defined as incomplete compressibility of a vein segment; 1 point was scored for partial incompressibility and 2 points for complete incompressibility. The thrombus score was assessed by counting the points for all vein

segments which is a validated method according to the International Consensus Committee on Chronic Venous Disease.[18]

Statistical analysis

Baseline characteristics of the continue-ECS group and stop-ECS group are expressed as numbers and percentages. We had a complete dataset for the outcome variables. Less than 1% of the data on the predictor variables was missing. Therefore we performed a complete case analysis. Continuous variables were changed to categorical by selecting the most predictive cut-off value for PTS, assessed by comparing the AUC of the ROC curves using the method proposed by Hanley & McNeil.[19] The first primary outcome of this study was to assess the predictive value of different clinical, biomarker and ultrasonography variables. The predictive values of all variables are presented as odds ratios (OR) with 95% confidence intervals (CI) calculated by univariate logistic regression analysis for the continue-ECS group and stop-ECS group separately. The second primary outcome was to find predictors to select patients who may benefit by continuing ECS therapy for 2 years to prevent PTS. To assess the effect modification of predictors for PTS by wearing ECS, ECS use was inserted as interaction term in the logistic regression analysis. Univariate tests of effect modification by ECS were performed first. The outcome measures of this analysis were odds ratios (OR) adjusted for wearing ECS, with statistical significance evaluated by the Wald test. For the multivariable analysis, it was predefined based on the sample size that only the four best predictors were run in multivariable backward conditional logistic regression analysis, again with ECS use as interaction term, OR as outcome and the Wald test for evaluation of statistical significance. Significant variables in multivariable analysis were considered to be independent predictors of PTS. Incidence of PTS was calculated in patients from the stop-ECS group and continue-ECS group separately without any versus with one or more of these independent predictors. Confidence intervals around these incidences were calculated based on the modified Wald method.[20] Based on these incidence numbers, positive predictive value, negative predictive value and relative risk for PTS based on presence of one or more versus none of these predictors were calculated. All statistics were performed using SPSS version 23 (IBM Corp, Armonk, NY). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 518 patients were included in the Octavia study, of whom 256 were allocated to the stop-ECS group and 262 to the continue ECS group. From the stop-ECS group, 51 (19.9%, 95%CI 16-24) patients were diagnosed with PTS in the first year following randomisation, compared to 34 (13.0%, 95%CI 9.9-17) in the continue-ECS group [7].

Relevant baseline characteristics are shown in **Table 1**. After locking the database, 28% of patients turned out to be incorrectly treated with class II (23-32 mm Hg) graduated active stockings instead of the intended class III (34-46 mm Hg). Ultrasound and laboratory measurements are shown in **Table 2**. Laboratory measurements were performed in three study sites for a total of 135 (53%) of patients from the stop-ECS group and 140 (53%) of patients from the continue-ECS group.

Table 1. Baseline characteristics assessed at time of the index DVT diagnosis and 1 year after DVT

Characteristics at time of the index DVT diagnosis	**Stop-ECS (n=256) N (%)**	**Continue-ECS (n=262) N (%)**
Age ≥65 years	88 (34)	86(33)
Male sex	152 (59)	155 (59)
BMI ≥26	163 (64)	162 (62)
Duration of symptoms before DVT diagnosis ≥8 days	84 (33)	90 (35)
History of VTE	37 (15)	38 (15)
Provoked index DVT	142 (55)	161 (62)
Cancer (active at diagnosis)	29 (11)	21 (8)
Thrombophilia*	17 (7)	24 (9)
History of varicose veins	36 (14)	29 (11)
Current or former smoking	67 (27)	68 (26)
Index DVT in left leg	158 (62)	144 (55)
Most proximal location of DVT:		
Iliac vein	23 (9)	25 (10)
Common femoral vein	44 (17)	31 (12)
Superficial femoral vein	58 (23)	54 (21)
Popliteal vein	131 (51)	152 (58)
Treatment of DVT, assessed 1year after DVT diagnosis		
LMWH use ≤6 days	36 (15)	41 (16)
VKA use ≤3 months	59 (24)	58 (23)
Anticoagulation treatment at baseline (1 year after DVT)	39 (15)	37 (14)
Frequent use of ECS at year 1 (≥6 days/week)	232 (91)	249 (95)
Villalta score 2-4 points at baseline	136 (53)	145 (56)

Note: BMI: Body Mass Index, VTE: Venous thromboembolism, DVT: Deep vein thrombosis, *Antithrombin, protein C or S deficiency, factor V Leiden or prothrombin mutation, presence of antiphospholipid antibodies, LMWH: low molecular weight heparin, ECS: elastic compression stockings, CRP: c-reactive protein

Predictors of PTS between one and two years after DVT diagnosis

With univariate logistic regression analysis, duration of symptoms ≥8 days before DVT diagnosis (OR 2.9, 95% CI 1.6-5.7), thrombophilia (OR 3.1, 95%CI 1.1-8.5), history of varicose veins at the moment of index DVT diagnosis (OR 2.7, 95%CI 1.3-5.8) and a Villalta score of 2-4 points 1 year after DVT diagnosis (OR 5.2, 95%CI 2.4-11) were statistical

Table 2. Ultrasound and laboratory measurements assessed 1 year after the index DVT diagnosis

Ultrasound measurements:	**Stop-ECS (n=256) N (%)**	**Continue-ECS (n=262) N (%)**
Reflux	180 (72)	174 (67)
Refluxscore ≥4*	57 (22)	53 (20)
Refluxscore, only deep veins ≥1*	145 (58)	136 (53)
Residual thrombosis	119 (46)	101 (39)
Thrombus score ≥3*	22 (9)	24 (9)
Laboratory measurements:	**Stop-ECS (n=135) N (%)**	**Continue-ECS (n=140) N (%)**
D-dimer >0.5 mg/L*	29 (21)	23 (16)
High sensitive CRP>3 mg/L*	43 (32)	52 (37)
Fibrinogen >4 g/L*	12 (9)	9 (6.4)

*Continuous variables were changed to categorical by selecting the most predictive cut-off value for PTS, assessed by comparing the AUC of the ROC curves using the method proposed by Hanley & McNeil

significant predictors for PTS in the stop-ECS group (**Table 3**). In the continue-ECS group, only a Villalta score of 2-4 points (OR 3.5, 95%CI 1.5-8.4) and Fibrinogen >4 g/L (OR 4.4, 95%CI 1.1-18) were significant predictors of PTS during follow-up. Univariate analysis in the complete study population with ECS use as interaction term showed no significant predictors, indicating that use of ECS did not change the predictive value of any of the variables to a relevant extent.

Multivariable analysis showed that a thrombus score ≥3 (OR 2., 95%CI 1.1-5.1), BMI ≥26 (OR 1.9 (95% CI 1.1-3.4), duration of symptoms before DVT diagnosis ≥8 days (OR 2.3, 95% 1.4-3.9), and a Villalta score of 2-4 points (OR 4.5, 95%CI 2.5-8.2) were independent predictors of PTS in both treatment arms of the study. Also, use of ECS therapy itself was an independent predictor for PTS with an OR 0.52 (0.34-0.93), indicating a ~50% lower risk (**Table 4**). Further analyses showed that although ECS use prevented PTS, patients with one of the risk factors had a higher risk of PTS in both treatment arms of the Octavia study. Sub analysis of patients that used class II and class III ECS graduated active stockings showed similar results for univariate and multivariable logistic regression analysis (data not shown).

Incidence of PTS in patients with one or more and without predictors

In the stop-ECS group, 31 (12%, 95%CI 9.1-16) out of 256 patients had none of the 4 predictors identified with multivariable analysis. One out of these 31 patients (3.2%, 95%CI 0.08-18) was diagnosed with mild PTS (Villalta score 5) during follow-up (**Table 5a)**. The percentage of patients with PTS increased in the group of patients with one or more predictors for PTS: 6.6% (95%CI 2.5-15) of patients with 1 predictor developed PTS, 25.5% (95%CI 18-35) with 2 predictors, 28% (95% CI 17-42) with 3 predictors and 60%

Table 3. Univariate logistic regression analysis

Baseline features	**Stop ECS group** OR (95% CI), p value	**Continue ECS group** OR (95% CI), p value
Age≥65	1.3 (0.69-2.4), 0.42	1.3 (0.62-2.8), 0.47
Male sex	1.1 (0.58-2.0), 0.82	0.98 (0.47-2.0), 0.96
BMI≥26	1.9 (0.94-3.7), 0.08	2.2 (0.94-5.0), 0.07
Duration of symptoms before DVT diagnosis ≥8 days	2.9 (1.6-5.7), 0.001#	1.9 (0.92-4.0), 0.08
History of VTE	1.6 (0.71-3.6), 0.25	1.3 (0.50-3.4), 0.59
Provoked index DVT	0.97 (0.52-1.8), 0.93	2.2 (0.97-5.2), 0.06
Trauma (<8 weeks before DVT)	0.97 (0.46-2.0), 0.97	2.0 (0.91-4.3), 0.09
Surgery (<8 weeks before DVT)	1.4 (0.59-3.3), 0.45	1.2 (0.44-3.4), 0.70
Immobilisation>6 days	1.6 (0.62-4.0), 0.35	1.5 (0.49-4.9), 0.46
Pregnant, post-partum or use of hormonal replacement therapy	0.73 (0.33-1.6), 0.44	0.94 (0.40-2.2), 0.89
Cancer (active at diagnosis)	0.61 (0.20-1.8), 0.38	1.6 (0.52-5.2), 0.40
Thrombophilia*	3.1 (1.1-8.5), 0.03#	1.4 (0.44-4.3), 0.59
History of varicose veins	2.7 (1.3-5.8), 0.01#	1.9 (0.71-5.1), 0.20
Current or former smoking	1.3 (0.64-2.5), 0.50	1.4 (0.65-3.1), 0.39
Index DVT in left leg	1.2 (0.62-2.2), 0.62	1.2 (0.58-2.5), 0.63
Most proximal location of DVT:		
Iliac vein	0.48 (0.14-1.7), 0.27	0.85 (0.23-3.1), 0.81
Common femoral vein	0.61 (0.25-1.5), 0.28	1.2 (0.42-3.5), 0.74
Superficial femoral vein	0.67 (0.31-1.5), 0.33	0.64 (0.23-1.8), 0.39
Popliteal vein (reference)		
Treatment of DVT		
LMWH use ≤6 days	1.3 (0.58-3.0), 0.50	0.94 (0.34-2.6), 0.94
VKA use ≤3 months	0.79 (0.37-1.7), 0.55	1.8 (0.81-3.9), 0.15
Anticoagulation treatment at baseline (1 year after DVT)	1.8 (0.81-3.9), 0.15	1.1 (0.38-2.9), 0.92
Frequent use of ECS at year 1 (≥6 days/week)	1.1 (0.36-3.4), 0.85	0.71 (0.15-3.4), 0.67
Villalta T=0 2-4 points	5.2 (2.4-11), 0.00#	3.5 (1.5-8.4), 0.005#
Ultrasound measurements		
Reflux	1.1 (0.60-2.1), 0.88	1.1 (0.51-2.5), 0.77
Refluxscore total ≥4	1.1 (0.53-2.3), 0.81	1.8 (0.80-4.0), 0.16
Refluxscore, only deep veins ≥1	1.0 (0.53-1.9), 0.91	1.2 (0.54-2.6), 0.69
Residual thrombosis	1.1 (0.62-2.1), 0.68	1.0 (0.49-2.2), 0.95
Thrombus score ≥3	2.0 (0.77-5.2), 0.15	2.5 (0.92-6.8), 0.07
Laboratory measurements		
D-dimer>0.5 mg/L	1.0 (0.40-2.53), 0.98	1.0 (0.31-3.3), 0.97
High sensitive CRP>3 mg/L	1.7 (0.77-3.8), 0.19	1.55 (0.64-3.76), 0.34
Fibrinogen>4 g/L	0.87 (0.22-3.4), 0.85	4.4 (1.1-18), 0.04#

Note:#p<0.05 BMI: Body Mass Index, VTE: Venous thromboembolism, DVT: Deep vein thrombosis, *Antithrombin, protein C or S deficiency, factor V Leiden or prothrombin mutation, presence of antiphospholipid antibodies, LMWH: low molecular weight heparin, ECS: elastic compression stockings, CRP: c-reactive protein

Table 4. Multivariable backward conditional logistic regression analysis, adjusted for ECS use

Variables*	β	Odds ratio (95%CI)
Use of ECS	-0.577	0.52 (0.34-0.93)
Thrombus score ≥3	0.877	2.4 (1.1-5.1)
BMI≥26	0.645	1.9 (1.1-3.4)
Duration of symptoms before DVT diagnosis ≥8 days	0.843	2.3 (1.4-3.9)
Villalta T=0 2-4	1.504	4.5 (2.5-8.2)

Variables entered on step 1: Use of ECS, Thrombus score ≥3, BMI>25, Duration of symptoms before DVT diagnosis ≥8 days, Villalta T=0 ≥2, Use of ECS Thrombus score ≥3, Use of ECS*BMI>25, Use of ECS* Duration of symptoms before DVT diagnosis ≥8 days, Use of ECS* Villalta T=0 ≥2

Table 5. Number(percentage) of patients diagnosed with PTS with no, one or more predictors

5a: Stop- ECS group:

	No PTS (Villalta <5)	Mild PTS (Villalta 5-9)	Moderate PTS (Villalta 10-14)	Severe PTS (Villalta ≥15)	PTS overall (Villalta 5-≥15)
0 predictors*	30 (97)	1(3.2)	0	0	1 (3.2)
1 predictor	71 (93)	5 (6.6)	0	0	5 (6.6)
2 predictors	70 (74)	22 (23)	2 (2.1)	0	24 (26)
3 predictors	36 (72)	12 (24)	2 (4.0)	0	14 (28)
4 predictors	2 (40)	2 (40)	1 (20)	0	30 (60)

* predictors: thrombus score ≥3, duration of symptoms before DVT diagnosis ≥8 days, Villalta score ≥2, BMI≥26

5b. Continue-ECS group:

	No PTS (Villalta <5)	Mild PTS (Villalta 5-9)	Moderate PTS (Villalta 10-14)	Severe PTS (Villalta ≥15)	PTS overall (Villalta 5-≥15)
0 predictors*	18 (86)	3 (14)	0	0	3 (14)
1 predictor	96 (95)	4 (4.0)	1 (1.0)	0	5 (5.0)
2 predictors	77 (89)	9 (10)	0	1 (1.2)	10 (12)
3 predictors	31 (67)	14 (30)	1 (2.2)	0	15 (33)
4 predictors	4 (57)	3 (43)	0	0	3 (42)

* predictors: thrombus score ≥3, duration of symptoms before DVT diagnosis ≥8 days, Villalta score ≥2, BMI≥26

5c. All patients

	No PTS (Villalta <5)	Mild PTS (Villalta 5-9)	Moderate PTS (Villalta 10-14)	Severe PTS (Villalta ≥15)	PTS overall (Villalta 5-≥15)
0 predictors*	48 (92)	4 (8)	0	0	4 (8)
1 predictor	167 (94)	9 (5)	1 (0.6)	0	10 (6)
2 predictors	147 (81)	31 (17)	2 (1)	1 (0.6)	34 (19)
3 predictors	67 (70)	26 (27)	3 (3)	0	29 (30)
4 predictors	6 (50)	5 (42)	1 (8)	0	6 (50)

* predictors: thrombus score ≥3, duration of symptoms before DVT diagnosis ≥8 days, Villalta score ≥2, BMI≥26

(95%CI 23-88) with 4 predictors. From the 225 patients with one or more predictors for PTS 41 (18%, 95%CI 14-24) were diagnosed with mild PTS (Villalta score 5-9), 5 (2.2%, 95%CI 0.81-5.2) with moderate PTS (Villalta score 10-14) and none with severe PTS, for a positive predictive value of 20% (95% CI 19-22), and a negative predictive value of 97% (95% CI 81-100). Relative risk of PTS in patients with 1-4 predictors was 6.34 (95%CI 0.91-44).

In the continue-ECS group 21 out of 262 patients had none of the 4 predictors (8.4%; **Table 5b**). Three out of these 21 patients were diagnosed with mild PTS during follow-up (14%, 95%CI 4.1-35). The incidence of PTS increased also with the number of predictors in the continue-ECS group: incidences were 5.0% (95%CI 1.9-11) (1 predictor), 12% (95%CI 6.2-20) (2 predictors), 33% (95%CI 21-47) (3 predictors) and 43% (95%CI 16-75) (4 predictors) respectively. From the 241 patients with one or more predictors for PTS, a total of 33 (14% 95%CI 10-19) were diagnosed with PTS during follow-up.

DISCUSSION

In this pre-defined endpoint analysis from the Octavia study, we identified 4 predictors of PTS occurring in the 2nd year after DVT, being, duration of symptoms before DVT diagnosis ≥8 days, BMI≥26, a thrombus score ≥3 and a Villalta score of 2-4 points, assessed 1 year after DVT diagnosis. Patients without any of these identified risk factors who discontinued ECS treatment had a low 3.2% incidence of mild PTS, and none developed severe PTS. However, since the upper level of the confidence interval was 18%, we cannot ultimately prove that the risk of developing PTS in this cohort is negligible. Even so, with an increasing risk associated with more predictors present, our data may be used to counsel the optimal duration of treatment in the individual patient in clinical practice. ECS treatment may be considered to be discontinued with few or none of the predictors present, especially in those patients who experience ECS treatment as very uncomfortable. Of note, only 8-12% patients had none of the predictors present, indicating that the impact of this strategy would be low.

The recently published IDEAL-DVT study confirmed that it may be possible to individualize ECS treatment. Patients were randomized to standard duration ECS therapy (24 months) or an individualised duration of ECS based on the Villalta score during follow-up.[8] All patients were treated with ECS class III. In the individualised ECS duration group, patients with a Villalta score ≤4 on two consecutive visits stopped ECS, after a minimal duration of ECS therapy of 6 months. Because the incidence of PTS was comparable between the two groups, it was concluded that individualised therapy is non-inferior to continuing ECS for 24 months. Our study provides some external validation of the

IDEAL-DVT, since we demonstrated that a higher Villalta score at one year following an index DVT diagnosis was associated with a higher risk of PTS.

Three other recent studies assessed clinical predictors for PTS. In the first study, two clinical risk scores for post-thrombotic syndrome were derived, including the variables age, BMI, varicose veins, smoking, residual vein obstruction, female sex, ileofemoral thrombosis and history of deep vein thrombosis. One assessed the 2-year risk of post-thrombotic syndrome at the moment of the index DVT diagnosis and the other assessed the risk of post-thrombotic syndrome in the sub-acute phase, 6 months after diagnosis of deep vein thrombosis.[12] The Sox-PTS score included 3 variables assessed at time of index DVT diagnosis which were predictive for PTS: DVT in iliac vein, BMI ≥35 and a moderate-severe Villalta score at moment of index DVT diagnosis.[14] The third score was derived for patients aged ≥65 years only.[13] Our study is different from previous ones and therefore not directly comparable, since we studied predictors for PTS occurring in the second year after DVT.

Most of the predictors identified in the current analysis have been associated with a higher risk of PTS in prior studies. Residual thrombosis for example was found to be associated with a 3-fold higher risk of PTS in a large study including 869 consecutive patients with proximal DVT who were assessed for residual thrombosis by ultrasound after three months of treatment.[11] The pathophysiologic mechanism of residual thrombosis causing PTS has also been widely described. Residual thrombosis causes damage to the venous valves, which leads to valve incompetence, reflux and venous hypertension, finally resulting in an absence of pressure decrease in the venous system during walking, the latter being one of the main pathophysiological mechanisms of PTS.[2] The second predictor, obesity, has been more often described as well.[9,21,22]

The third predictor, duration of symptoms before DVT diagnosis >8 days has not been previously described. However, this delay in diagnosing DVT is associated with a longer delay in initiation of adequate anticoagulant treatment. It has been shown earlier that absence of anticoagulant treatment strongly increases the risk of PTS,[23] as does sub-therapeutic use of vitamin K antagonists.[24,25]

The fourth identified predictor was a Villalta score of 2-4 points with PTS defined as a Villalta score ≥5. The likely associations explain this finding. First, it is plausible that patients with pre-clinical PTS one year after a DVT diagnosis are more likely to have progressive symptoms and meet the diagnostic criteria of PTS than patients with no signs of PTS at all. Second, a Villalta score of 2-4 points may not only be caused by preclinical PTS, but may also be due to venous insufficiency or other causes. The latter has been shown to be associated with higher risk of PTS.[10,26]

Interestingly, in univariate analysis, with popliteal vein thrombosis as reference, iliac vein thrombosis showed an OR of 0.48 (95% CI 0.14-1.7) and 0.85 (95% CI 0.23-3.1) in the stop-ECS group and continue-ECS group for PTS respectively. This is in contrast with

previous studies where iliac vein thrombosis was an important risk factor for PTS.[22] Since in this study only patients who did not develop PTS during the first year after DVT were included, we hypothesise that iliac vein thrombosis could mainly be a risk factor for early PTS within the first year after a DVT diagnosis.

The biomarkers that were measured in 275 patients from this study, e.g. CRP, D-dimer and fibrinogen, showed no predictive value for PTS. Only a fibrinogen level of >4g/dl was associated with PTS in the continue-ECS group. Previous studies have evaluated the association with D-dimer, CRP, fibrinogen and PTS.[9,27,28] One study assessed D-dimer levels one year after DVT in 228 patients. The authors of that study reported a significantly higher D-dimer level in patients with PTS as opposed to those without PTS, although after multivariate adjustment, D-dimer was not found to be independently predictive of PTS.[27] In contrast, CRP levels >5 mg/L did show a strong and independent association with PTS for an OR of 8.0 (95%CI 2.4-26). An association between fibrinogen and PTS has not been found in previous studies and should be further investigated in future studies.[29]

The main strength of this study is that this represents a pre-defined endpoint analysis from a randomised controlled trial. A limitation of this study is that laboratory tests were not performed in all patients. Further, only patients who already used ECS compliantly during the first year after PTS diagnosis were included, and patients who already developed PTS during the first year after DVT were excluded. Therefore, the results of this study cannot be generalised to unselected patients with DVT. Moreover, our findings require external validation before they may be incorporated in clinical practice. This is mainly necessary because of the multiple analysis steps were taken to identify the predictors. Nonetheless, results of the IDEAL study and the Octavia study both strongly suggest that it should be possible to better individualise ECS therapy in the future. It remains to be determined which clinical, radiological and biochemical variables are to be included in the optimal risk stratification tool for this purpose.

In conclusion, this study shows that a thrombus score ≥3, BMI ≥26, duration of symptoms before DVT diagnosis ≥8 days, and a Villalta score 2-4 were independent predictors of PTS in patients with proximal DVT who completed 1 year of compliant ECS use and were not diagnosed with PTS in the first year after DVT. The incidence of PTS in patients without any of these predictors was lower than in patients with one or more of these predictors present. Our findings may be used to individualise ECS treatment after one year of compliant ECS use.

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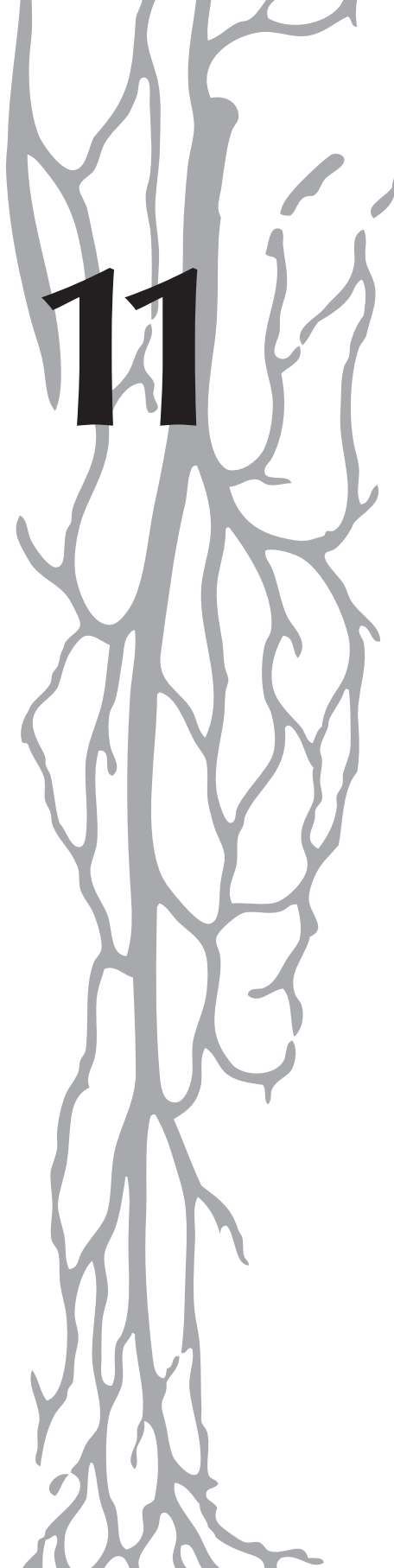
11

General discussion and summary



The studies described in the first part of this thesis aimed to improve the diagnostic management of deep vein thrombosis (DVT) in general, and in diagnostic challenging circumstances specifically. The second part of this thesis describes studies that aimed to improve the prognosis of DVT by evaluation of the persistence to prescribed therapy and predictors of the development of post thrombotic syndrome (PTS). **Chapter 1** provides a general introduction and overview of the presented studies.

PART I: CHALLENGES IN DIAGNOSTIC MANAGEMENT AND IMAGING OF DEEP VEIN THROMBOSIS

Chapter 2 gives first an overview of current and future perspectives in imaging of venous thromboembolism. The current favoured strategy for the diagnostic management of suspected first DVT is the combination of pre-test probability assessment by a clinical decision rule, D-dimer test and (serial) compression ultrasound (CUS). Notably, the 'gold standard' for a DVT diagnosis is still venography. The safety threshold against which all DVT diagnostic management studies are evaluated is therefore the known failure rate of venography, which has been shown to be 1.3% (upper limit 95% confidence interval 4.4%). This number represents the percentage of patients diagnosed with VTE (venous thromboembolism) during 3-month follow-up after a normal venography. The current used diagnostic strategy is much less invasive than venography, since no exposure to radiation and contrast material is needed. Therefore, the threshold for clinicians to order any test for DVT has become markedly lower, which has led to an even lower disease prevalence in study populations over the past years. Importantly, according to the theorem of Bayes, the failure rate, i.e. the post-test probability of having the disease, is associated with the disease prevalence in a population i.e. the pre-test probability of having the disease. In **chapter 3** we performed a systematic review and meta-analysis to evaluate the association between disease prevalence and failure rate over the last years in published studies on diagnosis of DVT, in order to propose a new diagnostic safety threshold for future studies on diagnostic management of suspected DVT. We selected all high quality DVT diagnostic management studies published since 1990. After plotting the published failure rates of all studies against the associated disease prevalence, we confirmed the association between both statistics with an absolute 1.0% higher DVT prevalence leading to a mean 0.026 percentage point's increase in failure rate. The formula of the upper level of the 95% CI of the reference line of this graph answered the formula: failure rate= 1.25 + 0.026*disease prevalence. We suggest that this formula should be incorporated in the power calculation of future studies. The adaption of the failure rate threshold by the expected disease prevalence in the studied population will prevent validation of insufficient diagnostic tests based on underpowered studies.

As discussed, the diagnostic workup of DVT ideally starts with calculating the pre-test probability of having DVT by a validated clinical decision rule. The most widely used rule is the Wells rule, but this rule consists of no less than 10 items with allocated different numbers of points. In clinical practice, this decision rule is therefore often incorrectly used leading to unneeded diagnostic tests and diagnostic failures. In **chapter 4,** we have developed a simpler rule by selecting the 4 items of the Wells rule which were - according to an expert panel - most predictive of DVT. These items were **I**mmobilization, >3 cm **D**ifference in calves circumferences, prior **V**enous thromboembolism (VTE) and active malignant **T**umor. This new clinical decision rule with one point for each variable was named the 'I-DVT score'. When both the Wells rule and I-DVT-score were applied to patients with clinically suspected DVT, the areas under the ROC curves (AUC) were 0.70 (95%CI 0.66-0.74) and 0.65 (95%CI 0.61-0.70) respectively, showing comparable accuracy. Notably, before the I-DVT score can be used in clinical practice, it has to be tested and validated in a prospective clinical management study.

Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a non-contrast enhanced MRI technique which has already been shown to accurately diagnose a first DVT and to distinguish acute thrombosis from chronic thrombus remains. This technique is based on the different paramagnetic properties of methemoglobin, which is formed in a fresh blood clot by the oxidation of hemoglobin, i.e. Fe^{2+} converted to Fe^{3+}. We hypothesized that this MRDTI technique can be a helpful solution in specific patient populations with suspected DVT, i.e. pregnant woman, patients with suspected ipsilateral DVT and patients with suspected upper extremity DVT (UEDVT).

The diagnostic management of pregnant woman is challenging mainly because there is a higher incidence of pelvic vein thrombosis than in the non-pregnant population. Pelvic vein thrombosis is very difficult to diagnose with compression ultrasound due to obvious anatomic reasons. In **chapter 5,** we have described the case of a 29 year old woman who was pregnant of a dichorionic diamniotic twin and presented with a high clinical suspicion of DVT. Repeated CUS was not diagnostic for DVT but showed reduced flow over the left external iliac vein, common femoral vein and superficial femoral vein. In pursue of a definite diagnosis, Magnetic Resonance Direct Thrombus Imaging (MRDTI) was performed showing a clear high signal in the left common iliac vein which was diagnostic for acute thrombosis in this venous segment. By performing MRDTI in this patient, we prevented exposure of the patient and her babies to ionizing radiation and contrast material. In **chapter 6** we discussed the additional value of a comparable direct thrombus imaging technique, the so called T1 weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery (TSE-SPAIR) sequence, in the diagnostic work-up of suspected ipsilateral recurrent DVT. This is a very challenging diagnosis because it is not possible with CUS to distinguish acute recurrent DVT from chronic thrombus remains. Residual thrombosis is present in up to 50% of patients after a first DVT and a definite

diagnosis cannot be made in ~30% of patients with CUS alone. We showed that the addition of the TSE-SPAIR sequence led to a higher diagnostic confidence of the radiologist when analysing the TSE-SPAIR sequence on top of the MRDTI sequence, most probably caused by the higher spatial resolution of the vessel wall. Although this study was not powered to analyse diagnostic accuracy, the sensitivity and specificity for proximal DVT was not changed by adding the TSE-SPAIR sequence to MRDTI. Therefore, there are no arguments to use the TSE-SPAIR sequence standardly in combination with the MRDTI sequence, although the extra TSE-SPAIR sequence may help to increase diagnostic confidence in case of uncertain diagnosis.

Upper extremity deep vein thrombosis (UEDVT) is very challenging to diagnose as well, especially when located in the subclavian vein. The main reasons for this are the overlying anatomic structures in the shoulder, such as the clavicle, hamper proper diagnosis with CUS. Since the MRDTI technique already showed to accurately diagnose DVT of the leg, we hypothesised that it should also be possible to diagnose UEDVT with MRDTI. In **chapter 7** we applied the two direct thrombus imaging techniques MRDTI and TSE-SPAIR in 3 patients who were already diagnosed with UEDVT by conventional techniques. In all three patients, UEDVT could be visualised successfully by the MRI.

PART II: PROGNOSTIC CHALLENGES OF DEEP VEIN THROMBOSIS

Adequate anticoagulant treatment is important to secure a favourable prognosis of DVT. Over the last years the treatment of choice shifted from vitamin K antagonists (VKAs) to direct oral anticoagulants (DOACs). DOACs have been shown to be equal in efficacy but have a lower bleeding risk than VKAs. Another advantage of DOACs is that regularly monitoring is not needed, since they have a more stable pharmacokinetic and pharmacodynamic profile than VKAs. A disadvantage of not monitoring the anticoagulant therapy however is a potential decrease in drug persistence. Adequate treatment is especially important in the first months as the risk of recurrence is higher after prematurely stopping anticoagulation treatment within 1 or 1.5 months after the VTE event than after 3 months. In **chapter 8** we found that, based on Dutch pharmacy registry data, 20% (95% CI 18-24) of patients stopped prematurely with their DOAC within the first 2 months from the DVT diagnosis. This stopping rate was comparable with drug persistence of treatment of other cardiovascular diseases such as oral antiplatelet therapy after acute coronary syndrome or secondary prevention treatment (statins, blood pressure lowering medication) after acute stroke. In patients who were taking VKA, and who were closely monitored by the anticoagulation clinic in Leiden, the stopping rate was much lower: 9.1% (95%CI 8.3-9.9). This study should therefore be used as a warning that

further investigation on the incidence and consequences of non-persistence in DOAC patients is urgently needed.

Post-thrombotic syndrome (PTS) is an important chronic complication after DVT. Elastic compression stockings (ECS) have been suggested to prevent PTS when they are compliantly used. ECS therapy is however notoriously uncomfortable and compliance is poor in clinical practice. Therefore, identification of predictors for PTS may help doctors to select patients who have a high risk for PTS and whom should be advised to wear their stockings compliantly for at least 2 years. In **chapter 9** we performed a systematic review and meta-analysis of all studies that included consecutive patients with DVT who received standardized anticoagulant treatment and had an ultrasonography assessing vascular damage after DVT during at least 6 months follow-up and were followed for the occurrence of PTS. We found that residual thrombosis and venous reflux were both predictive for PTS, for pooled Odds Ratios (OR) of 2.17 (95%CI 1.79-2.63) and 1.34 (95%CI 1.03-1.75) respectively. To select patients who could safely stop ECS therapy after one year we performed a pre-defined endpoint analysis of the Octavia study in **chapter 10.** The Octavia study was a multicentre single blind non-inferiority randomized controlled trial. Adequately anti-coagulated patients who were compliant to compression therapy for 12 months after a symptomatic, ultrasound proven proximal DVT were randomized between continuation and cessation of ECS therapy. Patients were followed for 12 months with as primary endpoint the incidence of PTS at the end of follow-up period. We found that thrombus score ≥3 (≥3 vein segments with residual thrombosis), BMI ≥26, duration of complaints before DVT diagnosis ≥8 days and a Villalta score of 2-4 points were independent significant predictors of PTS. When selecting patients without any of these predictors in the patient group that stopped ECS use after 1 year, 3.2% (95%CI 0.08-18) were diagnosed with mild PTS during follow-up and none with moderate or severe PTS. These findings suggest that after one year of compliant ESC use, stopping ECS treatment can be discussed in individual patients without any of the predictors present.

FUTURE PERSPECTIVES

With the MRDTI technique, a new era of diagnostic possibilities for suspected deep vein thrombosis has begun. Instead of diagnosing a thrombus indirectly by incompressibility of a venous segment via ultrasound or filling defects via venography, a thrombus can now be visualised directly.

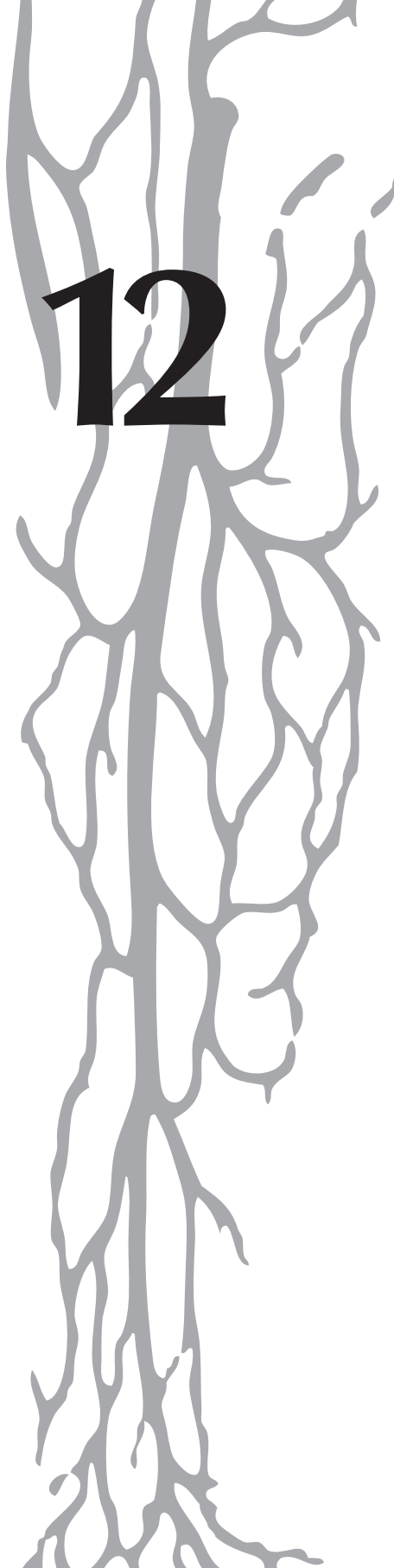
The solution for accurately diagnosing patients with a suspected ipsilateral recurrent DVT is nearby with the on-going Theia study. This is a diagnostic management study, in which patients with a suspected ipsilateral recurrent DVT are managed based on the results of the MRDTI scan only. When this study successfully proofs the safety of

this strategy, MRDTI can be directly implemented in clinical practice. The use of MRDTI for diagnosing UEDVT needs two extra steps before it can be used in clinical practice. The accuracy of MRDTI and TSE-SPAIR for diagnosing UEDVT will be explored with the MAGNITUDE/Selene study, and thereafter a diagnostic management study has to be performed as well. Moreover, MRDTI is a very promising technique to diagnose thrombosis in other difficult to image venous segments in the future. For instance, studies to test the feasibility of MRDTI to diagnose thrombosis in the splanchnic veins and cerebral veins are being planned.

The introduction of DOACs has largely changed the treatment landscape of VTE. However, there are still challenges to overcome. Large prospective studies are needed to study the efficacy in daily clinical practice where the risk of non-persistence due to lack of monitoring consists. On the other hand, when DOACs are adequately taken, some studies reported that DOACs can potentially lower the incidence of PTS because of the more constant anticoagulation level compared with VKAs. New studies are needed to proof this effect. Also, the effectiveness and optimal treatment duration of elastic compression stockings remains a point of discussion. Recent studies suggested tailoring ECS therapy per individual. However it remains to be determined which clinical, radiological and biochemical variables form the optimal risk stratification tool to select patients who can safely stop wearing ECS. A large patient-level database is needed to derive this tool and could for example be formed by pooling the results of 3 most recent large ECS studies: the Octavia, IDEAL and SOX trial. Thereafter, a randomized controlled trial should be performed to test a strategy that allows for the identification of low risk patients who can safely stop ECS after the first three to six months.

12

Nederlandse samenvatting



Dit proefschrift over diepe veneuze trombose (DVT) is tweeledig. Het eerste deel van dit proefschrift richt zich op de verbetering van de diagnostiek van DVT. Hierbij worden de algemene diagnostische strategieën onderzocht, maar ook diagnostische mogelijkheden in meer specifieke, diagnostisch uitdagende situaties. Het tweede deel van dit proefschrift richt zich op de verbetering van de prognose van DVT. Dit gebeurt door middel van het evalueren van de therapietrouw van de behandeling van DVT en het achterhalen van voorspellers voor het ontwikkelen van het post trombotisch syndroom (PTS). Ter introductie geeft **Hoofdstuk 1** een algemene inleiding op dit proefschrift en een overzicht van de beschreven studies.

DEEL I: VRAAGSTUKKEN OVER DE DIAGNOSTIEK EN BEELDVORMING VAN DIEPE VENEUZE TROMBOSE

Hoofdstuk 2 geeft een overzicht van de huidige en nieuwe beeldvormende technieken van veneuze trombo-embolieën en beschrijft de nog openstaande vraagstukken van de verschillende diagnostische strategieën. De huidige diagnostische strategie bij de verdenking op een eerste DVT is een combinatie van het schatten van de voorafkans op een DVT door middel van een gevalideerde klinische beslisregel, een D-dimeer test en een (herhaalde) compressie-echografie. De gouden standaard voor het diagnosticeren van DVT is echter venografie. Daarom wordt het percentage fout-negatieve uitslagen van venografie gebruikt als een 'veilige diagnostische grens' waartegen alle nieuwe diagnostische studies moeten worden geëvalueerd. Deze grens ligt op 1.3% met daarbij als bovengrens van het betrouwbaarheidsinterval (BI) een percentage van 4.4%. Dit getal beschrijft het percentage van patiënten die drie maanden na een niet afwijkende venografie alsnog met een symptomatische veneuze trombo-embolie (VTE) worden gediagnosticeerd.

De huidige diagnostische strategie met de drie genoemde testen is veel minder invasief dan venografie, omdat hierbij geen blootstelling aan radiologische straling en contrast vloeistof nodig is. Daarom is in de afgelopen jaren de drempel voor artsen om een diagnostische test voor DVT in te zetten veel lager geworden, wat heeft geleid tot een lagere ziekteprevalentie in studiepopulaties. Echter, volgens het theorema van Bayes is de post-test kans op een fout-negatieve testuitslag geassocieerd met de voorafkans op het hebben van een ziekte. Deze voorafkans op het hebben van een ziekte is weer afhankelijk van de ziekteprevalentie in een (studie) populatie. Om de associatie tussen de ziekteprevalentie en de kans op een fout-negatieve-test in studies naar de diagnostiek van DVT te evalueren hebben we in **hoofdstuk 3** een systematische review en een meta-analyse uitgevoerd. Het doel hiervan was een nieuwe 'veilige diagnostische grens' te bepalen voor toekomstige studies naar de diagnostiek van DVT. We selecteer-

den alle, sinds 1990 gepubliceerde studies van hoge kwaliteit waarin de diagnostiek van DVT werd onderzocht. Van elke studie werd de ziekte prevalentie en het aantal fout-negatieve testen genoteerd en deze twee getallen werden tegen elkaar uitgezet in een grafiek. Hiermee kon de associatie tussen het percentage fout-negatieve-testen en de ziekteprevalentie in de studiepopulatie worden bevestigd. De referentielijn van deze grafiek liet namelijk zien dat wanneer de prevalentie van DVT 1% hoger is, het percentage fout-negatieve testen met 0.026 procentpunten stijgt. De bovengrens van het 95% BI van de referentie lijn van deze grafiek is als volgt geformuleerd: *percentage fout-negatieve-testen= 1.25 + 0.026*ziekteprevalentie*. Onze suggestie is om deze formule in de powerberekening van alle toekomstige studies te gebruiken. Met de formule kan het maximale percentage fout-negatieve testen dat nog acceptabel is aangepast worden aan de ziekteprevalentie in een studiepopulatie. Hierdoor kan in de toekomst voorkomen worden dat diagnostische strategieën schijnbaar adequaat zijn getest maar feitelijk geëvalueerd zijn zijn in studies met te weinig statische power, en dus niet een afdoende bewijs geven van de veiligheid en nauwkeurigheid van de onderzochte test.

Zoals eerder besproken start de diagnostiek van DVT met het uitrekenen van de voorafkans op het hebben van DVT door middel van een gevalideerde klinische beslisregel. De meest gebruikte beslisregel is de Wells-regel, die uit 10 onderdelen bestaat waaraan een verschillend aantal punten wordt toegekend. Deze regel wordt in de klinische praktijk vaak verkeerd gebruikt wat kan leiden tot onnodige aanvullende diagnostische testen en fout-negatieve uitkomsten. In **hoofdstuk 4** hebben we daarom een nieuwe, eenvoudiger regel ontwikkeld. Een expertpanel selecteerde vier onderdelen van de Wells-regel die volgens hen het meest voorspelbaar zijn voor DVT. Deze vier onderdelen waren: **I**mmobilisatie, > 3 cm verschil (**D**ifference) in kuitomtrek, eerdere **V**eneuze trombo-embolie en actieve malignitei**T**. Deze nieuwe regel hebben we de 'I-DVT score' genoemd, waarbij aan elke variabele één punt wordt toegekend. Wanneer beide regels (de Wells regel en I-DVT score) werden toegepast bij patiënten met een klinische verdenking op een DVT bleken ze een vergelijkbare nauwkeurigheid te hebben, met oppervlaktes onder de ROC (receiver operating characteristic) curves van respectievelijk 0.70 (95%BI 0.66-0.74) en 0.65 (95%BI 0.61-0.70). Voordat de I-DVT score in de klinische praktijk kan worden toegepast, zal de score uiteraard eerst moeten worden getest in een prospectieve managementstudie.

Met de MRI techniek 'Magnetic Resonance Direct Thrombus Imaging' (MRDTI) kan trombose direct in beeld worden gebracht zonder het gebruik van veneus contrast. In voorgaande studies is aangetoond dat deze techniek nauwkeurig een eerste DVT kan vaststellen, en een acute trombose van reststolsels kan onderscheiden. Deze techniek is gebaseerd op het verschil in paramagnetische eigenschappen van methemoglobine. Methemoglobine wordt in een vers bloedstolsel gevormd door de oxidatie van hemoglobine, waarbij Fe2+ wordt omgezet naar Fe3+. Onze hypothese was dat deze

MRDTI-techniek een goede oplossing kan zijn voor de diagnostiek van DVT in specifieke patiënt populaties, zoals zwangere vrouwen, patiënten met een verdenking op een ipsilateraal recidief DVT en patiënten met een verdenking op een armvene trombose. De diagnostiek van DVT bij zwangere vrouwen is lastig, voornamelijk door de hogere incidentie van geïsoleerde bekkenvene trombose in vergelijking met de niet-zwangere populatie. Bovendien is een geïsoleerde bekkenvene trombose moeilijk vast te stellen met een compressie-echografie door de anatomische ligging. **In hoofdstuk 5** beschrijven we de casus van een 29-jarige vrouw met een dichoriale diamniotische tweeling-zwangerschap en een hoge klinische verdenking op een DVT. De diagnose DVT kon bij herhaling niet met compressie echografie worden vastgesteld. Bij de echo werd wel een verminderde flow over de linker vena iliaca externa, vena femoralis communis en vena femoralis superficialis gevonden. Om de definitieve diagnose te kunnen stellen werd een MRDTI-scan gemaakt. Deze liet een hoog signaal in de linker vena iliaca communis zien, waarmee een acute trombose in dit veneuze segment kon worden vastgesteld. Door het maken van de MRDTI-scan bij deze patiënte hebben we kunnen voorkomen dat een CT-scan of venografie nodig was waarbij zowel de patiënte als haar ongeboren baby's aan ioniserende straling of contrastvloeistof werden blootgesteld.

In hoofdstuk 6 beschrijven we de toegevoegde waarde van een vergelijkbare techniek, de zogenoemde 'T1 weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery' (TSE-SPAIR) sequentie, bij de diagnostiek van een verdenking op een ipsilateraal recidief DVT. Het is lastig deze aandoening te diagnosticeren, omdat het met een compressie-echografie niet mogelijk is een acuut recidief DVT te onderscheiden van een chronische resttrombose. Tot 50% van de patiënten behoudt na een eerste DVT een chronische resttrombose. Hierdoor kan bij ongeveer 30% van de patiënten met een verdenking op een ipsilateraal recidief trombose de diagnose niet met compressie echografie worden vastgesteld. We toonden aan dat radiologen een hogere diagnostische zekerheid kregen over de diagnose ipsilateraal recidief DVT, wanneer ook de TSE-SPAIR-sequentie werd beoordeeld naast de MRDTI-sequentie. De toename van de diagnostische zekerheid wordt hoogstwaarschijnlijk veroorzaakt door de hogere ruimtelijke resolutie van de vaatwand bij de TSE-SPAIR-sequentie. Hoewel deze studie niet groot genoeg was om de diagnostische nauwkeurigheid te analyseren, veranderde de sensitiviteit en specificiteit voor de diagnose proximale DVT niet wanneer de TSE-SPAIR-sequentie aan de MRDTI-sequentie werd toegevoegd. Daarom zijn er geen argumenten om de TSE-SPAIR-sequentie standaard aan de MRDTI-sequentie toe te voegen. De TSE-SPAIR sequentie kan wel worden gebruikt om de diagnose met meer zekerheid vast te stellen in gevallen waarbij de diagnose op MRDTI beelden onduidelijk blijft.

Ook de diagnose arm vene trombose is vaak moeilijk te stellen, vooral in het geval van trombose in de vena subclavia. Door de overliggende anatomische structuren in de schouder, zoals de clavicula, is een goede diagnose met compressie echografie vaak

niet mogelijk. Omdat de diagnose DVT in het been nauwkeurig met MRDTI in beeld gebracht kan worden, was onze hypothese dat het ook mogelijk zou moeten zijn een arm vene trombose met MRDTI te diagnosticeren. Daarom pasten we in **hoofdstuk 7** de twee eerder beschreven 'trombus imaging' technieken MRDTI en TSE-SPAIR toe, bij drie patiënten bij wie al een arm vene trombose was vastgesteld door conventionele technieken. Bij alle drie de patiënten kon de arm vene trombose ook succesvol met MRI worden vastgesteld.

DEEL II: PROGNOSTISCHE VRAAGSTUKKEN BIJ DIEPE VENEUZE TROMBOSE

Voor een gunstige prognose na de diagnose DVT is een adequate behandeling met anticoagulantia van belang. In de laatste jaren is men voor de behandeling van VTE overgestapt van vitamine K antagonisten (VKAs) naar directe orale anticoagulantia (DOACs). DOACs zijn even effectief als VKAs, maar geven een lager bloedingsrisico vergeleken met VKAs. Een ander voordeel van DOACs is dat regelmatige controle (door de trombosedienst) niet nodig is doordat ze een stabieler farmacokinetisch en farmacodynamisch profiel hebben ten opzichte van VKAs. Echter, het achterwege laten van regelmatige controle bij het gebruik van anticoagulantia kan nadelig zijn vanwege een mogelijke afname in therapietrouw. Juist in de eerste maanden na de diagnose VTE is adequate behandeling belangrijk. Het risico op een recidief is namelijk groter wanneer patiënten hun antistolling al na een maand of anderhalve maand voortijdig stoppen, in plaats van het minimaal 3 maanden te gebruiken. In **hoofdstuk 8** hebben we aan de hand van het Nederlandse register van apotheken (Stichting Farmaceutische Kengetallen; SFK) berekend dat 20% (95% BI 18-24) van de patiënten binnen 2 maanden nadat een VTE is vastgesteld voortijdig stopt met het gebruik van DOACs. Dit percentage is vergelijkbaar met de therapietrouw bij de behandeling van andere cardiovasculaire ziektes zoals het gebruik van plaatjesremmers na een acuut coronair syndroom of medicatie voor secundaire preventie (statines, bloeddrukverlagers) na een acuut herseninfarct. Bij patiënten met een VTE die een VKA gebruiken en hierbij nauwkeurig werden gemonitord door de Leidse trombosedienst, was het percentage patiënten dat vroegtijdig stopte met antistolling veel lager: 9.1% (95% BI 8.3-9.9). Met deze studie willen we de risico's van het gebruik van DOACs in de klinische praktijk onder de aandacht te brengen en ook duidelijk maken dat verder onderzoek naar zowel de incidentie als de gevolgen van slechte therapietrouw bij gebruik van DOACs absoluut noodzakelijk is.

Een belangrijke en chronische complicatie na een DVT is het post-trombotisch syndroom (PTS). In de literatuur wordt gesuggereerd dat elastische steunkousen PTS zouden kunnen voorkomen, mits ze trouw worden gedragen. Het dragen van steun-

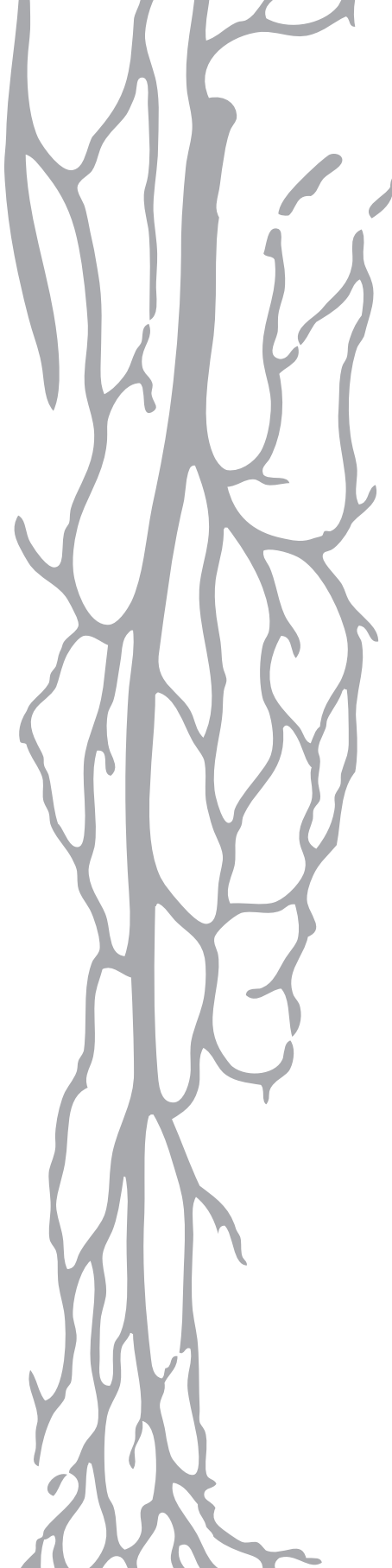
kousen is echter erg oncomfortabel en daarom is de therapietrouw hiervan in de dagelijkse praktijk ook laag. Artsen zouden geholpen zijn als ze nauwkeuriger patiënten met het hoogste risico op PTS en/of met de meeste baat van de steunkousen zouden kunnen selecteren. Aan deze patiënten zou kunnen worden geadviseerd om de steunkousen zeker gedurende twee jaar trouw te dragen. In **hoofdstuk 9** hebben we een systematische review en meta-analyse uitgevoerd over alle studies waarbij patiënten zijn geïncludeerd met een DVT en waarbij tijdens follow-up een echografie is gemaakt om vasculaire schade na een DVT vast te stellen. Overige inclusiecriteria waren een gestandaardiseerde behandeling met anticoagulantia en een follow-up periode van ten minste 6 maanden waarbij als uitkomst PTS werd geregistreerd. In deze meta-analyse hebben we aangetoond dat rest-trombose en veneuze reflux voorspellers zijn voor PTS, met gepoolde Odds ratios (OR) van respectievelijk 2.17 (95%BI 1.79-2.63) en 1.34 (95%BI 1.03-1.75). Om patiënten te kunnen selecteren die na 1 jaar veilig met steunkousen zouden kunnen stoppen hebben we in **hoofdstuk 10** een tweede, vooraf gedefinieerde, eindpuntanalyse van de Octavia studie uitgevoerd. De Octavia studie is een multicenter, enkel geblindeerde, non-inferieure, gerandomiseerd gecontroleerde studie. Voor deze studie werden patiënten geïncludeerd die adequaat waren behandeld met antistolling en gedurende 12 maanden trouw hun steunkousen hebben gedragen na een symptomatische, echo bewezen, proximale DVT. Patiënten werden gerandomiseerd tussen doorgaan of stoppen met het dragen van steunkousen. Beide groepen werden gedurende 12 maanden gevolgd met als primair eindpunt de incidentie van PTS aan het einde van de follow-up periode. We vonden vier onafhankelijke significant voorspellende factoren voor het ontwikkelen van PTS in het tweede jaar na de diagnose DVT: een trombus score ≥3 (≥3 veneuze segmenten met rest trombose, gemeten met compressie echografie), een Villalta score van 2-4, een BMI ≥26 en ≥8 dagen symptomen voordat de diagnose DVT werd gesteld. Van de groep patiënten die na 1 jaar zijn gestopt met het dragen van steunkousen en geen enkele van deze voorspellers hadden, werd 3.2% (95%CI 0.08-18) gediagnostiseerd met mild PTS gedurende de follow-up periode, en geen enkele patiënt kreeg matig ernstige of ernstige PTS. Deze uitkomsten suggereren dat met patiënten die de steunkousen gedurende 1 jaar trouw hebben gedragen en geen één van de voorspellers hebben, besproken kan worden dat ze met het dragen van steunkousen zouden kunnen stoppen.

TOEKOMST PERSPECTIEF

Met de MRDTI techniek is het begin van een nieuw tijdperk vol mogelijkheden voor het diagnosticeren van DVT aangebroken. Het stolsel kan nu direct in beeld worden gebracht, in plaats van indirect door een niet comprimeerbare vene bij echografie of

een vullingsdefect bij venografie. Met de Theia studie, die op dit moment wordt uitgevoerd, kan op korte termijn een oplossing geboden worden voor een meer nauwkeurige diagnose van patiënten met verdenking op een ipsilateraal recidief DVT. De Theia studie is een diagnostische management studie, waarbij de beslissing om al dan niet te starten met een aanvullende behandeling bij patiënten met een verdenking op een ipsilateraal recidief DVT enkel op basis van de resultaten van de MRDTI scan wordt gemaakt. Wanneer deze studie laat zien dat dit een veilige strategie is, kan MRDTI direct worden geïmplementeerd in de klinische praktijk. Voordat MRDTI in de klinische praktijk kan worden gebruikt om een arm vene trombose vast te stellen, zijn er echter nog twee extra stappen nodig. In eerste instantie zal de nauwkeurigheid van de MRDTI en TSE-SPAIR sequentie om een arm vene trombose te diagnosticeren worden onderzocht in de MAGNITUDE/Selene studie. Als de MAGNITUDE/Selene studie succesvolle resultaten laat zien zal daarna ook een diagnostische management studie worden uitgevoerd. MRDTI is tevens een veelbelovende techniek om trombose vast te stellen in veneuze segmenten die met de huidige technieken moeilijk in beeld kunnen worden gebracht. Daarom worden nu meerdere studies gepland om te onderzoeken of het mogelijk is met MRDTI trombose in de mesenteriale en cerebrale venen in beeld te brengen.

Met de introductie van DOACs is er veel veranderd rond de behandeling van VTE. Veel vraagstukken zijn echter nog niet beantwoord. Door het gebrek aan regelmatige controle (door de trombosedienst) bij de behandeling met DOACs bestaat het risico op verminderde therapietrouw. Om de daadwerkelijke effectiviteit van DOACs in de klinische praktijk te onderzoeken zijn grote prospectieve studies nodig. Anderzijds beschrijven sommige studies dat DOACs de incidentie van PTS zouden kunnen verlagen, mits ze adequaat worden ingenomen. Dit omdat ze vergeleken met VKAs een meer constant niveau van antistolling geven. Nieuwe studies zijn nodig om dit effect te bewijzen. Ook de effectiviteit en de optimale behandelduur van elastische kousen blijven een punt van discussie. Recente studies suggereren dat een op het individu afgestemde behandel strategie met steunkousen nodig is. Echter zal dan eerst nog moeten worden bepaald welke klinische, radiologische en biochemische variabelen het optimale risicostratificatie instrument vormen om patiënten te selecteren die veilig met steunkousen zouden kunnen stoppen. Om dit instrument te kunnen ontwikkelen is een grote database met patiënten nodig. Dit zou bijvoorbeeld kunnen worden bereikt door de resultaten van de Octavia studie, IDEAL studie en SOX trial, de meest recente grote steunkousen studies, bij elkaar te voegen. Vervolgens zal een gerandomiseerde gecontroleerde trial moeten worden uitgevoerd om te testen of dit instrument het inderdaad mogelijk maakt individuele patiënten met een laag risico op PTS te identificeren die na de eerste 3 tot 6 maanden veilig met het gebruik van steunkousen zouden kunnen stoppen.



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CURRICULUM VITAE

Charlotte Emilia Annemie Dronkers werd geboren op 28 maart 1990 te Breda. In 2007 behaalde ze haar Gymnasium diploma aan het Stedelijk Gymnasium te Breda. In datzelfde jaar startte zij met de studie geneeskunde aan de Universiteit Leiden. De eerste ervaringen met wetenschappelijk onderzoek werden opgedaan tijdens de wetenschapsstage op de afdeling Endocrinologie onder begeleiding van prof. dr. J.W.A. Smit. Met de start van de coschappen in 2011 werden ook haar klinische vaardigheden ontwikkeld en in 2013 behaalde zij het artsexamen. Aansluitend werkte zij als arts-assistent niet in opleiding op de afdeling Interne Geneeskunde en Intensive Care van het Alrijne ziekenhuis te Leiderdorp (opleiders S. Anten en dr. M.J.F.M Janssen). In 2015 begon zij aan wetenschappelijk onderzoek onder begeleiding van prof. dr. M.V. Huisman en dr. F.A. Klok, waarvan de resultaten zijn beschreven in dit proefschrift. Sinds januari 2018 is zij in opleiding tot internist in het Haaglanden Medisch Centrum (opleiders dr. A.H. Bootsma, dr. Y.W.J. Sijpkens, dr. E.D. Beishuizen en M.J.M de Vreede).