Novel imaging strategies in venous thromboembolism

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CONTENTS

CHAPTER

Introduction and outline of this thesis

Venous thromboembolism (VTE) encompasses pulmonary embolism (PE) and deep vein thrombosis (DVT). DVT most commonly occurs in the deep veins of the lower extremity but can also occur in the veins of upper extremity, abdomen and cerebrum. As symptoms of VTE are nonspecific, the diagnosis of VTE is based on diagnostic tests, including clinical decision rules (CDR), D-dimer tests and imaging. Although the diagnostic management of VTE has greatly advanced in recent years with the introduction of novel CDRs and high-sensitive D-dimer tests, the diagnosis may still be challenging in certain settings. The latter is mainly caused by the indirect way of thrombus visualisation by current imaging tests, such as by showing incompressibility with compression ultrasonography (CUS) or a filling defect on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI).

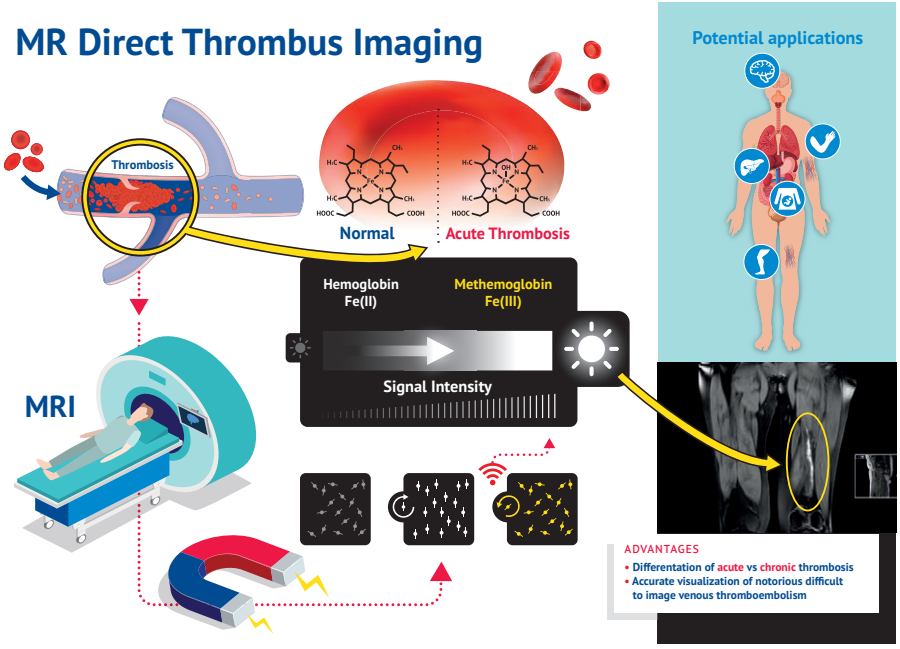
This thesis focuses on challenging settings for diagnosing VTE. One of these settings is suspected *recurrent VTE.* CUS is the current imaging test of choice in both patients with suspected first and recurrent DVT.[1] However, in suspected *recurrent ipsilateral DVT* the diagnosis with CUS is complicated as persistent vascular abnormalities after a previous DVT are present in up to 50% of patients after one year.[2] Magnetic Resonance Non-Contrast Thrombus Imaging (MR-NCTI) is a non-invasive MRI technique that can directly visualize thrombosis and may be of value in the diagnostic management of recurrent VTE. MR-NCTI is based on the formation methemoglobin when blood clots, resulting in shortening of the MR signal on a T1-weighted MRI sequence. Therefore, acute thrombi are visible as a 'white' signal, which disappears when a thrombus is formed (**Figure 1**).[3,4] Magnetic Resonance Direct Thrombus Imaging (MRDTI), a MR-NCTI sequence, has previously been shown to accurately distinguish acute recurrent DVT from chronic thrombotic remains.[5] Its safety to exclude acute recurrent ipsilateral DVT was evaluated in the Theia study. Results of this prospective multicentre diagnostic management study are described in **Chapter 2**. Since it is unknown whether the application of MRDTI in the diagnostic management of suspected recurrent ipsilateral DVT is costeffective, an analysis to compare the one-year healthcare costs between 10 diagnostic scenarios with and without MRDTI was performed. The results are described in **Chapter 3**. The combination of a CDR and D-dimer test is used to exclude a first episode of DVT without performing imaging tests. The diagnostic performance of a CDR combined with a D-dimer test has not yet been sufficiently evaluated in patients with suspected recurrent DVT.[6] One of the predefined secondary outcomes of the Theia study was to assess the diagnostic accuracy of the combination of the Wells rule for DVT and a D-dimer test for suspected recurrent ipsilateral DVT (**Chapter 4**).

MR-NCTI may also be useful in the diagnostic management of *upper extremity deep vein thrombosis* (UEDVT), where CUS examination is hindered by overlying anatomic structures. The alternative diagnostic imaging test is contrast venography, which has several disadvantages including radiation exposure and risk for contrast allergic reactions.[7] In **Chapter 5**, the results of the Selene study are provided, in which the diagnostic accuracy of MR-NCTI for the diagnosis of UEDVT was evaluated. Another setting where MR-NCTI could be a valuable diagnostic test is in *portal vein thrombosis* (PVT). Differentiation between acute and chronic thrombosis is of paramount importance in the management of PVT, since the anticoagulant strategy in patients with acute PVT differs of that in patients with chronic thrombosis.[8] It is however not always possible with currently available imaging tests to make this distinction. As MR imaging of the portal veins can be more challenging than of the veins in the extremities due to bowel movements and the presence of intestinal air, we performed a study to identify the most optimal MR-NCTI sequence for PVT imaging (**Chapter 6**). In **Chapter 7**, an overview of different imaging techniques including MR-NCTI and their diagnostic accuracy in suspected acute *cerebral vein thrombosis* (CVT) is provided. Based on our studies and increasing experience with MR-NCTI, this technique is now more and more used to guide treatment decisions in other settings, such as in the patients in **Chapter 8** and **Chapter 9**. The first patient (**Chapter 8**) was suspected of an acute CVT but had an inconclusive CT and MR venography. The second patient described in **Chapter 9** had an extensive *aortic thrombosis* on CT angiography of unknown age, and a strong contraindication to anticoagulant treatment.

The last chapters of this thesis focus on the application of CT in the diagnostic and prognostic management of acute PE. CT pulmonary angiography (CTPA) is the current diagnostic imaging of choice for the diagnosis of PE.[9] New CT techniques have been developed in recent years including techniques that can provide perfusion or iodine maps, representing the hemodynamic and functional impact of PE. This so-called CT pulmonary perfusion (CTPP) imaging may have an added value on top CTPA reading for initial risk stratification of acute PE. In **Chapter 10**, the correlation between perfusion defects on CTPP and symptoms at presentation as well as short-term adverse outcome was assessed. Furthermore, as extensive perfusion defects on CT at the time of PE diagnosis may also correlate to long-term symptoms and outcome [10], we evaluated the association between perfusion defects on CTPP at initial PE-diagnosis and persistent symptoms, including dyspnea, chest pain, functional impairment and adverse outcomes after 3-months of follow-up in **Chapter 11**. CTPA is also used in the diagnostic management of

patients with coronavirus disease 19 (COVID-19) pneumonia who are suspected of concomitant acute PE. COVID-19 has been associated with high rates of VTE [11], particularly PE. Based on the results of autopsy studies it was suggested that thrombosis may often be the result of an in-situ immunothrombosis rather than conventional thromboembolism.[12] To further evaluate whether COVID-19 associated PE differs from conventional PE, clinical and CT characteristics of PE in patients with COVID-19 pneumonia were compared to those in patients without COVID-19 pneumonia (**Chapter 12**).

Figure 1. Infographic of the Magnetic Resonance Direct Thrombus Imaging technique.



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2

CHAPTER

Magnetic resonance imaging for diagnosis of recurrent ipsilateral deep vein thrombosis

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Blood, 2020 Apr; 135 (16):1377-1385

ABSTRACT

The diagnosis of recurrent ipsilateral deep vein thrombosis (DVT) is challenging, because persistent intravascular abnormalities after previous DVT often hinder a diagnosis by compression ultrasonography. Magnetic resonance direct thrombus imaging (MRDTI), a technique without intravenous contrast and with a 10-minute acquisition time, has been shown to accurately distinguish acute recurrent DVT from chronic thrombotic remains. We have evaluated the safety of MRDTI as the sole test for excluding recurrent ipsilateral DVT. The Theia Study was a prospective, international, multicenter, diagnostic management study involving patients with clinically suspected acute recurrent ipsilateral DVT. Treatment of the patients was managed according to the result of the MRDTI, performed within 24 hours of study inclusion. The primary outcome was the 3-month incidence of venous thromboembolism (VTE) after a MRDTI negative for DVT. The secondary outcome was the interobserver agreement on the MRDTI readings. An independent committee adjudicated all end points. Three hundred five patients were included. The baseline prevalence of recurrent DVT was 38%; superficial thrombophlebitis was diagnosed in 4.6%. The primary outcome occurred in 2 of 119 (1.7%; 95% confidence interval [CI], 0.20-5.9) patients with MRDTI negative for DVT and thrombophlebitis, who were not treated with any anticoagulant during follow-up; neither of these recurrences was fatal. The incidence of recurrent VTE in all patients with MRDTI negative for DVT was 1.1% (95% CI, 0.13%-3.8%). The agreement between initial local and post hoc central reading of the MRDTI images was excellent (k statistic, 0.91). The incidence of VTE recurrence after negative MRDTI was low, and MRDTI proved to be a feasible and reproducible diagnostic test.

INTRODUCTION

Despite major technical advances in recent years, critical limitations to current available diagnostic techniques for venous thromboembolism (VTE) exist in specific settings. The failure to provide an accurate diagnosis may lead to misdiagnosis and subsequent mistreatment, affecting both morbidity and mortality.[1,2] One of these settings is suspected recurrent ipsilateral deep vein thrombosis (DVT) of the leg, in which the safety of ruling out recurrent DVT by applying clinical decision scores and D-dimer testing has not been established.[2] Moreover, the diagnosis of recurrent DVT using compression ultrasonography (CUS) is complicated by residual vascular abnormalities following a first DVT episode in up to 50% of patients after one year despite adequate anticoagulant treatment.[3-5] CUS has been proposed to be diagnostic for recurrent DVT in case of a new non-compressible venous segment or a ≥2-4 mm increase in vein diameter of a previously non-compressible vein, in comparison with a prior CUS.[6-9] However, in clinical practice a prior CUS is often unavailable and comparisons with previous CUS examinations are subject to major interobserver variability.[10] Similarly, these residual vascular abnormalities complicate the interpretation of all other diagnostic modalities, including contrast venography. As a consequence, recurrent ipsilateral DVT cannot be ruled out in up to 30% of patients in daily practice, resulting in overtreatment.[3]

Magnetic resonance direct thrombus imaging (MRDTI) is a technique with a short 10-minute acquisition time that is based on the formation of methemoglobin in a fresh thrombus which appears as a high signal when imaged on a T1 weighted MRI sequence by measurement of the shortening T1 signal.[11] This technique does not require intravenous gadolinium contrast. MRDTI can accurately diagnose a first DVT and distinguish acute recurrent DVT from chronic residual thrombotic abnormalities with a sensitivity and specificity of at least 95%.[12,13] MRDTI therefore has potential to be used as a single test to diagnose or rule out recurrent ipsilateral DVT, but a formal outcome study had not been performed previously.[14] We have conducted a prospective management study to evaluate the safety of ruling out acute recurrent ipsilateral DVT of the leg by a MRDTI negative for DVT.

METHODS

Study design and patients

The Theia study was a prospective international multicenter diagnostic management study conducted at five academic and seven non-academic teaching hospitals across five countries. From March 2015 to March 2019, we included patients aged 18 years or older with clinically suspected acute recurrent ipsilateral DVT of the leg. Exclusion criteria were DVT diagnosed by CUS within six months before presentation (to prevent false positive MRDTI findings because of a previous recent DVT episode[15]), symptom duration of more than ten days, suspected concurrent acute pulmonary embolism (PE), hemodynamic instability at presentation (as a consequence of concurrent PE or other clinical conditions), medical or psychological condition not permitting completion of the study or signing informed consent (including life expectancy less than three months) and general contraindications for MRI. Furthermore, patients treated with full-dose anticoagulation that had been initiated ≥48 hours before the eligibility assessment were excluded. Notably, from August 2015 onwards, patients with suspected recurrent DVT while receiving therapeutic anticoagulant treatment ≥48 hours were also allowed in the study as they were found to represent a high proportion of the screened study population (30%) in the first year after study initiation and thus formed a clinically relevant patient group.

The study protocol and its amendments were approved by the institutional review board of the Leiden University Medical Center (LUMC) Leiden, the Netherlands; for all participating hospitals in the Netherlands), by the institutional review board at the Danderyd Hospital (Stockholm, Sweden), Østfold Hospital (Østfold, Norway), the Ottawa Hospital (Ottawa, Canada) and Rambam Health Care Campus (Haifa, Israel). All patients provided written informed consent. All participating centers were provided with a training set of MRDTI images and performed a test MRDTI prior to study start. The study was only initiated if the quality of this scan was judged adequate by the LUMC radiologists' expert team. The study was designed by the authors with no involvement of any commercial entity. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol. No one who is not an author contributed to the writing of the manuscript.

Procedures

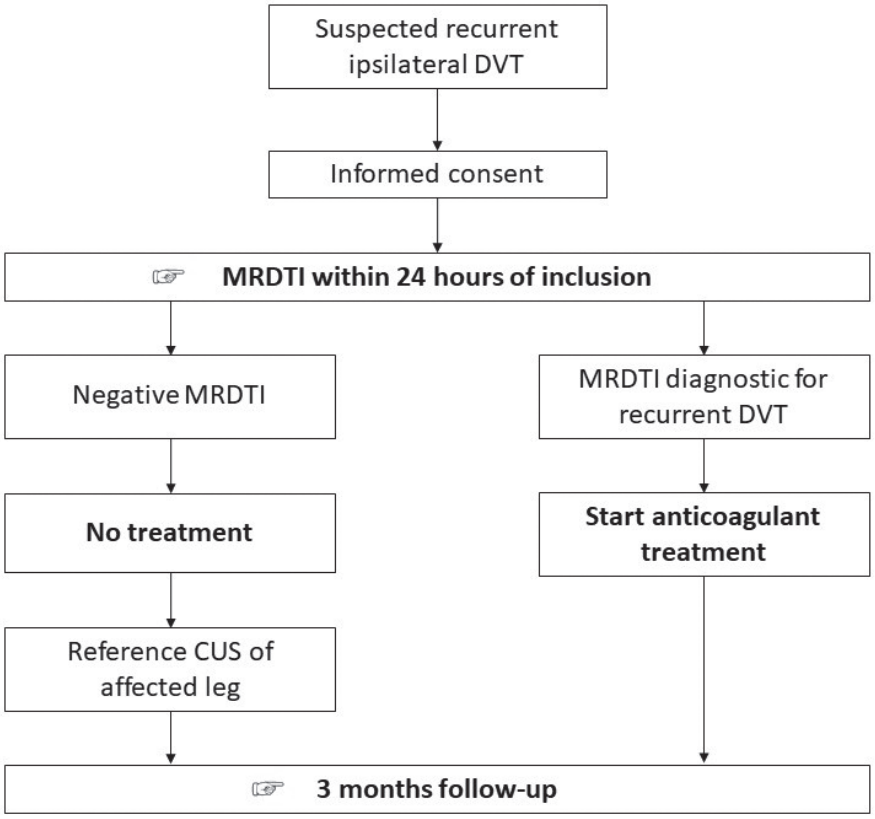
Consecutive patients who fulfilled all inclusion criteria and met none of the exclusion criteria were eligible for inclusion and managed according the study algorithm (**Figure 1**). The diagnosis and treatment decision were based solely on the result of the MRDTI of the affected leg which was performed within 24 hours of inclusion. MRDTI was performed with a 1.5 or 3.0 Tesla unit with maximum gradient amplitude of 45 mT/m, slew rate of 200 T/m/s, using an integrated 16-channel posterior coil and a 16-channel anterior body coil for signal reception.[15-17]

In case MRDTI was not instantly available at the time of presentation, and in the absence of absolute contraindications, patients received a single dose of therapeutic anticoagulation as per local treatment guidelines. Acute recurrent DVT as diagnosed by the MRDTI protocol was defined as a high signal in the location of a deep vein segment against the suppressed background greater than that observed in the corresponding or contiguous segments of the ipsilateral vein as judged by the attending radiologist.[12,13]

Patients with a MRDTI negative for DVT were left untreated, or treatment remained unadjusted if they already received anticoagulant treatments due to a previous indication. In these patients a standardized CUS examination within 48 hours after the MRDTI was performed. This examination served as a reference test in case a patient returned with symptoms of DVT recurrence during the follow-up period but was not used for management decisions at baseline. In case of a MRDTI positive for DVT, anticoagulant treatment was initiated in accordance with international and local guidelines or modified in patients with a recurrent DVT *on* anticoagulant therapy.

All patients were followed for the occurrence of recurrent symptomatic VTE, anticoagulation-associated major bleeding and all-cause mortality over a period of three months after inclusion. Patients were instructed to return to the hospital before the 3-month appointment if symptoms of recurrent VTE occurred, at which time objective tests were performed.[18-20]

Figure 1. Study flowchart in patients with clinically suspected acute recurrent ipsilateral DVT.



The reference CUS in patients with MRDTI negative for DVT was performed within 48 hours and did not influence the treatment decision.

Outcomes

The primary outcome was the 3-month incidence of recurrent symptomatic VTE in patients with MRDTI negative for DVT. The diagnosis of recurrent DVT during follow-up was defined as incompressibility of a new venous segment or a ≥2-4 mm increase in vein diameter of a previous non-compressible venous segment upon CUS.[9] In case of suspected recurrence during the follow-up period investigators were also encouraged to perform a repeat MRDTI. PE was considered to be present if computed tomography pulmonary angiography (CTPA) showed at

least one filling defect in the pulmonary artery tree and if PE was judged to be a probable cause of unexplained death unless proven otherwise by autopsy. An independent committee, who were blinded for all diagnostic procedures and treatment decisions at baseline, assessed and adjudicated all suspected cases of VTE and deaths that occurred during follow-up.
After study initiation we observed a relevant prevalence of patients with a MRDTI negative for DVT but positive for superficial thrombophlebitis. These patients were not anticipated in the protocol and were mostly treated with half-therapeutic dose of anticoagulants for six weeks as per local guidelines. Since patients who are treated with anticoagulants have a lower risk to develop a recurrent DVT during follow-up, the primary outcome was modified by adding an additional subgroup: patients with MRDTI negative for both DVT and thrombophlebitis *off* anticoagulant treatment at inclusion.

The main secondary outcome was the interobserver agreement of MRDTI in daily clinical practice. This was assessed post-hoc: the first 10 scans of each study site were re-assessed by the expert team in the LUMC, blinded to the clinical presentation and follow-up of the study patients. Their ruling was compared to the ruling of the attending local radiologist at the moment of clinical presentation. Also, we assessed the feasibility of MRDTI, i.e. the number of patients who could not be included due to MRDTI unavailability as well as the median time between study inclusion and MRDTI scanning.

Statistical analysis

We aimed to mirror the risk of false-negative test ruling by MRDTI to that of ruling by CUS. In the 2012 ACCP guidelines, the upper limit of the 95% confidence interval (95%CI) of the risk of a false negative serial CUS result in suspected recurrent ipsilateral DVT was estimated to be 6.5% in the setting of a 15% DVT prevalence.[9] In the largest relevant published study, the overall diagnostic failure rate of normal ultrasound findings compared to a reference CUS was 3.3% (5/153, 95%CI 1.2-7.6).[7] Accordingly, assuming a 3.3% incidence of our primary outcome and considering a maximum recurrent VTE failure rate of 6.5% as the upper limit of a safe test, we determined that a sample of 246 patients who had a MRDTI negative for DVT and who completed follow-up would provide 80% power to reject the null hypothesis that the incidence of recurrent symptomatic VTE would be greater than 6.5%, at an overall one-sided significance level of 0.05. Assuming a 15% prevalence of DVT at baseline and anticipating a 5% incidence of loss to follow-up, we aimed to include

305 patients.

Baseline characteristics are described as mean with standard deviation (SD) or median with interquartile range (IQR). The primary outcome was calculated with corresponding exact 95%CI. For the secondary outcome, in which we assessed interobserver agreement of MRDTI reading, the κ-statistic was calculated. The kappa value for agreement was interpreted as follows: poor (<0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or excellent (0.81–1.00).[21] Analyses were performed with the use of SPSS software, version 25.0.

RESULTS

Patients

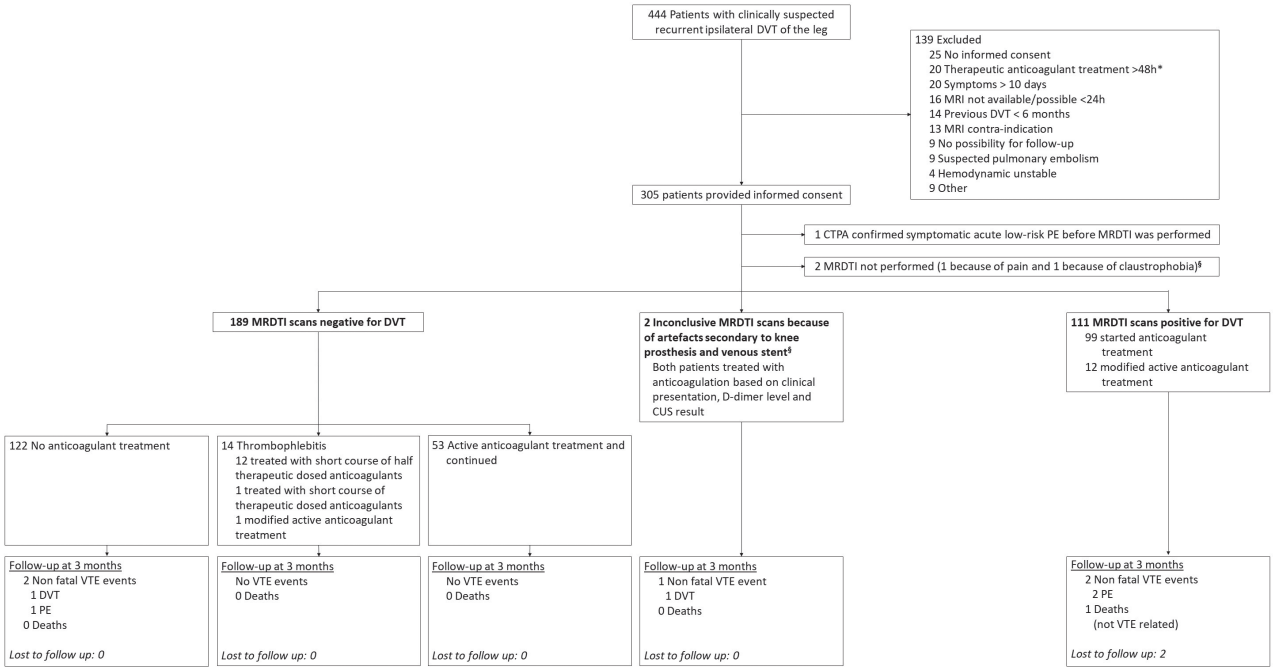
From March 2015 to March 2019, a total of 444 consecutive patients with clinically suspected acute recurrent ipsilateral DVT of the leg were screened; 139 patients (31%) were excluded for various reasons as per predefined exclusion criteria (**Figure 2**). The baseline characteristics of the 305 study patients are summarized in **Table 1.**

Table 1. Baseline characteristics of 305 patients with suspected recurrent ipsilateral DVT of the leg.

Mean age (+/- SD) – years	58 (16)
Male – no (%)	152 (50)
Median duration of complaints (IQR) – days	4 (2-7)
More than 1 prior VTE episode – no (%)	98 (32)
Mean time since the last DVT episode (+/- SD) – years	7 (9)
Active malignancy – no (%)	18 (5.9)
Immobility for > 3 days or recent long travel >6 hours in the past 4 weeks – no (%)	21 (6.9)
Trauma/surgery during the past 4 weeks – no (%)	11 (3.6)
Hormone (replacement) therapy – no (%)	6 (2.0)
Known genetic thrombophilia – no (%)	42 (14)

SD, standard deviation.

Figure 2. Flowchart of study patients.



**From August 2015 onwards, patients with suspected acute recurrent ipsilateral DVT on anticoagulant treatment were allowed in the study as they were found to represent a high proportion (30%) of the screened study population.*

§The patient with a venous iliac stent in whom the stent could not be visualized and the patient in whom MRDTI could not be performed because of extreme pain were both on anticoagulant treatment at inclusion.

Hence, a total of 68 patients were on anticoagulant treatment at inclusion, including 12 patients with a MRDTI scan positive for DVT, 1 patient with inconclusive MRDTI scan, 1 patient in whom MRDTI could not be performed, 53 patients with MRDTI negative for DVT and 1 patient with MRDTI negative for DVT but diagnostic for superficial thrombophlebitis.

MRDTI results

Of the 305 study patients, 189 patients (62%) had a MRDTI negative for DVT (**Figure 2**). Of the 189 patients, 122 patients (65%) had a MRDTI negative for both DVT and thrombophlebitis and were *off* anticoagulant treatment at inclusion. These patients were left untreated.

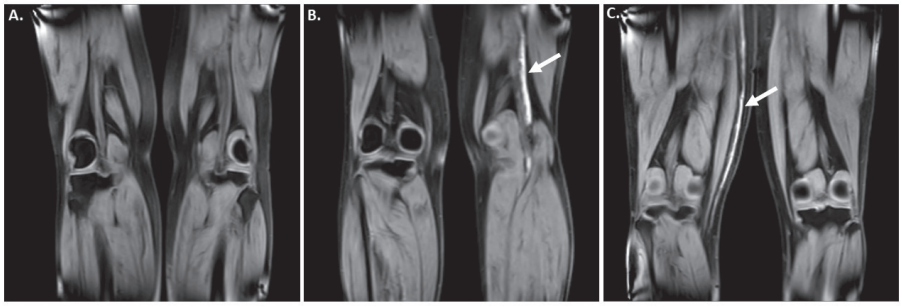
The MRDTI was negative for DVT but positive for superficial thrombophlebitis in 14 patients (7.4%). Twelve of these were treated with a short course of half-therapeutic dosed anticoagulants, while one patient was treated with short course of therapeutic dosed anticoagulants. One patient diagnosed with superficial thrombophlebitis was *on* anticoagulant treatment at time of inclusion and treatment was modified.

The remaining 53 patients (28%) were *on* anticoagulants at inclusion and continued with unmodified treatment as per previous indication.

Two of the 305 patients (0.66%) had an inconclusive MRDTI; one patient due to imaging artefacts secondary to a knee prosthesis and one patient with a venous iliac stent in whom the stent could not be visualized. Both patients were considered to have recurrent DVT based on elevated D-dimer and ultrasound results. MRDTI could not be performed in two additional patients: one due to extreme pain and one due to claustrophobia. These two patients were also judged to have recurrent DVT based on available diagnostic tests. One patient was incorrectly included and had both suspected recurrent DVT and acute PE at baseline; CTPA confirmed acute PE and treatment was started before MRDTI of the leg could be performed (which was considered as a protocol deviation).

A total of 111 patients (36%) had a MRDTI positive for DVT, of whom 99 patients were *off* anticoagulant treatment at the time of inclusion into the study and started anticoagulant treatment (**Figure 2**). Twelve patients were *on* anticoagulants at the time of study inclusion and their treatment was modified after diagnosis. Thus, the overall prevalence of recurrent DVT at baseline, including 111 patients with a MRDTI positive for DVT and the abovementioned 5 patients with recurrent VTE diagnosed otherwise, was 38% (116/305). The baseline prevalence of recurrent DVT in patients *on* anticoagulants at inclusion was 21% (14/68; **Figure 2**). **Figure 3** shows examples of MRDTI images of three individual patients in which a clear high signal intensity is seen in case of an acute thrombus and a symmetrical low signal intensity in the absence of an acute thrombus.

Figure 3. Coronal MRDTI images from three study patients: MRDTI negative for DVT with symmetric low signal intensity in both popliteal veins despite incompressible popliteal vein of the left leg upon CUS (Panel A); asymmetrical high signal intensity in the left popliteal vein diagnostic for acute recurrent DVT of the left leg (white arrow, Panel B); asymmetrical high signal intensity in the right great saphenous vein diagnostic for acute thrombophlebitis -but not DVT- in the right leg (white arrow, Panel C).



Primary outcome

In total, five patients met the primary outcome (**Table 2**), including two of the 122 patients with MRDTI negative for both DVT and thrombophlebitis and *off* anticoagulant treatment at baseline. The first patient developed CUS-confirmed ipsilateral DVT 21 days after immobilization during a long-haul flight. In addition to CUS, showing new incompressible venous segments compared to the reference CUS, a repeat MRDTI showed a positive signal for acute recurrent DVT. The second patient was referred for a reference CUS one day after the MRDTI negative for DVT, but instead presented at the emergency department with sudden shortness of breath. CTPA showed segmental PE. Both patients were treated with anticoagulants in an outpatient setting and had an uncomplicated follow-up. Three of the 122 patients developed thrombophlebitis during follow-up and were treated with anticoagulants; recurrent DVT was ruled out in all three patients. The incidence of recurrent VTE in patients with MRDTI negative for both DVT and thrombophlebitis and who were not treated with any anticoagulant during follow-up was thus 1.7% (2/119; 95%CI 0.20-5.9%; **Table 3**).

The 3-month incidence of the primary outcome in all patients with a MRDTI negative for DVT was 1.1% (2/189; 95%CI 0.13-3.8%; **Table 3**). Overall, two patients were lost to follow-up (0.66%; **Figure 2**).

Table 2. Overview of confirmed venous thromboembolism events during follow-up.

Baseline							Follow-up			
	Sex	Age (years)	Wells' score (points)	D-dimer concentration (ng/mL)	Anticoagulant therapy at presentation	MRDTI result	Interval to event (days)	Outcome	Clinical presentation	Adjudication
Patient 1	Female	60	2	6200	No	Negative	1	Pulmonary embolism	Patient was referred for a reference CUS 1 day after MRDTI negative for DVT, but presented at the emergency department with sudden shortness of breath. CTPA showed bilateral PE.	Non-fatal pulmonary embolism
Patient 2	Male	75	1	3200	No	Positive	4	Pulmonary embolism	Patient presented with acute dyspnea. CTPA showed PE in left pulmonary artery and bilaterally in lobar arteries.	Non-fatal pulmonary embolism
Patient 3	Female	33	1	< 220	No	Negative	22	Proximal DVT	Patient had recurrent ipsilateral proximal DVT after immobilization during a long-haul flight as demonstrated by a D-dimer test 3291 ng/mL, a CUS showing new incompressible venous segments and MRDTI indicative of acute DVT.	Non-fatal recurrent DVT
Patient 4	Male	27	2	860	No	Positive	26	Pulmonary embolism	Patient presented at emergency department with 2 days of thoracic pain. CTPA showed PE in right segmental pulmonary artery.	Non-fatal pulmonary embolism
Patient 5	Male	48	5	240	Yes	In-conclusive	77	In-stent thrombosis	Patient was diagnosed on CUS with recurrent iliac in-stent thrombosis.	Non-fatal recurrent DVT

Table 3. Primary outcome of the study.

Category	Patients (n)	Incidence of the primary outcome (%, 95%CI)
Patients with MRDTI negative for both DVT and thrombophlebitis who were not treated with any anticoagulant during follow-up*	119	1.7 (0.20-5.9)
All patients with MRDTI negative for DVT	189	1.1 (0.13-3.8)

**Patients who developed thrombophlebitis during follow-up were not included in this cohort because they received a course of anticoagulant treatment.*

Reference CUS

All 189 patients with MRDTI negative for DVT were subjected to a reference CUS examination *after* the treatment decision was made, showing incompressibility in 88 (47%). In the report of these reference CUS examinations, it was mentioned specifically that recurrent DVT was likely or could not be excluded in 57 patients (30%). Notably, prior CUS examinations for comparison were only available in 90 patients with MRDTI negative for DVT (48%). Of these 90 patients, recurrent DVT was likely or could not be excluded in 24 (27%).

Secondary outcomes

The agreement between initial local reading and post-hoc central reading of the MRDTI images was excellent (kappa statistic 0.91). Among the 444 screened patients, only 16 patients (3.6%) could not be included because the MRDTI was not available or possible to perform within 24 hours. The median time from study inclusion to performing the MRDTI was 4 hours (interquartile range 2-22 hours).

DISCUSSION

Our study demonstrates that the incidence of VTE recurrence after negative MRDTI was low. The failure rate among patients with baseline MRDTI negative for DVT who remained without anticoagulant treatment during follow-up was 1.7%,

with the upper limit of the 95%CI well below the predefined 6.5% safety threshold, as was the failure rate and upper limit of the confidence interval in all patients with a MRDTI negative for DVT.

MRDTI is a non-invasive technique that can visualize the metabolism of a fresh thrombus. When red bloods cells are trapped within a thrombus, hemoglobin within the red blood cells undergo oxidative denaturation to methemoglobin, which will cause shortening of T1-signal and this results in a high signal on a T1-weighted sequence.[11] Before the DTI signal will become positive, methemoglobin must be formed reliably within an acute clot. Profuse acquired or congenital methemoglobinemia will therefore not result in a positive DTI signal.[11] MRDTI was first described to diagnose a first episode of DVT, an observation that was confirmed in several cohorts.[11-13,15] Histological proof of the ability of MRDTI to detect acute thrombosis has been provided in the setting of chronic thromboembolic pulmonary hypertension: the location of a positive MRDTI signal in the pulmonary artery correlated 1:1 with fresh clots found in the surgical specimens of pulmonary artery endarterectomy performed one day after the MRDTI.[22]

The main advantage of the MRDTI technique in the setting of suspected recurrent ipsilateral DVT is the clear distinction between acute and chronic thrombosis, leading to a large reduction of inconclusive diagnoses from 30% in a previous cohort (mainly due to the poor interobserver agreement of the thrombus diameter measurement by CUS and the unavailability of reference CUS examinations) to less than 1% (2/305) in the present study.[3] The interobserver agreement of the MRDTI in our study was excellent (kappa statistic 0.91). This finding is consistent with the interrater agreement observed in a prospective study that evaluated the diagnostic accuracy of MRDTI for distinguishing acute recurrent ipsilateral DVT from chronic thrombi in leg veins (kappa statistic 0.98).[13] Moreover, MRDTI proved to be a feasible and reproducible diagnostic test across international academic and non-academic study sites.

An important methodological aspect of our study requires comment. From August 2015 onwards, patients with suspected acute recurrent ipsilateral DVT while on therapeutic anticoagulant treatment were allowed in the study as they were found to represent a high proportion of the screened study population. Canadian researchers have recently reported that 15% of VTE patients in a large management study were subjected to testing for suspected recurrence within the first year of treatment, underlining our experience.[23] In the setting of our study, many of the clinical presentations of recurrent DVT during anticoagulant treatment could likely

be attributed to the post-thrombotic syndrome (PTS), considering overlapping symptoms as well as the established association between incomplete thrombus resolution for both PTS and recurrent VTE.[24,25] To date, no published study has focused on the optimal diagnostic management of suspected recurrent ipsilateral DVT in anticoagulated patients. Given the clinical relevance and considering this current 'evidence free zone', we decided it was reasonable to allow these patients in the study. The 21% baseline prevalence of confirmed DVT in this patient group reassured us of the importance and validity of that decision.

What are the clinical implications of our study? First, MRDTI can now be used for therapeutic management decisions in patients with suspected recurrent ipsilateral DVT. Considering the relatively limited availability of MRI and its associated costs, MRDTI can currently not be suggested to be performed in *all* patients with suspected recurrent DVT. CUS is sufficient when there are no incompressible vein segments or if a thrombus is detected in a venous segment that was previously not affected by DVT, or that was normalized on a reference CUS. Secondly and equally important, the application of MRDTI in several other settings of notoriously difficult to diagnose acute VTE is now worthwhile evaluating, including upper extremity vein thrombosis[26], isolated pelvic vein thrombosis in pregnancy[27], cerebral vein thrombosis[28] and splanchnic vein thrombosis.

Strengths of our study include the prospective design, a large number of consecutive patients, near complete follow-up and independent adjudication of suspected endpoints. Moreover, the study was performed across several countries and hospital settings, and both 1.5 and 3.0 Tesla MRI machines of several manufacturers were used. Importantly, two thirds of the study sites had not performed MRDTI before the start of the study. This supports the external validity of our study and the wide applicability of our method and its results.

The main limitation of our study is the absence of a control group. Because this was not a randomized study, we could not compare the safety of MRDTI to the current standard diagnostic approach with CUS nor accurately determine the number of patients in whom anticoagulant treatment was prevented by MRDTI. Based on the reports of the reference CUS performed in patients with MRDTI negative for DVT, we estimate this latter number to be up to 19% (57/305) of the total study population, which is a considerable improvement of current practice. Second, although we do not expect a fast normalization of the MRDTI signal in patients with symptom duration exceeding 10 days, we excluded such patients from our study. Therefore, we cannot exclude the possibility of a lower sensitivity of MRDTI in patients with

longer or unknown duration of symptoms. Furthermore, 29% of patients with MRDTI negative for DVT were *on* anticoagulants at inclusion and continued this during the follow-up period and were thus largely protected from recurrent VTE. By analyzing the patients without any anticoagulant treatment during follow-up separately, we have corrected for this potential bias. Moreover, the high number of patients *on* anticoagulant treatment presenting with suspected recurrent DVT and their high 21% baseline prevalence of recurrent DVT support the decision to include these patients, especially in regard to the lack of evidence of diagnostic and therapeutic management of this patient subgroup. Lastly, we had estimated that 246 patients with MRDTI negative for DVT would be necessary to reject the null hypothesis. Due to the baseline prevalence of recurrent DVT being higher than anticipated and the inclusion of patients *on* anticoagulant treatment, this number was not met. The sample size was not adjusted as this was not anticipated in the study protocol and due to feasibility after study initiation. Nevertheless, the upper limit of the 95%CI of the primary endpoint in patients with MRDTI negative for DVT left untreated remained well below the predetermined safety threshold. Furthermore, according a recent statement of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, our observed low rate of diagnostic failures in the perspective of the high baseline DVT prevalence underlines the safety of ruling out recurrent ipsilateral DVT by MRDTI.[29]

In conclusion, the incidence of VTE recurrence after negative MRDTI was low. MRDTI proved to be a simple, feasible and reproducible diagnostic test. We suggest, that MRDTI can now be considered for therapeutic management decisions in patients with suspected recurrent ipsilateral DVT and an inconclusive compression ultrasound result. Furthermore, MRDTI creates new opportunities for accurate diagnosis in other challenging settings of suspected acute venous thrombosis.

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3

CHAPTER

Cost-effectiveness of magnetic resonance imaging for diagnosing recurrent ipsilateral deep vein thrombosis

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ABSTRACT

The diagnostic workup of recurrent ipsilateral deep vein thrombosis (DVT) using compression ultrasonography (CUS) can be complicated by persistent intravascular abnormalities after a previous DVT. We showed that magnetic resonance direct thrombus imaging (MRDTI) can exclude recurrent ipsilateral DVT. However, it is unknown whether the application of MRDTI in daily clinical practice is cost-effective. We aimed to evaluate the cost-effectiveness of MRDTI-based diagnosis for suspected recurrent ipsilateral DVT during first year of treatment and follow-up in the Dutch health care setting.

Patient-level data of the Theia study (NCT02262052), were analyzed in 10 diagnostic scenarios, including a clinical decision rule (CDR) and D-dimer test, and imaging with CUS and/or MRDTI. The total costs of diagnostic tests and treatment during 1-year follow-up, including costs of false-positive and false-negative diagnoses, were compared and related to the associated mortality. The 1-year health care costs with MRDTI (range, €1219 to €1296) were generally lower than strategies without MRDTI (range, €1278 to €1529). This was because of superior specificity, despite higher initial diagnostic costs. Diagnostic strategies including CUS alone and CUS followed by MRDTI in case of an inconclusive CUS were potential optimal cost-effective strategies, with estimated average costs of €1529 and €1263 per patient and predicted mortality of 1 per 737 patients and 1 per 609 patients, respectively. Our model shows that diagnostic strategies with MRDTI for suspected recurrent ipsilateral DVT have generally lower 1-year health care costs than strategies without MRDTI. Therefore, compared to CUS alone, applying MRDTI did not increase health care costs.

INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), poses a major health care burden.[1] In the Netherlands alone the costs for VTE management in 2015 was approximately 23 million euros for hospital treatment of almost 25,000 VTE patients, and 14.4 million euros for anticoagulants which increased to 38.2 million euros in 2017 because of the introduction of direct oral anticoagulants (DOACs).[2] The yearly total annual health care costs for VTE in the United States were estimated to be 2 to 10 billion dollars for 300,000-600,000 incident cases.[3] These costs were exclusive of costs for anticoagulant-related bleeding complications and thus true VTE costs are even higher. Therefore, an accurate VTE diagnosis to prevent false-positive diagnosis and subsequent mistreatment is crucial both for individual patients and society as a whole. Notably, the diagnostic management of suspected VTE is still complex in certain settings such as suspected recurrent DVT. The safety of using a clinical decision rule (CDR) in combination with D-dimer testing to rule out recurrent DVT is not established [4,5] and seems not as efficient as in patients with a suspected first DVT episode.[5,6] Moreover, ultrasonographic differentiation of acute recurrent ipsilateral DVT from chronic residual thrombi is difficult, with persisting thrombi being present in up to 50% of patients after 1 year despite adequate treatment.[6-8]

Magnetic resonance direct thrombus imaging (MRDTI) is a non-invasive magnetic resonance imaging technique that directly visualizes acute thrombi.[9] MRDTI has been shown to accurately distinguish acute recurrent DVT from chronic residual thrombotic abnormalities [10-12] and was proven to be an accurate, simple, feasible and reproducible diagnostic test for ruling out acute recurrent ipsilateral DVT.[13] Importantly, compression ultrasonography (CUS), which currently is the imaging test of choice in suspected recurrent DVT, was found to be associated with an excess of false-positive diagnoses of 19% compared to MRDTI [13]. Furthermore, in contrast to MRDTI, the CUS interpretation may vary greatly among radiologists.[14] As MRDTI is more expensive than CUS the cost aspect should also be taken into account when determining the optimal diagnostic strategy.

We set up to perform a 1-year cost-effectiveness analysis of different diagnostic scenarios with or without MRDTI for suspected recurrent ipsilateral DVT, specifically in the Dutch health care setting to better determine the potential role of MRDTI in daily clinical practice.

METHODS

Study population

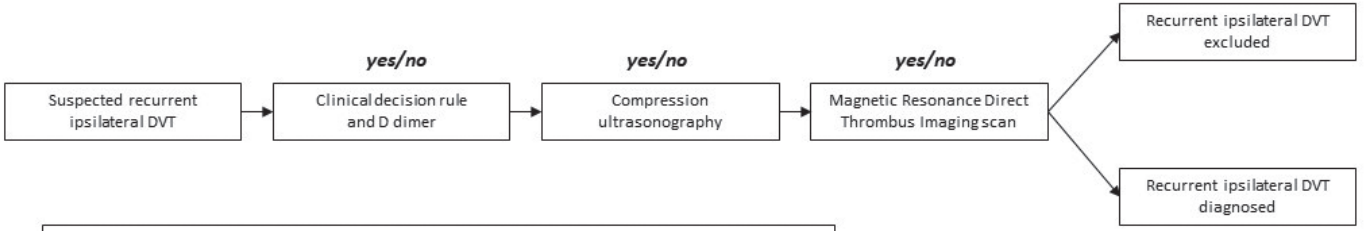
This study was a predefined secondary analysis of the Theia study (NCT02262052), a prospective international multicenter outcome study in which we evaluated the safety of excluding recurrent ipsilateral DVT with MRDTI. The full details of the study design and outcomes have been described previously.[13] In summary, between March 2015 to May 2019 adult patients with suspected recurrent ipsilateral proximal DVT of the lower extremity on or off anticoagulant treatment were managed according the result of the MRDTI scan. Main exclusion criteria were suspected concomitant acute PE, CUS-proven acute DVT within 6 months of presentation and general contra-indications for magnetic resonance imaging. CUS was performed as a reference examination in all patients with a MRDTI negative for DVT to guide diagnostic testing if suspected recurrence occurred during follow-up. Furthermore, the protocol dictated CDR assessment using the original Wells rule and D-dimer testing in all patients. Importantly, CUS, CDR assessment and D-dimer results did not influence management decisions. All included patients were followed for a 3-month period for the occurrence of recurrent VTE (DVT or PE), anticoagulation-associated major bleeding and all-cause mortality. For the current analysis, the results of the Theia study were extrapolated to the Dutch situation, excluding patients who were on anticoagulant treatment ≥48 hours prior to inclusion.

Study objectives and outcomes

The aim of this analysis was to compare the health care costs between 10 diagnostic scenarios for the diagnostic management of suspected recurrent ipsilateral DVT, in relation to the associated mortality. The scenarios included CDR assessment according to the Wells criteria in combination with D-dimer testing, and diagnostic imaging with CUS and/or MRDTI (**Figure 1**). In the scenarios including CUS, results were defined as either normal/abnormal or positive/negative/inconclusive; the latter is only applicable if a reference CUS was available.[15]

The first five scenarios included only diagnostic imaging tests. In the first scenario, MRDTI would have been performed in all patients and anticoagulant treatment

Figure 1. Ten diagnostic scenarios for the diagnostic workup of suspected recurrent ipsilateral deep vein thrombosis (DVT), applying various combinations of a clinical decision rule and D-dimer testing (CDR+DD) and diagnostic imaging with compression ultrasound (CUS) and/or magnetic resonance direct thrombus imaging (MRDTI).



10 diagnostic scenarios:

1. MRDTI only
2. CUS (normal/abnormal) only
3. CUS (positive/negative/inconclusive) only
4. Only CUS (normal/abnormal) in case of a likely CDR and/or abnormal DD
5. Only CUS (positive/negative/inconclusive) in case of a likely CDR and/or abnormal DD
6. Only MRDTI in case of an abnormal CUS
7. Only MRDTI in case of an inconclusive CUS
8. Only MRDTI in case of a likely CDR and/or abnormal DD
9. Only MRDTI in case of a likely CDR and/or abnormal DD and an abnormal CUS
10. Only MRDTI in case of a likely CDR and/or abnormal DD and an inconclusive CUS

would have been started in case of a MRDTI positive for DVT. In the second scenario, all patients would have been referred for CUS, which was either normal or abnormal, and anticoagulant treatment would have been started in case of an abnormal CUS. In the third scenario, CUS would have been performed in all patients, but the results were judged as positive/negative/inconclusive and anticoagulant treatment would have been started in patients with a positive or inconclusive CUS. In the fourth scenario, all patients would have been referred for CUS and MRDTI would be performed in case of an abnormal CUS. Anticoagulant treatment would have been started in patients with a MRDTI positive for recurrent DVT. In the fifth scenario, CUS would have been performed in all patients and only patients with an inconclusive CUS would have been referred for MRDTI. Anticoagulant treatment would have been started based on a positive MRDTI or positive CUS result. In scenario 6 to 10, the combination of CDR assessment and D-dimer testing was added as initial step to scenario 1 to 5. Diagnostic imaging (CUS and/or MRDTI) would only be performed in patients with a likely clinical probability and/or abnormal D-dimer result.

Definitions

A likely clinical probability according the Wells rule was defined as a Wells score of ≥2 points.[16] An abnormal D-dimer test was defined as abnormal according the assay dependent threshold, because this differed between the various assays used in the Theia study. An evaluation of the diagnostic performance of the Wells rule and D-dimer testing in the Theia study was recently published.[17] A normal CUS was defined as full compressibility along the venous system. An abnormal CUS was defined as 1 or more non-compressible venous segments. A positive CUS was defined as a new non-compressible segment or a ≥2-4 mm increase in vein diameter of a previously non-compressible venous segment when compared to a reference CUS. A negative CUS was defined as the absence of a non-compressible segment or the absence of a new non-compressible segment in comparison with a reference CUS and a <2 mm increase in vein diameter of a previously non-compressible vein. An inconclusive CUS was defined as 1 or more non-compressible venous segment(s) in the absence of a reference CUS for comparison. An MRDTI scan positive for acute DVT was defined as a high signal intensity in the location of a deep vein against the suppressed background greater than that observed in the contiguous segments or corresponding ipsilateral vein. Major bleeding

and clinically relevant non-major (CRNM) bleeding were defined according to the *International Society on Thrombosis and Haemostasis* (*ISTH*) criteria.[18,19]

Costs

One-year health care costs are reported in euros at price level of 2019 and included diagnostic, anticoagulant medication, management and bleeding complication costs (**Table 1**). The diagnostic costs included initial admission costs at the emergency department (ED) and costs for basic laboratory measurements for all patients. Depending on the diagnostic scenario, additional costs for the diagnostic tests (D-dimer, CUS and/or MRDTI) were included.

Anticoagulant medication costs for a 1-year period were calculated including the price of the medication itself (including value-added tax) and an additional €6 delivery costs of the medication per regular delivery.[20] Data from IQVIA, a global health care data source company, were used to estimate the proportions of the different types of anticoagulants, including DOACs, vitamin K antagonists (VKAs) and low-molecular weight heparins (LMWHs). For the estimation of the costs of LMWH, the price of Nadroparin was used, since it is the most prescribed LMWH in the Netherlands.[21] Since data of the average body weight in the Theia study population were not available, we used the mean body weight from a recent Dutch study, in which a CDR was evaluated in patients with suspected acute PE.[22]

For the estimation of the management costs, costs for hospital admission, outpatient visits and compression stockings for patients diagnosed with recurrent DVT were calculated. Data on hospital admission rate and duration were not available for the Theia study population. Therefore, hospital admission costs were estimated assuming that 14% of patients diagnosed with recurrent DVT would be hospitalized, for a mean duration of 7.2 days, based on available literature.[23,24] The outpatient visit costs included 2 routine visits which was in accordance with local hospital protocols. We estimated that all patients diagnosed with recurrent DVT (at baseline or during follow-up period) would be treated with (at least) 1 pair of class II compression stockings.

Finally, costs caused by bleeding complications were calculated by multiplying the costs per complication with the estimated risk for bleeding in VKA and DOAC treatment and the estimated number of VKA and DOAC users (**Table 1**). The risk for bleeding in VKA versus DOAC treatment was obtained from previous publications

and was set at 1.7% versus 1.1% for non-intracranial major bleeding, 0.25% versus 0.09% for intracranial bleeding and 8.4% versus 6.6% for CRNM bleeding.[25]

For this analysis, initial diagnostic costs were defined as diagnostic costs including ED admission, and both laboratory and imaging costs for the first hospital presentation. Return diagnostic costs included the costs for ED readmission, and both laboratory and imaging costs for patients returning for repeated diagnostic imaging after a missed DVT diagnosis. The treatment costs were defined as anticoagulant medication costs, management costs and costs for bleeding complications for all patients with recurrent DVT. The overtreatment costs included the anticoagulant medication costs, management costs and costs for bleeding complications for patients who were falsely diagnosed with recurrent DVT.

Decision analytic model

From patient-level data of the Theia study, the prevalence of recurrent ipsilateral DVT was calculated as was the diagnostic accuracy of each test, conditional to the outcome of preceding tests and disease prevalence (**Figure 1**). From these, the true-positive, false-negative, true-negative, and false-positive rates of each of the 10 diagnostic scenarios were estimated. False negative diagnoses (also referred to as misdiagnosis in this analysis) were defined as 1) patients in whom recurrent DVT was excluded based on an unlikely CDR in combination with a normal D-dimer or based on a negative CUS but with a positive MRDTI for recurrent DVT or 2) patients in whom recurrent DVT was excluded based on a negative MRDTI but with recurrent VTE during 3 months of follow-up. False positive diagnoses were defined as patients with a positive or inconclusive CUS, but negative MRDTI for recurrent DVT. For reference, we also assessed scenarios that treat all patients, treat no patients and treat only those patients with a likely CDR and/or abnormal D-dimer (i.e. scenarios without imaging tests). These reference scenarios are hypothetical and do not serve as a realistic or ethically defendable scenarios for clinical practice.

For each scenario, costs of diagnostic tests were counted for the number of patients undergoing the tests. For each true-negative outcome, only the initial diagnostic costs were counted (**Figure 2**). For each true-positive and false-positive outcome additional treatment and overtreatment costs, respectively were counted. For false-negative outcomes, we conservatively made the following three assumptions. First, we assumed that all patients with a false-negative diagnosis would return to the ED for repeated diagnostic testing. Second, the costs of the

Table 1. The total 1-year health care costs, including diagnostic, anticoagulant medication, management and bleeding complication costs

Resources		Specification	Prices, € (2019)	Volume	Percentage	Average costs per patient per year	Source
Diagnostic costs	ED admission		276.61	1.00	100%	276.61	Kanters et al, 2017[40]
	Laboratory test*	Without D-dimer	24.84	1.00	100%	24.84	Kosteninkaart, 2018[41]
		Including D-dimer	34.54	1.00	100%	34.54	Kosteninkaart, 2018[41]
	Radiologic imaging	CUS	107.60	1.00	100%	107.60	Kosteninkaart, 2018[41]
		MRDTI	237.87	1.00	100%	237.87	Kosteninkaart, 2018[41]
Anticoagulant medication costs	DOACS (day)	Apixaban	4.49 the first 7 days, 2.25 thereafter	1.00	17.2%	143.95	Zorginstituut N.[20]
		Rivaroxaban	4.71 the first 21 days, 2.35 thereafter for 6 months, 2.50 thereafter	1.00	53.6%	501.19	Zorginstituut N.[20]
		Dabigatran	2.44, prior 5 day LMWH use	1.00	4.8%	45.23	Zorginstituut N.[20]
		Edoxaban	2.44, prior 5 day LMWH use	1.00	4.8%	45.23	Zorginstituut N.[20]
	VKA (day)		0.09, prior 7-day LMWH use	1.00	17%	17.89	Zorginstituut N.[20]
	LMWH (day)		10.34	1.0	2.6%	0.27	Zorginstituut N.[20]
Management costs	Hospital admission (day)		512.44	7.2	14%	512.44	Kanters et al, 2017[40]
	Outpatient visit		97.19	2.0	100%	194.38	Kanters et al, 2017[40]
	Compression stockings		71.45	1.0	100%	71.45	Steunkousen.nl[42]
Bleeding costs	Non-intracranial major bleeding		5,348.23	1.0	1.14%	60.93	De Jong et al, 2017[43]
	Intracranial bleeding (acute care)		21,759.32	1.0	0.10%	21.87	De Jong et al, 2017[43]
	Intracranial bleeding (long-term care)		62,838.54	1.0	0.10%	63.17	De Jong et al, 2017[43]
	CRNM bleeding		32.62	1.0	6.72%	2.19	De Jong et al, 2017[43]

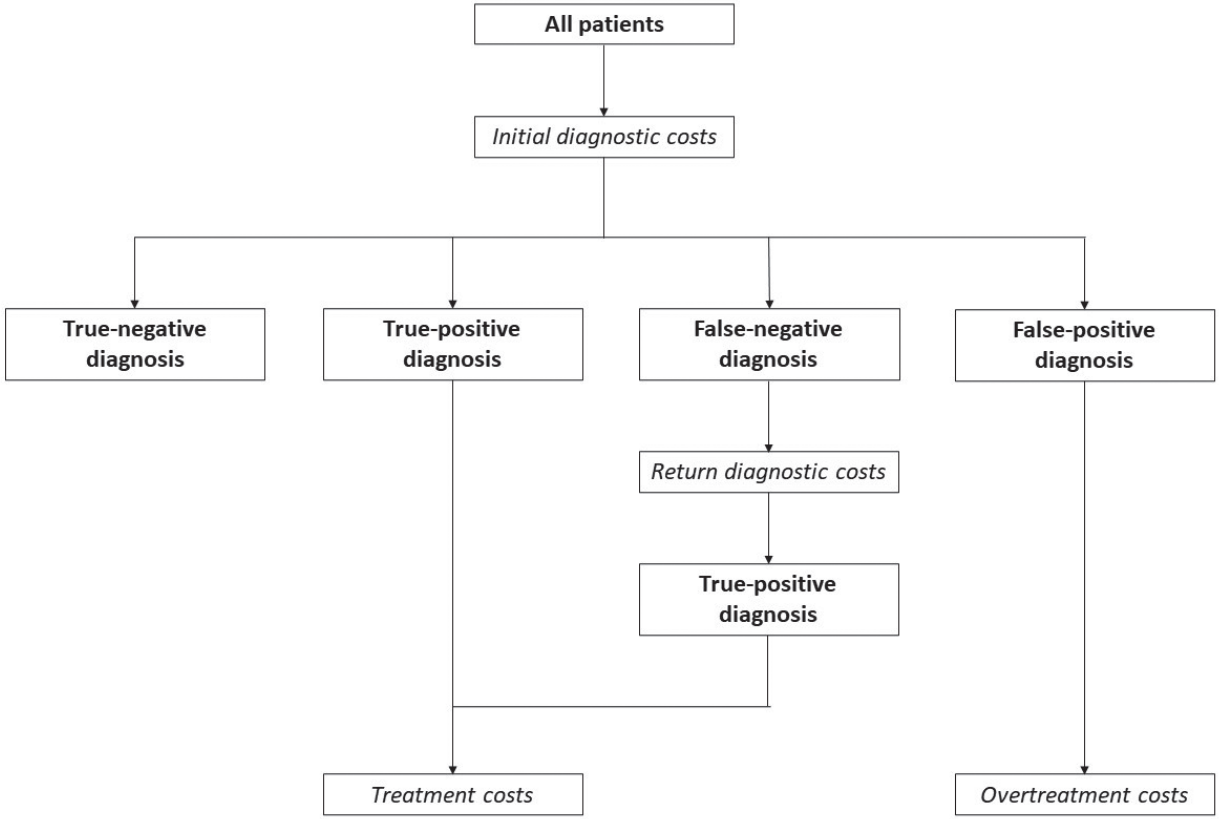
**Laboratory costs included order for collection of blood, hemoglobin/hematocrit and cell indices, leukocytes, thrombocytes, creatine (and estimated glomerular filtration rate), urea, sodium and potassium levels, and bleeding time tests.*

repeated diagnostic testing (i.e. return diagnostic costs) would be the same as at initial presentation, except for the following scenarios: a) in scenarios including CDR assessment and D-dimer testing and radiologic imaging (CUS and/or MRDTI) were only repeated radiological testing would be performed and b) in scenarios including MRDTI after CUS were only repeated CUS would be performed. And thirdly, we assumed that all patients with an initial false-negative diagnosis would have a true-positive diagnosis at the repeated diagnostic testing and thus included treatment costs as for models were a true-positive diagnosis was made.

The mortality risk included three types of mortality: 1) mortality from misdiagnosis, 2) from recurrent fatal PE and 3) from anticoagulant-related bleeding.1) For the mortality risk associated with misdiagnoses, we considered the probability of death for the time period between the false-negative diagnosis and the moment of the true-positive diagnosis, using the exact timelines observed in the Theia study. This was estimated as a fixed 2.05% of the number of false-negative diagnoses, i.e. obtained from previous publications that 50% of the patients with DVT would have asymptomatic PE and 4.1% of all PEs is fatal [26-30]. 2) The mortality risk as a result of recurrent fatal PE during 1-year follow-up period was calculated for patients with a false-positive, true-positive or initial false-negative and true-negative diagnosis. 2a) The risk for mortality from recurrent fatal PE in patients with a false-positive diagnosis was set as 0.0%, as the risk for fatal PE in patients with no recurrent DVT at baseline, but who were falsely treated with anticoagulants is estimated to be negligible. 2b) The risk for mortality from recurrent fatal PE during anticoagulant treatment in patients with a true-positive diagnosis and an initially false-negative diagnosis was set at 0.07%, which was obtained from previous publications.[25] 2c) Mortality as result of recurrent fatal PE in true-negative patients without anticoagulant treatment was estimated as 0.18%, also obtained from previous studies.[31,32] 3) The mortality risk as a result of bleeding related to anticoagulant treatment was estimated as 0.07% of the number of those treated with anticoagulants (i.e. true-positives, false-negatives and false-positives), including 0.06% among DOAC users versus 0.17% among VKA users.[25]

For each diagnostic scenario, the estimated 1-year health care costs were plotted against the estimated mortality. Diagnostic scenarios with costs and mortality equal or higher than other scenarios were not considered cost-effective.[33] The remaining scenarios constitute the efficient frontier, i.e. the set of potentially most cost-effective strategies. For these scenarios incremental cost-effectiveness ratios (ICERs) were calculated, defined by the difference in costs divided by the difference in mortality. The estimated costs per-prevented-death ratios were used

Figure 2. Flowchart of diagnostic and (over)treatment costs for each diagnosis



to select the optimal scenario. In the Netherlands, interventions are considered cost-effective up to 20,000 to 80,000 euros per quality-adjusted life years (QALY).[34] Assuming a quality-adjusted life expectancy of about 25 years in our population, these thresholds translates to 0.5 to 2 million euros per prevented death.[35,36] Microsoft Excel (2016) was used to perform all analyses.

RESULTS

Study patients

The Theia study flowchart was described in previous publications from the Theia study.[13,17] A total of 234 patients were included in this analysis, excluding 71 patients for the following reasons: therapeutic anticoagulant treatment ≥48 hours prior to presentation (n=68), inconclusive MRDTI because of artefacts (n=1), MRDTI not performed because of claustrophobia (n=1) and protocol deviation (n=1). The baseline characteristics of the study population are shown in **Table 2**. The DVT prevalence (baseline and 3-months follow-up combined) was 43% (100/234). The diagnostic accuracy of each test, depending on preceding tests, are reported in **Table 3**.

Table 2. Baseline characteristics of 234 patients with suspected recurrent ipsilateral deep vein thrombosis included in this analysis.

Characteristics	*Data*
Mean age (+/- SD) – years	56 (16)
Male – no (%)	110 (47)
Median duration of complaints (IQR) – days	4 (2-7)
More than 1 prior VTE episode – no (%)	50 (21)
Mean time since the last DVT episode (+/- SD) – years	6.9 (9.2)
Active malignancy – no (%)	10 (4.3)
Immobility for >3 days or recent long travel >6 hours in the past 4 weeks – no (%)	15 (6.4)
Trauma/surgery during the past 4 weeks – no (%)	9 (3.8)
Hormone (replacement) therapy – no (%)	5 (2.1)
Known genetic thrombophilia – no (%)	19 (8.1)

Table 3. Average 1-year health care costs and mortality for 10(+3) diagnostic scenarios for the diagnostic workup of suspected recurrent ipsilateral deep vein thrombosis (DVT).

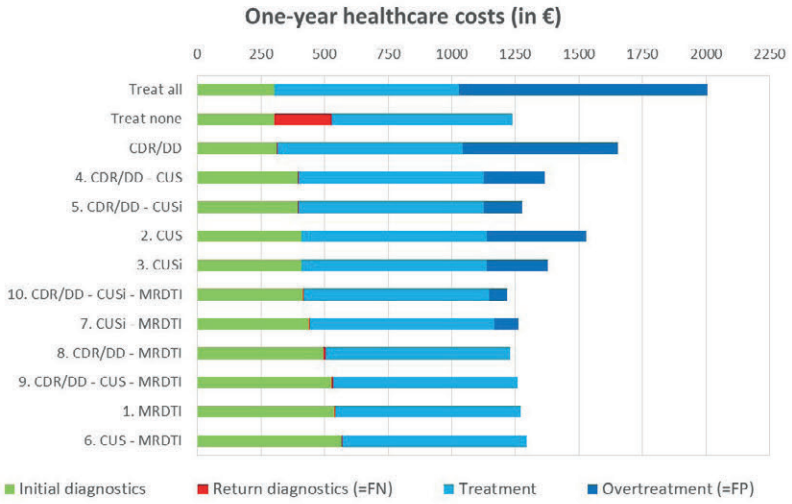
Diagnostic scenario	Sensitivity (%)	Specificity (%)	Initial diagnostics costs (€) (All patients)	Return diagnostic costs (€) (For FN)	Treatment costs (€) (For TP+FN)	Overtreatment costs (€) (For FP)	Total 1-year health care costs (€)	Mortality due to misdiagnosis per 10,000	Mortality recurrent fatal PE per 10,000	Mortality due to bleeding per 10,000	Total mortality per 10,000 patients
Treat all	100	0	301	0	727	975	2004	0	3	7	10
Treat none	0	100	301	225	727	0	1239	88	13	3	104
CDR+DD	98	37	311	5	727	611	1654	2	7	5	14
1. MRDTI	98	100	539	5	727	0	1271	2	13	3	18
2. CUS	100	60	409	0	727	393	1529	0	9	4	14
3. CUSi	99	75	409	2	727	240	1378	1	11	4	15
4. CDR+DD-CUS	98	75	395	3	727	240	1365	2	11	4	16
5. CDR+DD-CUSi	98	84	395	3	727	153	1278	2	12	3	17
6. CUS-MRDTI	98	100	566	3	727	0	1296	2	13	3	18
7. CUSi-MRDTI	99	90	440	2	727	95	1263	1	12	3	16
8. CDR+DD-MRDTI	97	100	496	7	727	0	1230	3	13	3	19
9. CDR+DD-CUS-MRDTI	97	100	528	5	727	0	1260	3	13	3	19
10. CDR+DD-CUSi-MRDTI	98	93	415	3	727	73	1219	2	13	3	17

CDR+DD, clinical decision rule + D-dimer testing; CUSi, compression ultrasonography is positive, negative, or inconclusive; FN, false negatives; TP, true positive; FP, false positive.

Costs

The estimated total 1-year health care costs per patient for all diagnostic scenarios are shown in **Figure 3** and **Table 3**. Although MRDTI itself is more expensive than CUS, health care costs of diagnostic management strategies including MRDTI (range €1219 to €1296) were calculated to be comparable or lower than diagnostic strategies without MRDTI (range €1278 to €1529) because of superior specificity (sensitivity, 97-99% vs 98-100%; specificity, 90-100% vs 60-84%).

Figure 3. One-year health care costs per patient for the 10 diagnostic scenarios, and a scenario to treat all, treat none and treat those with a likely clinical probability and/or abnormal D-dimer without diagnostic imaging.



CDR+DD, clinical decision rule + D-dimer testing; CUSi, compression ultrasonography is positive, negative, or inconclusive; FN, false negatives; FP, false positives.

When CDR and D-dimer testing were applied as initial diagnostic tests, health care costs were lower, even considering the higher false negative rate. This could be explained by the lower initial diagnostic costs, because of decreased imaging costs, and the lower false-positive rate. The diagnostic strategy including CDR and D-dimer testing, CUS and subsequent MRDTI in case of an inconclusive CUS was associated with the lowest 1-year health care costs of €1219 (scenario 10). The diagnostic strategy including CUS (normal/abnormal) and treatment in all patients

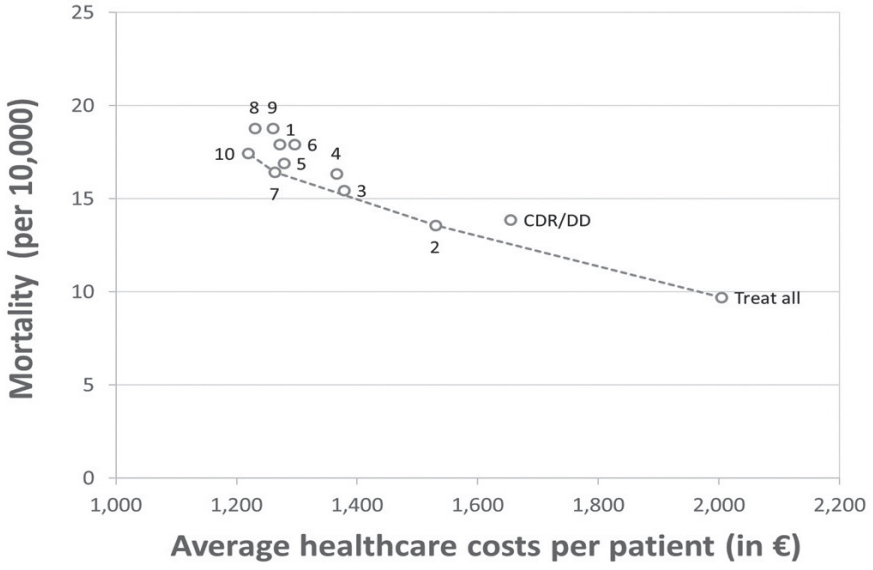
with an abnormal CUS (scenario 2) would be the most expensive strategy (1-year health care costs of €1529), because of high false-positive rates. Notably, the most and least expensive strategy differed for only €320, which is a relatively limited difference.

Cost-effectiveness

The estimated total 1-year health care costs of each diagnostic scenario were plotted against the predicted mortality per 10,000 patients (**Figure 4** and **Table 3**). Strategies at the bottom left of the figure are optimal, with low costs and low mortality. The diagnostic strategy that treats all patients had the lowest predicted mortality (1 per 1029 patients), but with highest estimated total health care costs. Four diagnostic scenarios were on the efficient frontier and thus potentially the most cost-effective strategies: CDR and D-dimer testing followed by CUS (positive/negative/inconclusive) and MRDTI (scenario 10), CUS (positive/negative/inconclusive) followed by MRDTI (scenario 7), CUS (normal/abnormal) alone (scenario 2) and the treat all scenario. All other strategies were dominated, with either higher health care costs or higher mortality.

Of the four scenarios on the efficient frontier, diagnostic scenario 10 has the lowest estimated costs of on average €1219 per patient with a predicted mortality of about 1 per 573 patients. Compared to this scenario 10, diagnostic scenario 7 increases average costs by €45 per patient and reduces mortality to 1 per 609 patients. The associated ICER for scenario 7 versus 10 is 0.4 million euros per prevented death. Scenario 2 further increases average costs by €266 per patient and decreases the predicted mortality to 1 per 737 patients. Here, the associated ICER of scenario 2 versus 7 is 0.9 million euros per prevented death. In the treat all scenario the average cost per patient further increases with €475 compared to scenario 2, while the estimated mortality decreases to 1 per 1029 patients. The associated ICER of the treat all scenario versus scenario 2 is 1.2 million euros per prevented death. For an acceptability threshold of 0.5 to 2 million euros per prevented death, scenario 10 is discarded, because scenario 7 provides lower mortality at acceptable costs (as $0.4 < 0.5$ million). Thus, scenarios 7 and 2 and the treat all scenario remain as potentially optimal strategies (as $0.5 < 0.9 < 1.2 < 2$ million).

Figure 4. Cost-effectiveness plane and efficient frontier (dashed lines) indicating the possibly cost-effective options among the 10 diagnostic scenarios and a scenario to treat all, treat none and treat those with a likely clinical probability and/or abnormal D-dimer without diagnostic imaging (depending on willingness to pay to prevent mortality)**.**



DISCUSSION

Our aim of this analysis was to compare the estimated total 1-year health care costs in the Dutch clinical setting between different diagnostic scenarios in case of suspected recurrent ipsilateral DVT, in relation to the associated predicted mortality. We found that diagnostic strategies applying MRDTI have comparable or higher diagnostic accuracy at generally lower 1-year health care costs. Moreover, the diagnostic strategy including CUS followed by MRDTI in case of an inconclusive CUS was a potential optimal cost-effective strategy. The diagnostic strategies including CUS alone and treat all were also potential optimal strategies, but the treat all scenario is not realistic or ethically defendable for clinical practice.

Recently, MRDTI was proven to be an accurate, simple, feasible and reproducible diagnostic test in suspected recurrent ipsilateral DVT.[13] Even so, as a MRDTI scan is more expensive and less available than a CUS examination, hospitals may choose diagnostic strategies with CUS over strategies including MRDTI. Our model shows

that the total health care costs of strategies including MRDTI were comparable or even lower compared to strategies without MRDTI. Savings on treatment costs resulted from the higher specificity of MRDTI and thus less false-positive diagnoses compared to CUS. This was also found in previous publications in which CUS could not exclude recurrent DVT in 30% of patients with suspected recurrent ipsilateral DVT[7,13], resulting in overtreatment and subsequent risk for major bleeding.

Strengths and limitations

This study presents a cost-effectiveness model in which detailed estimation of patient-level costs for different diagnostic strategies are calculated. The strength of this analysis is the use of a large patient cohort to estimate the diagnostic accuracy of each test and estimate the true-positive, false-negative, true-negative, and false-positive rate of each of the 10 diagnostic scenarios. Moreover, the original study included an accurate follow-up of the included patients and adjudication of endpoints by an independent committee. Therefore, we believe that this analysis provides an accurate overview of the total health care costs in different diagnostic strategies for a Dutch health care setting.

Our model has also limitations especially since the validity and robustness of the model is depending on the impact of uncertainties in key input parameters. First, the results must be interpreted within the framework and limitation of findings of the Theia study. One of these limitations is that Theia study included a relatively limited number of patients resulting in broad confidence interval of the primary outcome. Moreover, this was a management study in which a cohort of patients followed a study algorithm in which they were subjected and treated according the MRDTI result and not according CDR, D-dimer and CUS results. Also, D-dimer levels and CUS results were not available for all patients. Even so, since few limiting exclusion criteria were applied in the Theia study, the presented results of the current study are more generalizable to a broad patient population than those from a randomized controlled trial.

Second, accurate mortality estimates could not be obtained from our Theia cohort, as none of the patients died from a missed diagnosis, recurrent fatal-PE or anticoagulant-related bleeding. We therefore estimated these risks from available literature, but this resulted in some counter-intuitive estimates: anticoagulation treatment was optimal even for true negative patients, as the 0.18% decrease in recurrent PE mortality outweighed the 0.07% bleeding mortality from

anticoagulation treatment. It is possible that the mortality risk as a result of anticoagulant-related bleeding is underestimated, as this was extrapolated from randomized controlled trials that included low-risk patients. As a result, the treat all strategy provided the lowest possible mortality in our analysis. Nevertheless, we do not consider this strategy a good advice.

Third, long-term complications of a missed DVT, including post-thrombotic syndrome (PTS), chronic thrombo-embolic pulmonary hypertension (CTEPH) and post-PE syndrome due to delayed or total lack of anticoagulant treatment, were not included in the analyses.[37-39] The reason is difficulty in estimating the impact of these long-term complications on health care costs.

Fourth, we estimated costs per prevented death, whereas in the Netherlands only threshold for costs per QALY are used. These QALY thresholds roughly translate to 0.5 to 2 million euros per prevented death in our population. Based on this range of acceptability thresholds the diagnostic scenarios including CUS alone, CUS followed by MRDTI in case of an inconclusive CUS and treat all were potential optimal strategies.

Finally, this analysis was based on a Dutch health care setting and health care costs for DVT may vary by country. Also, the hospital length of stay (LOS) may differ in other settings. For the current analysis, LOS was based on available literature which included no studies specifically in patients with suspected recurrent DVT. It is therefore possible, that the true LOS is higher due to higher comorbidity rate in suspected recurrent DVT patients compared to patients with suspected first DVT episode. On the other hand, most studies were performed before the DOAC era and thus LOS in these studies may be longer due to routine laboratory monitoring and injectable bridging therapy in anticoagulant management with LMWHs and VKA's. We performed a sensitivity analysis to compare the total health care costs in the setting with 3 hospitalization days instead of 7.2 days and did not find relevant differences.

Clinical implications

What is the relevance of our findings for clinical practice? First, our model shows that there is a very small difference in the total 1-year health care costs between the different diagnostic scenarios. In contrast to what many clinicians may believe, strategies including MRDTI were not more expensive than strategies without

MRDTI but had comparable or higher diagnostic certainty. Importantly, due to uncertainty of the risk for recurrent VTE, bleeding and mortality at long-term, we did not calculate the total health care costs >1 year. Even so, the results would then be even more favorable for strategies including MRDTI, with a lower false-positive rate, since patients diagnosed with recurrent DVT are often treated with lifelong anticoagulants with subsequent risk for bleeding. This result, in the view of this detailed cost-effectiveness analysis, is an argument to incorporate the MRDTI scan in local protocols and international guidelines for the diagnostic work-up of suspected recurrent ipsilateral DVT in daily clinical practice. Since we did not directly compare the different strategies prospectively and had to base the model on several assumptions, we cannot determine which one would be the best strategy. Our analysis does however suggest to omit costs as a reason to dismiss the use of MRDTI in the diagnostic management of suspected recurrent ipsilateral DVT.

In conclusion, our analysis shows that the diagnostic strategies involving MRDTI for suspected recurrent ipsilateral DVT have comparable or lower total 1-year health care costs, compared to strategies without MRDTI. Therefore, compared to CUS alone, applying MRDTI in clinical practice will not increase health care costs.

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4

CHAPTER

Safety of using the combination of the Wells rule and D-dimer test for excluding acute recurrent ipsilateral deep vein thrombosis

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ABSTRACT

Background: The diagnostic accuracy of clinical probability assessment and D-dimer testing for clinically suspected recurrent deep vein thrombosis (DVT) is largely unknown.

Aim: To evaluate the safety of ruling out acute recurrent DVT based on an unlikely Wells score for DVT and a normal D-dimer test.

Methods: This was a predefined endpoint of the Theia study in which the diagnostic accuracy of magnetic resonance direct thrombus imaging in acute recurrent ipsilateral DVT was validated. The Wells rule and D-dimer test, performed as part of the study protocol, were not used for management decisions. The primary outcome of this analysis was the incidence of recurrent DVT at baseline or during 3-month follow-up for patients with an unlikely Wells score and a normal D-dimer test.

Results: Results of both Wells score and D-dimer tests were available in 231 patients without anticoagulant treatment. The recurrent DVT prevalence was 45% (103/231). Forty-nine patients had an unlikely Wells score and normal D-dimer test, of whom 3 (6.1%, 95%CI 1.3-18%) had recurrent DVT at baseline/follow-up, yielding a sensitivity of 97% (95%CI 92-99%) and specificity of 36% (95%CI 28-45%). Thus, if clinical probability scoring and D-dimer testing would have been applied, radiological imaging could have been omitted in 21% of patients with a diagnostic failure rate of 6.1%.

Conclusion: By applying clinical probability scoring and D-dimer testing, radiological imaging could be spared in a fifth of patients with suspected recurrent ipsilateral DVT. However, the high failure rate does not support implementation of this strategy in daily practice.

INTRODUCTION

The diagnosis of suspected recurrent deep vein thrombosis (DVT) can be challenging, since there are critical limitations to current diagnostic techniques.[1-3] Diagnostic algorithms incorporating the combination of a clinical decision rule (CDR) and D-dimer tests prior to imaging tests have proved to be useful and safe in a first episode of suspected DVT of the leg. However, the diagnostic performance of these algorithms has not been evaluated in large cohorts of patients with suspected recurrent DVT.[1,2,4] Additionally, due to chronic thrombosis persisting in up to 50% of patients despite adequate anticoagulant treatment, conventional diagnostic imaging tests such as compression ultrasound (CUS) and computed tomography venography are often non-diagnostic in the setting of suspected recurrent ipsilateral DVT. As a result, recurrent DVT cannot be excluded in up to 30% of patients.[2,5,6]

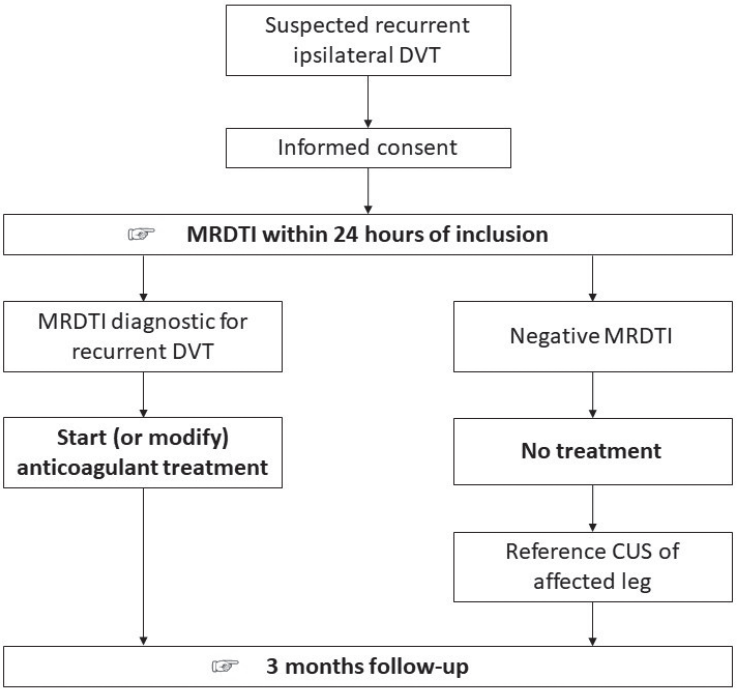
Magnetic resonance direct thrombus imaging (MRDTI), a non-contrast-enhanced magnetic resonance imaging (MRI) technique, has been shown to accurately distinguish acute recurrent DVT from chronic residual thrombosis.[7-10] In a recent prospective outcome study (the Theia study), MRDTI was proven to be an accurate, simple, feasible and reproducible diagnostic test for ruling out acute recurrent ipsilateral DVT.[11] Considering both the limited availability and associated costs of MRI and the poor performance of CUS in suspected recurrent ipsilateral DVT, a safe and efficient diagnostic algorithm to reduce the need of diagnostic imaging is an unmet clinical need. We therefore set out to evaluate the diagnostic accuracy of the combination of the Wells rule for DVT and D-dimer measurement for suspected recurrent ipsilateral DVT.

METHODS

Study population

In this analysis, we report on a predefined secondary endpoint of the Theia study (NCT02262052). The full details of the study design and results have been published previously.[11] In summary, 305 consecutive adult patients with suspected recurrent ipsilateral DVT were managed according to the Theia study algorithm with MRDTI as standalone test to guide therapeutic management (**Figure 1**). The main exclusion

Figure 1. The Theia study flowchart in patients with clinically suspected acute recurrent ipsilateral DVT.[11]



CUS, compression ultrasound; DVT, deep vein thrombosis; MRDTI, magnetic resonance direct thrombus imaging.

criteria were DVT diagnosed by CUS <6 months before presentation, symptom duration of >10 days, suspected concomitant acute pulmonary embolism and general contraindications for MRI.[11] Patients treated with full-dose anticoagulation initiated ≥48 hours before eligibility assessment were initially excluded, but allowed later on as they represented a high proportion of the screened population (30%) in the first year after study initiation. According to the Theia study algorithm, patients with a MRDTI negative for DVT were subjected to a standardized CUS examination within 48 hours after the MRDTI; this CUS served as a reference test in case a patient would return with symptoms of DVT recurrence during the follow-up period. However, the management decision was based on the MRDTI results only. Assessment of the Wells rule and measurement of D-dimer was performed in all patients. All study patients received a 3-month follow-up for the outcome

of recurrent venous thromboembolism (VTE), anticoagulation-associated major bleeding and all-cause mortality. Finally, all endpoints were adjudicated by an independent committee. For the current analysis, patients with unavailable Wells rule scores and/or D-dimer levels were excluded.

Wells rule and D-dimer

CDR assessment included both the original and modified Wells rule for DVT, since previous studies have suggested that the modified Wells rule may be more sensitive for recurrent DVT than the original rule.[12] D-dimer levels were measured with an automated, well-validated, high-sensitivity, quantitative D-dimer assay in accordance with local guidelines (STA-Liatest, Diagnostica Stago; Tina-quant, Roche Diagnostics; Innovance, Siemens).

Primary and secondary aims

The primary aim of this analysis was to evaluate the safety of ruling out acute recurrent (ipsilateral) DVT among patients without anticoagulant treatment. The incidence of recurrent DVT was evaluated in patients with an unlikely ruling according to the original and modified Wells rule separately, in combination with a normal D-dimer test result at baseline. The incidence of recurrent DVT included both recurrent DVT diagnosed at baseline by a MRDTI positive for DVT as well as recurrent VTE during the 3-month follow-up period in patients with a MRDTI negative for DVT.

Secondary aims were twofold: 1. to evaluate the safety of ruling out acute recurrent DVT based on an unlikely CDR, according the Wells rule and modified Wells rule separately, in combination with a normal D-dimer test in patients who were on anticoagulant treatment at inclusion; 2. to estimate the number of 'spared' diagnostic imaging tests (MRTDI and/or CUS) when the original or modified Wells rule and D-dimer test would be applied before imaging tests.

Definitions

An unlikely CDR according the Wells rule was defined as a score of less than 2 points as described in **Table 1.** In the modified Wells rule one extra point is given to

patients with a history of DVT. An abnormal D-dimer test was defined as abnormal according to the assay dependent threshold, which differed between the different assays used in the study.

We considered different classifications of CUS results: normal/abnormal and positive/negative/inconclusive, reflecting clinical practice where the presence of a reference CUS is varied. A normal CUS was defined as full compressibility along the venous system. An abnormal CUS was defined as one or more non-compressible venous segments. A positive CUS was defined as a new non-compressible segment or a ≥2-4 mm increase in vein diameter of a previously non-compressible venous segment when compared to a prior reference CUS of the leg.[2,13] A negative CUS was defined as the absence of any non-compressible segments or the absence of a new non-compressible segment in comparison with a prior reference CUS and a <2 mm increase in vein diameter of a previous non-compressible venous segment. An inconclusive CUS was defined as a non-compressible vein segment in the absence of a prior reference CUS for comparison.

A MRDTI positive for acute recurrent DVT was defined as a high signal intensity in the location of a deep venous segment against the suppressed background greater than that observed in the contiguous segments or corresponding ipsilateral vein. Pulmonary embolism was considered to be present if computed tomography pulmonary angiography showed at least one filling defect in the pulmonary artery tree and if pulmonary embolism was judged to be a probable cause of unexplained death unless proven otherwise by autopsy.

Statistical analysis

Baseline characteristics are described as mean with standard deviation (SD) or median with interquartile range (IQR). The primary outcome was calculated with corresponding exact 95% confidence interval (95% CI). Also, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with corresponding 95% CI of a combination of an unlikely CDR and a normal D-dimer test were calculated. The reference standard for a correct negative ruling by the CDR and the D-dimer test was a negative MRDTI for DVT at baseline and an uneventful 3-month follow-up period. We defined the sensitivity to be adequate if its point estimate would exceed 96%, which was the upper limit of the 95% CI of the sensitivity of D-dimer testing for recurrent DVT in a large multicenter management trial.[14]

Table 1. Clinical decision rule according the original and modified Wells rule for deep vein thrombosis (DVT)

Clinical characteristics	***Score***
Active cancer (Treatment or palliation within 6 months)	1
Bedridden recently > 3 days or major surgery within 12 weeks	1
Calf swelling > 3 cm compared to the other leg	1
Collateral (non-varicose) superficial veins present	1
Entire leg swollen	1
Localized tenderness along the deep venous system	1
Pitting edema, confined to symptomatic	1
Paralysis, paresis or recent plaster immobilization of the lower extremity	1
Previously documented DVT*	1
Alternative diagnosis of DVT as likely or more likely	-2

Note: Cut-off points for both original and modified Wells rule: unlikely clinical probability (0-1 point), likely clinical probability (≥2 points).

**Criterion added for the modified Wells rule.*

For the secondary outcome, we repeated the analysis of the primary outcome in patients on anticoagulant treatment at baseline. Next, we evaluated the effect of applying the combination of CDR assessment and D-dimer measurement to the diagnostic work-up of suspected recurrent DVT on the number of required diagnostic imaging tests to three diagnostic algorithms including imaging with MRDTI and/or CUS. Scenario 1-3 included diagnostic algorithms consisting only of imaging tests. In the first scenario, MRDTI would have been performed in all patients (as was performed in the Theia study population). In the second scenario, all patients with suspected recurrent ipsilateral DVT would have been referred for CUS with MRDTI only to be performed in case of an abnormal CUS. In the third scenario, the same diagnostic algorithm was used, but MRDTI would have been restricted to patients with an inconclusive CUS. In scenario 4-6 the original and modified Wells rule in combination with D-dimer testing was added as initial step of scenarios 1-3 (**Figure 2**). The difference in the number of required imaging tests between the scenarios was calculated. All analyses were performed with the use of SPSS software, version 25.0.

RESULTS

Study population

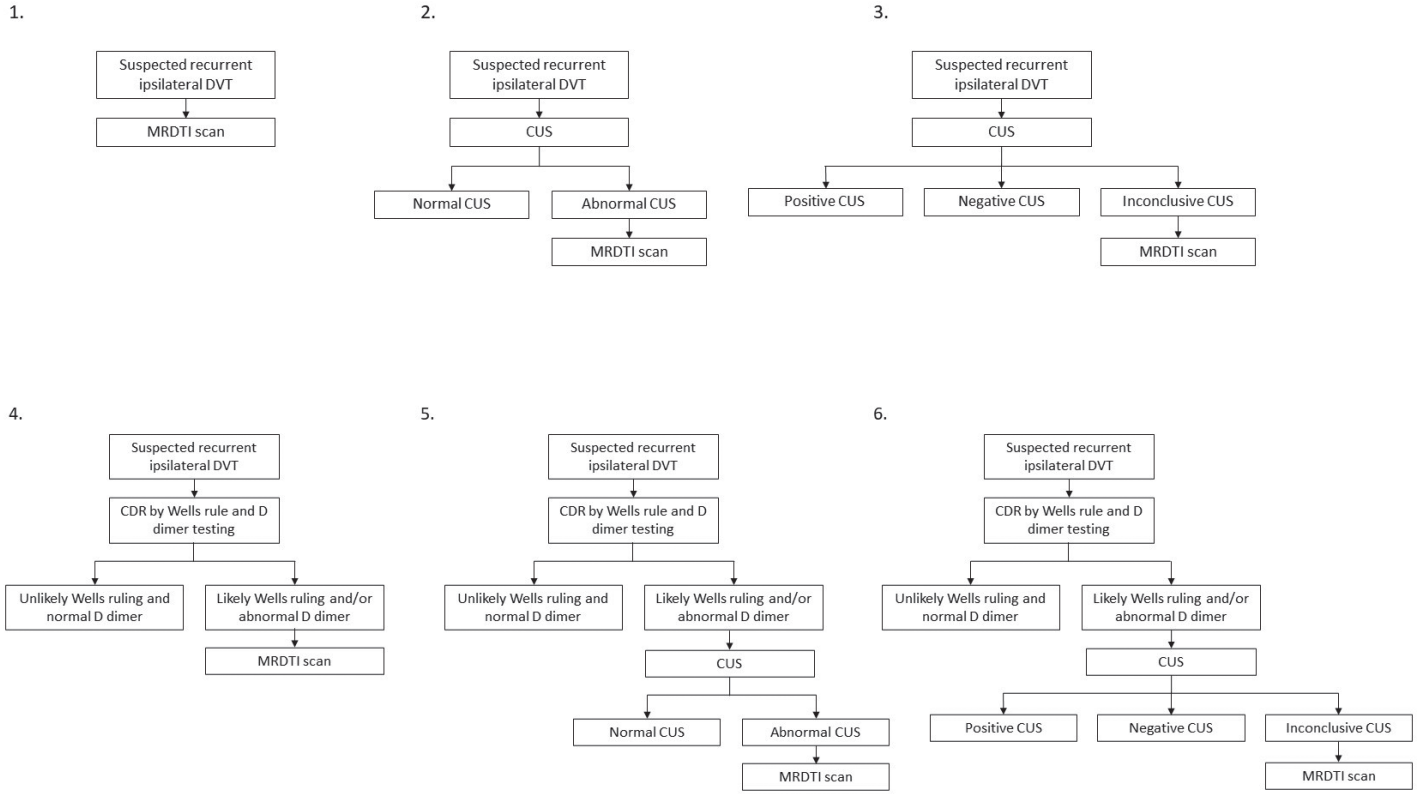
The Wells rule was calculated in all 305 Theia study patients, of whom 163 (53%) had an unlikely CDR. In 10 patients who had an unlikely CDR according the original Wells rule, D-dimer results were unavailable for unknown reasons. These 10 patients were excluded in this analysis, leaving 295 patients of whom 64 patients (22%) were on anticoagulant treatment ≥48 hours at study inclusion. The baseline characteristics of the included patients in this analysis are shown in **Table 2**. The recurrent DVT prevalence was 45% (103/231; 95%CI 36-54%) in patients without anticoagulant treatment and 22% (14/64; 95%CI 12-37%) in patients with anticoagulant treatment.

Table 2. Baseline characteristics of 295 patients with suspected recurrent ipsilateral DVT of the leg and with results of clinical probability assessment and D-dimer testing available

	Patients without anticoagulant treatment at baseline	**Patients treated with anticoagulant treatment at baseline**
	(n = 231)	**(n = 64)**
Mean age (+/- SD) – years	56 (16)	56 (17)
Male – no (%)	109 (53)	38 (59)
Median duration of complaints (IQR) – days	4 (2-7)	4 (2-7)
More than 1 prior VTE episode – no (%)	50 (22)	44 (69)
Mean time since the last DVT episode (+/- SD) – years	6.9 (9.2)	4.6 (7.5)
Active malignancy – no (%)	10 (4.3)	8 (13)
Immobility for > 3 days or recent long travel >6 hours in the past 4 weeks – no (%)	15 (6.5)	6 (9.4)
Trauma/surgery during the past 4 weeks – no (%)	9 (3.9)	2 (3.1)
Hormone (replacement) therapy – no (%)	5 (2.2)	1 (1.6)
Known genetic thrombophilia – no (%)	18 (7.8)	21 (33)

DVT, deep vein thrombosis; IQR, interquartile range; no, number of patients; SD, standard deviation; VTE venous thromboembolism.

Figure 2. Six hypothetical scenarios for the diagnostic management of suspected recurrent ipsilateral DVT, including clinical probability assessment using the Wells rule for DVT, D-dimer testing and diagnostic imaging with compression ultrasound (CUS) and magnetic resonance direct thrombus imaging (MRDTI)



Primary outcome

Among the 231 patients who were not treated with anticoagulants, 119 patients (52%) had an unlikely CDR according to the original Wells rule, 66 patients (29%) had a normal D-dimer test and 49 patients (21%) had a combination of an unlikely CDR and a normal D-dimer test. All results of the combination of CDR assessment and D-dimer testing are presented in **Appendix A**. Three of 49 patients (6.1%; 95%CI 1.3-18%) with an unlikely original Wells score and a normal D-dimer test had recurrent DVT at baseline or during 3-month follow-up (**Table 3**). The combination of the original Wells rule and D-dimer test yielded a sensitivity of 97% (95%CI 92-99%) and specificity of 36% (95%CI 28-45%).

When using the modified Wells rule in combination with D-dimer testing, 3 of the 28 patients (11%; 95%CI 2.2-31%) with an unlikely CDR and a normal D-dimer test had recurrent DVT at baseline or during 3-month follow-up. The sensitivity was 97% (95%CI 92-99%) and the specificity was 20% (95%CI 14-27%).

Secondary outcomes

The incidence of recurrent DVT in patients treated with anticoagulants at baseline who had an unlikely probability according to the original Wells rule in combination with a normal D-dimer test was 2 of 30 patients (6.7%; 95%CI 0.81-24%) (**Table 3**). The sensitivity and specificity of the combination of an unlikely probability by the original Wells rule and a normal D-dimer test for acute recurrent DVT were 86% (95%CI 60-96%) and 56% (95%CI 42-69%), respectively. When applying the modified Wells rule, the sensitivity was 93% (95%CI 69-99%) and the specificity was 32% (95%CI 21-46%).

The number of required diagnostic imaging tests in the different scenarios for the diagnostic work up of suspected recurrent DVT are shown in **Table 4**. Depending on the diagnostic scenario, CUS was needed in 71-100% of patients and MRDTI in 33-100% of patients. When CDR assessment in combination with D-dimer testing was applied before diagnostic imaging, CUS was needed in 71-83% of patients and MRDTI in 33-83% of patients.

Table 3. Overview of patients with confirmed recurrent DVT but unlikely clinical probability and normal D-dimer test at baseline.

	Sex	Age (years)	Wells' rule (points)	Modified Wells' rule (points)	D-dimer concentration	Reference level D-dimer assay	MRDTI result	Outcome
Patients without anticoagulant treatment at baseline:								
Patient 1	Female	25	0	1	<220 ng/mL	<500 ng/mL	Negative	PE at baseline, diagnosed by CTPA
Patient 2	Female	33	0	1	<220 ng/mL	<500 ng/mL	Negative	Proximal recurrent ipsilateral DVT at 22 days of follow-up after immobilization during a long-haul flight; D-dimer elevated (3291 ng/mL)
Patient 3	Female	50	0	1	<220 ng/mL	<500 ng/mL	Positive	DVT at baseline
Patients treated with anticoagulants at baseline:								
Patient 1	Female	52	0	1	<220 ng/mL	500 ng/mL	Positive	DVT at baseline
Patient 2	Male	66	1	2	<250 ng/mL	250 mg/L	Positive	DVT at baseline

CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 4. Required diagnostic imaging tests (compression ultrasonography (CUS) and/or magnetic resonance direct thrombus imaging (MRDTI)) in the different hypothetical diagnostic scenarios for the diagnostic management of suspected recurrent ipsilateral deep vein thrombosis

Scenario	Wells rule + D-dimer test	CUS	MRDTI	Modified Wells rule + D-dimer test	CUS	MRDTI
Patients without anticoagulant treatment at baseline:						
1	-	-	100%	-	-	100%
2	-	100%	52%	-	100%	52%
3	-	100%	40%	-	100%	40%
4	100%	-	71%	100%	-	83%
5	100%	71%	39%	100%	83%	44%
6	100%	71%	33%	100%	83%	36%
Patients treated with anticoagulants at baseline:						
1	-	-	100%	-	-	100%
2	-	100%	54%	-	100%	54%
3	-	100%	42%	-	100%	42%

DISCUSSION

In this predefined analysis of the Theia study, we demonstrated that the combination of an unlikely CDR with a normal D-dimer test yielded a sensitivity of 97% (95%CI 92-99%) and a specificity of 36% (95%CI 28-45%) for recurrent ipsilateral DVT. Even though the predefined threshold for 'adequate' sensitivity was met, a failure rate of 6.1% (95%CI 1.3-18%) was observed.

Our results are in line with a patient-level meta-analysis, in which it was concluded that an unlikely CDR by the original Wells rule combined with a normal D-dimer was not safe for excluding recurrent DVT (failure rate of 2.5%; 95%CI 1.2%-5.4%) in 941 patients with a history of DVT.[12]

The modified Wells rule was created to improve the diagnostic performance of the original Wells rule.[12] However, applying the modified Wells rule to our cohort lead to an even higher failure rate of 11% (95%CI 2.2-31%), mainly because fewer patients were categorized as having an unlikely CDR. These results are in contrast with the above-mentioned meta-analysis, in which the modified Wells rule was associated with an adequately low failure rate of 1.0% (95%CI 0.6-1.6%).[12] Importantly, the lower 24% recurrent DVT prevalence in this meta-analysis [12] needs to be taken into account when comparing the results with our study (prevalence of 45%). As the failure rate is dependent on the disease prevalence in a population or cohort, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) has suggested a DVT prevalence-dependent diagnostic safety threshold.[15,16] The estimated sensitivity of the modified Wells rule in combination with D-dimer testing in the aforementioned meta-analysis was 99% [12], compared to a sensitivity of 97% in our study cohort. Therefore, our study results are in line with previous literature and places this sensitivity in the context of a large cohort consisting exclusively of patients with suspected recurrent ipsilateral DVT.

It must also be taken into account that for the estimation of the failure rate of an unlikely CDR in combination with a normal D-dimer test, we calculated the incidence of recurrent DVT at baseline and that of recurrent VTE during 3 months of follow-up after a MRDTI negative for DVT. Although it is possible that a recurrent DVT during follow-up was provoked by a newly emerged risk factor (e.g. immobilization or surgery), the chosen reference standard was in accordance with current guidelines in which it is stated that the standard against which all DVT

diagnostic management studies should be evaluated is the percentage of patients with VTE during 3 months of follow-up despite a normal venography finding.[17]

There are limited data on the utility of D-dimer testing in patients with suspected recurrent DVT while on anticoagulant treatment.[17] It was previously shown that the D-dimer concentration decreases during anticoagulant therapy, which leads to a decrease in sensitivity from 96% to 89%.[18] This was confirmed in our analysis: the sensitivity of the Wells rule/D-dimer combination decreased from 97% to 86% in patients on anticoagulant therapy.

Strengths of the study are the prospective design, the large sample size, the accurate follow-up of the included patients as well as the adjudication of the endpoints by an independent committee. Also, the study included university and non-university hospitals from several European countries, and different quantitative D-dimer assays were used, all contributing to the external validity of our findings. The main limitation of this analysis is that patients were not managed according the results of CDR and D-dimer testing. Also, D-dimer levels were not available for all patients. Due to the limited number of study patients our data should be considered to be hypothesis generating. Future studies with a larger study cohort, including an upfront determined sample size calculation are needed.

In conclusion, although the sensitivity of the (modified) Wells rule in combination with D-dimer testing was sufficient as predefined in the Theia study protocol, we observed a 6.1% diagnostic failure-rate. Importantly, the combination of an unlikely CDR and normal D-dimer test was only present in 21% of patients when using the original Wells rule, and 14% when using the modified Wells rule. Our data do not support routine assessment of CDR and D-dimer in the diagnostic workup of suspected recurrent (ipsilateral) DVT. Based on the results of our analysis we suggest imaging in all patients with suspected recurrent (ipsilateral) DVT starting with CUS and a MRDTI scan in patients with an abnormal or inconclusive CUS result.

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Appendix A. Diagnostic test results of the combination of clinical decision rule (CDR) according (original and modified) Wells rule and D-dimer testing in suspected recurrent ipsilateral DVT

In patients without anticoagulant treatment at baseline:

Original Wells rule in combination with D-dimer testing

	Recurrent DVT	No recurrent DVT	*Total*
Likely original Wells rule and/or abnormal DD	100	82	*182*
Unlikely original Wells rule and normal DD	3	46	*49*
Total	*103*	*128*	*231*

Sensitivity: 97% (95%CI 92-99%)
Specificity: 36% (95%CI 28-45%)
PPV: 54% (95%CI 51-58%)
NPV: 94% (95%CI 83-98%)

Modified Wells rule in combination with D-dimer testing

	Recurrent DVT	No recurrent DVT	*Total*
Likely modified Wells rule and/or abnormal DD	100	103	*203*
Unlikely modified Wells rule and normal DD	3	25	*28*
Total	*103*	*128*	*231*

Sensitivity: 97% (95%CI 92-99%)
Specificity: 20% (95%CI 14-27%)
PPV: 49 (95%CI 47-52%)
NPV: 89% (95%CI 72-96%)

In patients with anticoagulant treatment at baseline:

Original Wells rule in combination with D-dimer testing

	Recurrent DVT	No recurrent DVT	*Total*
Likely original Wells rule and/or abnormal DD	12	22	*34*
Unlikely original Wells rule and normal DD	2	28	*30*
Total	*14*	*50*	*64*

Sensitivity: 86% (95%CI 60-96%)
Specificity: 56% (95%CI 42-69%)
PPV: 35% (95%CI 27-44%)
NPV: 93% (95%CI 79-98%)

Modified Wells rule in combination with D-dimer testing

	Recurrent DVT	No recurrent DVT	*Total*
Likely modified Wells rule and/or abnormal DD	13	34	*47*
Unlikely modified Wells rule and normal DD	1	16	*17*
Total	*14*	*50*	*64*

Sensitivity: 93% (95%CI 69-99%)
Specificity: 32% (95%CI 21-46%)
PPV: 28% (95%CI 23-33%)
NPV: 94% (95%CI 70-99%)


5

CHAPTER

Detection of upper extremity deep vein thrombosis by magnetic resonance non-contrast thrombus imaging

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ABSTRACT

Background: Compression ultrasonography (CUS) is the first line imaging test for diagnosing upper extremity deep vein thrombosis (UEDVT), but often yields inconclusive test results. Contrast-venography is still considered the diagnostic standard but is an invasive technique.

Aim: We aimed to determine the diagnostic accuracy of Magnetic Resonance Non-Contrast Thrombus Imaging (MR-NCTI) for the diagnosis of UEDVT.

Methods: In this international multicentre diagnostic study, we prospectively included patients with clinically suspected UEDVT who were managed according to a diagnostic algorithm that included a clinical decision rule (CDR), D-dimer test and diagnostic imaging. UEDVT was confirmed by CUS or (computed tomography (CT)) venography. UEDVT was excluded by 1) an unlikely CDR and normal D-dimer, 2) a normal serial CUS or 3) a normal (CT) venography. Within 48 hours after the final diagnosis was established, patients underwent MR-NCTI. MR-NCTI images were assessed post-hoc by two independent radiologists unaware of the presence or absence of UEDVT. The sensitivity, specificity and interobserver agreement of MR-NCTI for UEDVT were determined.

Results: MR-NCTI demonstrated UEDVT in 28 of 30 patients with UEDVT and was normal in all 30 patients where UEDVT was ruled out, yielding a sensitivity of 93% (95%CI 78-99%) and specificity of 100% (95%CI 88-100%). The interobserver agreement of MR-NCTI had a kappa value of 0.83 (95%CI 0.69-0.97).

Conclusions: MR-NCTI is an accurate and reproducible method for diagnosing UEDVT. Clinical outcome studies should determine whether MR-NCTI can replace venography as the second-line imaging test in case of inconclusive CUS.

INTRODUCTION

Upper extremity deep vein thrombosis (UEDVT) is an uncommon presentation of venous thromboembolism (VTE), accounting for approximately 5-10% of all thromboses in the deep veins.[1,2] As in lower extremity deep vein thrombosis (DVT), the first line imaging test is compression ultrasonography (CUS).[3] Diagnosing UEDVT with ultrasonography is more complex than in the lower extremities due to the local anatomy, especially in the axillary and clavicular areas where veins may be difficult to visualize and compress. Therefore, CUS is commonly used in combination with doppler ultrasonography to diagnose or exclude UEDVT. Contrast-venography is the diagnostic standard for UEDVT, but it is an invasive imaging test where patients are exposed to intravenous contrast and radiation. Furthermore, as venography is not routinely performed anymore, radiologists have limited experience evaluating UEDVT by this method.[4,5] Computed tomography (CT) venography is often used as an alternative, although studies regarding its diagnostic accuracy in UEDVT are scarce.[6] Moreover, CT venography may be less applicable in patients with severe chronic kidney disease (e.g. stage 4) given the need for intravenous contrast dye. The validation of an alternative, non-invasive imaging technique would therefore satisfy an unmet clinical need.

Magnetic Resonance Non-Contrast Thrombus Imaging (MR-NCTI) is an imaging technique that may have the potential to replace venography as second-line diagnostic test in case of inconclusive CUS. MR-NCTI is a non-contrast-enhanced magnetic resonance (MR) technique used to directly visualize acute thrombi utilizing the formation of methemoglobin in a fresh thrombus, which appears as a high signal intensity.[7,8] Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a T1-weighted MR-NCTI sequence that previously has been shown to be an accurate and reproducible diagnostic test in patients with suspected first and recurrent ipsilateral DVT.[9-11] Moreover, MR-NCTI has shown to be useful in other locations where the diagnosis of thrombosis can be difficult, including isolated pelvic vein thrombosis in pregnant patients and portal vein thrombosis.[12,13] Three Dimensional Turbo Spin-echo Spectral Attenuated Inversion Recovery (3D TSE-SPAIR) is another T1-weighted MR-NCTI sequence that could be useful in the diagnostic management of UEDVT. Both MRDTI and 3D TSE-SPAIR were found feasible for the diagnosis of UEDVT in a recent small pilot study.[14] We aimed to more accurately determine the diagnostic accuracy of MR-NCTI, combining MRDTI and 3D TSE-SPAIR for the diagnosis of UEDVT.

METHODS

Study design and patients

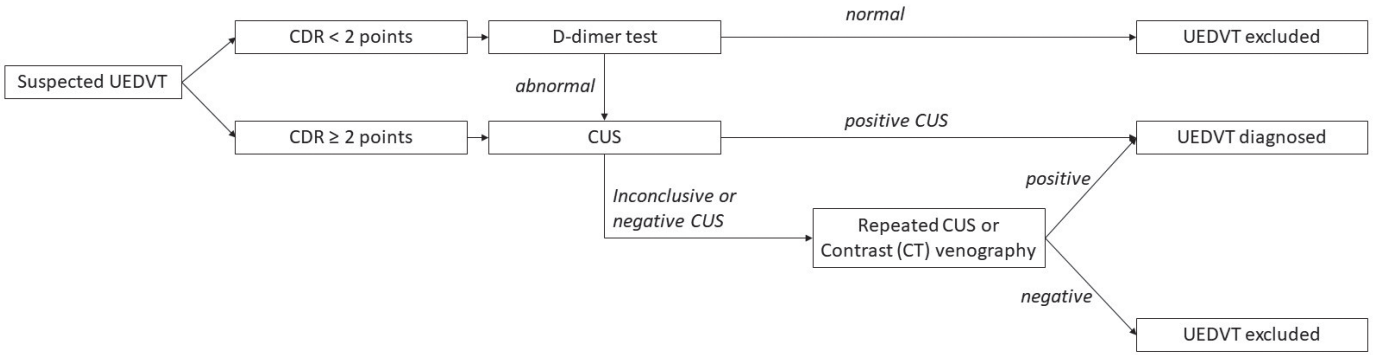
The Selene study was a prospective, international, multicenter diagnostic study conducted at three hospitals across three countries from December 2016 to December 2020 (NTR5738). Patients aged 18 years or older with clinically suspected UEDVT, in whom UEDVT was confirmed or excluded by a diagnostic algorithm, were included in the study. Exclusion criteria were suspected recurrent ipsilateral UEDVT, onset of symptoms of more than 10 days prior to presentation, medical or psychological condition not permitting completion of the study or signing informed consent, and general contraindications for MRI, including but not limited to a cardiac pacemaker or subcutaneous defibrillator. The study protocol was approved by the institutional review board of the Leiden University Medical Center ((LUMC) Leiden, the Netherlands), Danderyd Hospital (Stockholm, Sweden) and Østfold Hospital (Østfold, Norway). All patients provided written informed consent.

Procedures

Patients were managed by a predefined diagnostic algorithm, consisting of a clinical decision rule (CDR) for UEDVT by Constans et al [15], a D-dimer test and imaging including (repeat) CUS and/or (CT) venography (**Figure 1**).[16] D-dimer levels were measured with an automated, well-validated, high-sensitivity, quantitative D-dimer assay in accordance with local guidelines (STA-Lia test or Siemens dependent on study site). UEDVT was excluded by either an unlikely clinical probability according the Constans rule in combination with a normal D-dimer test, a normal serial CUS or a normal (CT) venography. UEDVT was confirmed by a positive CUS or (CT) venography. Anticoagulant treatment was started when UEDVT was confirmed according to local protocols.

In all patients with confirmed (group 1) or excluded UEDVT (group 2) MR-NCTI, including both MRDTI and 3D-TSE SPAIR sequences, was performed within 48 hours of the initial diagnosis. MRI scans were performed with a 1.5 or 3.0 Tesla unit using an integrated 16-channel posterior coil and a 16-channel anterior body coil for signal reception.[9,10,17] The complete MRDTI and 3D-TSE SPAIR sequence

Figure 1. Diagnostic algorithm in suspected upper extremity deep vein thrombosis (UEDVT)



CDR, clinical decision rule; CT, computed tomography; CUS, compression ultrasonography

parameters are provided in **Table 1.** All MR-NCTI scans were evaluated by a radiologist (L.K.) for assessment of image quality. Patients with MR images with insufficient image quality were excluded for further analysis. We continued the recruitment of patients in group 1 and 2 until inclusion of 30 patients in each group with MR images of sufficient image quality was achieved.

Patients in whom UEDVT was ruled-out were followed for the occurrence of symptomatic venous thromboembolism (VTE) over a period of three months after inclusion.

Table 1. Details of MRDTI and 3D TSE-SPAIR scan parameters applied in the study.

	MRDTI	**3D TSE-SPAIR**
Technique	T1TFE	TSE
Orientation	Coronal	Coronal
FOV	400 x 405	350 x 400
Slices	60	180
Slice thickness (mm)	4.0	1.1
Reconstructed slice thickness (mm)	2.0	-
Voxel size (mm)	1.6 x 2.24 acq.	1.09 x 1.1 acq.
	1.6 x 1.6 recon	0.5 x 0.5 recon
Scan time (min)	5:53	5:33
Echo time (ms)	5.4	23
Repetition time (ms)	11	400
Flip angle	15	90
TFE prepulse inversion time (ms)	1200	-
SPAIR inversion delay (ms)	-	110

This table was originally published in Thrombosis Research. Dronkers, C.E.A., et al. Thromb. Res.[14]

3D TSE-SPAIR, three-dimensional turbo spin-echo spectral attenuated inversion recovery; acq, acquired; FOV, field of view; MRDTI, magnetic resonance direct thrombus imaging; recon, reconstructed; TFE, turbo field-echo; TSE, turbo spin-echo.

Image assessment and interpretation

MR-NCTI scans were evaluated post-hoc by two radiologists (L.K. and L.S.) with over 20 years and 3 years of experience with vascular MRI respectively, who independently reviewed the images unaware of clinical and radiological (ultrasound and venography) information. In case of any dispute, consensus reading between the two radiologists was performed. They noted the presence or absence of UEDVT for each patient based on all available MR images.

Outcomes

The primary outcome was the sensitivity and specificity of MR-NCTI for the diagnosis of UEDVT. The secondary outcome was the interobserver agreement of MR-NCTI reading for suspected UEDVT.

Definitions

An unlikely clinical probability according the Constans rule was defined as a score of less than 2 points (**Table 2**).[15] A normal D-dimer test was defined as normal according to the assay dependent threshold, which differed between the different assays used in the study. A positive CUS for UEDVT was defined as the presence of venous segment area of the upper extremity including subclavian, axillary, brachial or brachiocephalic vein with > 4mm of non-compressibility.[3] A positive (CT) venography for UEDVT was defined as presence of a constant intraluminal filling defect in the deep veins of the arms (subclavian, axillary, brachial or brachiocephalic vein), as shown on at least two projections. A positive MR-NCTI scan for UEDVT was defined as an increased or aberrant signal intensity in the location of the subclavian, axillary, brachial or brachiocephalic vein against the suppressed background.[14] Pulmonary embolism (PE) during follow-up was diagnosed with computed tomography pulmonary angiography (CTPA) if there was an intraluminal defect in a segmental or greater pulmonary artery.[3,18] For ventilation-perfusion (VQ) scanning PE was defined as a perfusion defect, segmental or more proximal on lung perfusion scan, and in presence of a mismatch with the concomitant ventilation scan. PE found at autopsy was also considered diagnostic of VTE. Death related to PE was defined according the following criteria 1) Certain: hypotension, hypoxia, cardiac arrest with no other explanation other than PE with autopsy or radiographic confirmation; 2) Highly probable: criterion for certain fulfilled but another plausible factor/disease as cause of death also present; 3) Probable: other cause suspected based on clinical evidence but 100% certainty not available and 4) Unlikely: all other cases.[19]

Table 2. Clinical decision rule for upper extremity deep vein thrombosis by Constans et al

Item	Value
Venous material*	1 point
Localized pain along deep veins of the upper arm	1 point
Unilateral pitting edema of the upper arm	1 point
Other diagnosis at least as plausible	-1 point
	Cut-off points
Unlikely clinical probability	< 2
Likely clinical probability	≥ 2

** Venous material including catheter or access device in a subclavian or jugular vein or pacemaker*

Statistical analysis

Baseline characteristics are described as mean with standard deviation (SD) or median with interquartile range (IQR).

For the primary outcome, we estimated the sensitivity of MR-NCTI for the diagnosis of UEDVT which was determined by calculating the proportion of MR scans that were read as "positive for UEDVT" in patients with CUS or (CT) venography proven UEDVT. Specificity was determined by calculating the proportion of MR scans that were read as "negative for UEDVT" in patients where UEDVT was ruled-out by either an unlikely CDR and normal D-dimer test or a normal serial CUS or normal (CT) venography both followed by a 3-month follow-up without VTE. The corresponding 95% confidence interval (95%CI) of both the sensitivity and specificity were calculated. A point estimate of the sensitivity of >90% was defined as acceptable for initiating a future management study. We estimated that a sample size of 30 patients in each group (positive and negative UEDVT diagnosis) was needed to reach the sensitivity of greater than 90% with a corresponding 95%CI of ±15%. Therefore, we aimed to include 60 patients in total.

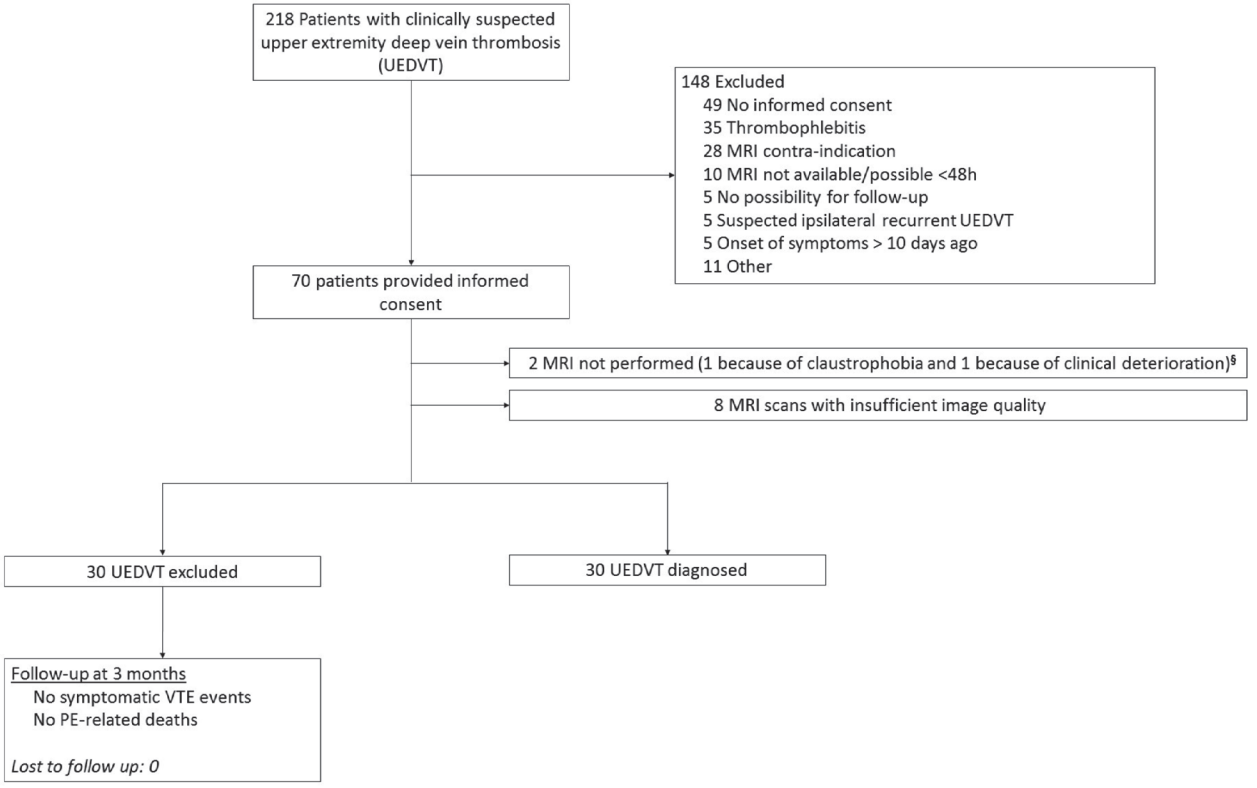
For the secondary outcome, in which we assessed interobserver agreement of MR-NCTI reading, the κ-statistic was calculated. The kappa value for agreement was interpreted as follows: poor (<0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or excellent (0.81–1.00).(20) Analyses were performed in SPSS version 25 (IBM, Armonk, NY, USA).

RESULTS

Patients

A total of 218 consecutive patients with clinically suspected UEDVT were screened, of whom 148 patients (68%) were excluded for various reasons as per predefined exclusion criteria (**Figure 2**). Among the 148 patients excluded, 22 patients (15%) could not be included because of the presence of an implantable device not compatible with MRI (e.g. pacemaker). A total of 70 patients provided written informed consent. MR-NCTI images were adequate for interpretation in 89% of the cases: eight patients were excluded from the main analysis due to MR imaging artefact issues rendering image quality insufficient for final diagnosis. In one patient MRI could not be performed due to claustrophobia, whilst another patient experienced acute clinical deterioration during scanning. Hence, 60 patients could be included, of whom 30 patients had a confirmed UEDVT and 30 patients had UEDVT ruled out. All patients were subjected to MRDTI, but due to logistical reasons, 3D TSE-SPAIR sequence could not be performed in 8 (13%). The baseline characteristics of the 60 study patients are shown in **Table 3**. In two patients (3.3%) UEDVT was excluded based on an unlikely clinical probability according the Constans rule in combination with a normal D-dimer result and these patients had no VTE at follow-up. UEDVT was ruled out based on diagnostic imaging in 28 patients and none of these patients were diagnosed with VTE during follow-up (**Figure 2**). The diagnosis was based on (repeat) ultrasonography in 43 patients (72%) and (CT)venography in 15 patients (25%). In 12 patients (20%) (CT)venography was performed because of an inconclusive CUS or negative CUS but high clinical suspicion. Of these 12 patients, 3 patients had a negative (repeat) CUS for UEDVT of whom 2 patients were diagnosed with UEDVT based on (CT)venography and in one patient UEDVT was also excluded based on (CT)venography. In 9 patients (repeat) CUS was positive for UEDVT, but the diagnosis was uncertain and were thus referred for (CT)venography. UEDVT was excluded based on (CT)venography in one patient and also positive for UEDVT in 8 patients.

Figure 2. Flowchart of study patients



MRI, magnetic resonance imaging; PE, pulmonary embolism; UEDVT, upper extremity deep vein thrombosis; VTE, venous thromboembolism

Table 3. Baseline characteristics of 60 patients with suspected upper extremity deep vein thrombosis (UEDVT)

	Patients with confirmed UEDVT	**Patients with UEDVT excluded**
Mean age (+/- SD) – years	50 (16)	58 (17)
Male – no (%)	16 (53)	18 (60)
Median duration of complaints (IQR) – days	4.0 (2.0-8.0)	2.5 (2.0-6.3)
Malignancy – no (%)	7 (23)	10 (33)
Trauma/surgery during the past 4 weeks – no (%)	5 (17)	4 (13)
Hormone (replacement) therapy – no (%)	5 (17)	2 (6.7)
Paralysis, paresis or plaster immobilization – no (%)	0 (0)	1 (3.3)
Intravenous material in subclavian or jugular vein	7 (23)	5 (17)
(catheter or access device)		

SD: standard deviation, IQR: interquartile range

Primary outcome

MR-NCTI was positive in 28 of 30 patients with UEDVT and normal in two patients (**Table 4** and **5**). Of these two, the first patient was a 66-year-old female patient with known leiomyosarcoma. She presented with a six-day episode of pain and swelling of the left upper and lower arm in which a central venous catheter was in situ. At presentation, the patient had a likely clinical probability according the Constans rule (3 points) and D-dimer level of 1975 ng/mL. CT venography was performed because of an inconclusive CUS examination. CT showed a hypoplastic left internal jugular vein with an intraluminal hypodensity, compatible with thrombosis, at the confluence and in the proximal hypoplastic left internal jugular vein. MR-NCTI was performed at 48 hours after the diagnosis. MRDTI and 3D TSE-SPAIR sequences were considered diagnostic for DVT in the left jugular vein according one reviewer and negative for DVT according to the second reviewer. Consensus reading resulted in a negative DVT diagnosis. The second case with UEDVT and a normal MR-NCTI was a 52-year-old male patient presenting with pain and pitting edema of the right arm since three days. At presentation, the patient had a likely clinical probability according the Constans rule (2 points) and a D-dimer result of 1600 ng/mL. CT venography showed thrombosis in the right subclavian vein. MR-NCTI scan was performed at two hours after the diagnosis. Both MRDTI and 3D

TSE SPAIR sequences were negative for DVT according to both reviewers. In both patients, therapeutic anticoagulant treatment was started based on the results of CT venography.

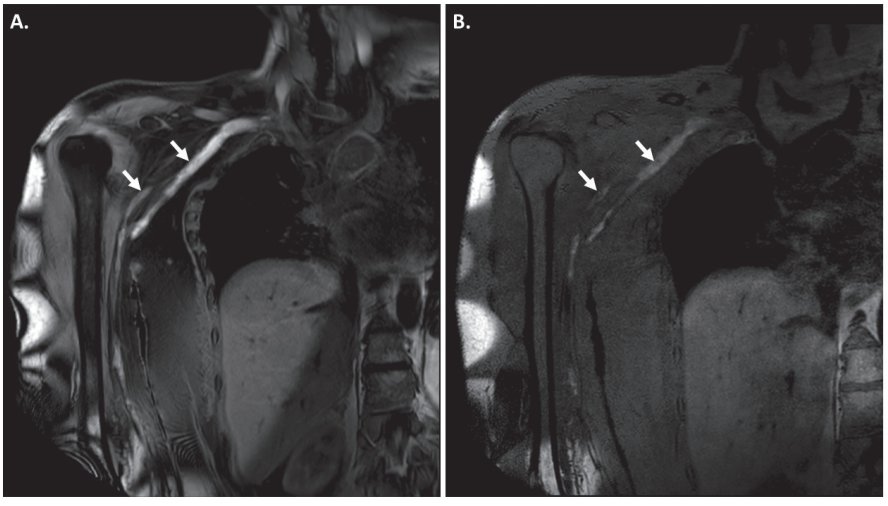
MR-NCTI was normal in all 30 patients in whom UEDVT was ruled out (**Table 4**). Hence, the sensitivity of MR-NCTI for the diagnosis of UEDVT was 93% (95%CI 78-99%) and the specificity was 100% (95%CI 88-100%). **Figure 3** shows MR images diagnostic for UEDVT.

Table 4. Comparison of MR-NCTI results in patients with UEDVT and without UEDVT

		UEDVT	*No UEDVT*
MR-NCTI	*Abnormal*	28	0
	Normal	2	30

CDR, clinical decision rule; MR-NCTI, magnetic resonance noncontrast thrombus imaging; UEDVT, upper extremity deep vein thrombosis; US, ultrasonography.

Figure 3. Magnetic resonance imaging of the right upper extremity in coronal view of a patient diagnosed with acute deep vein thrombosis in right brachial and axillar vein; A. Magnetic Resonance Direct Thrombus Imaging (MRDTI) and B. Three Dimensional Turbo Spin-echo Spectral Attenuated Inversion Recovery (3D TSE-SPAIR) showing high signal intensity in brachial and axillar vein (arrows) compatible with an acute thrombus.



Secondary outcomes

The two independent reviewers disagreed on 5 of the 60 MR-NCTI readings. Hence, the interobserver agreement between two independent readers had a kappa value of 0.83 (95%CI 0.69-0.97). Consensus reading of the MR-NCTI scans with discrepancy between the two readers resulted in a correct positive diagnosis in four patients and a falsely negative UEDVT diagnosis in one patient.

Table 5. Characteristics of the two patients with false-negative MR-NCTI result

	Sex	**Age (years)**	**Symptom duration (days)**	**Constans' score (points)**	**D-dimer (ng/mL)**	**MR-NCTI**	**Contrast venography**
Patient 1	Female	66	6	3	1975	Negative for UEDVT	Hypoplastic left internal jugular vein and intraluminal hypodensity at the confluence of the left subclavian and internal jugular vein and in the proximal hypoplastic jugular vein
Patient 2	Male	52	3	2	1600	Negative for UEDVT	Thrombus in right subclavian vein

MR-NCTI, magnetic resonance non-contrast thrombus imaging; UEDVT, upper extremity deep vein thrombosis.

DISCUSSION

In this study, we showed that MR-NCTI is accurate for the diagnosis of UEDVT, with a sensitivity of 93% (95%CI 78-99%) and specificity of 100% (95%CI 88-100%). Moreover, the interobserver agreement was excellent with a kappa value of 0.83 (95%CI 0.69-0.97).

Current guidelines recommend CUS combined with doppler ultrasonography as the first line imaging test in patients with suspected UEDVT, due to its availability, relatively low cost and non-invasive nature.[3] Since the diagnosis of UEDVT can be difficult as deep axillary and retro-clavicular areas cannot be well visualized nor compressed due to overlying (bone) structures, both CUS and doppler ultrasonography can be used to confirm UEDVT in the presence of non-compressibility of a venous segment and/or in the absence of a color or doppler signal within the lumen of the vein or to exclude UEDVT in the absence of these findings. Moreover, follow-up imaging including repeat CUS combined with doppler, contrast-venography or CT venography is recommended in patients with high clinical suspicion but negative ultrasound.[3]

Previously, MR venography (time-of-flight and contrast-enhanced) has been evaluated as alternative in the diagnostic management of UEDVT, but was not safe to exclude UEDVT (sensitivity of 71% (95%CI 29-96%) and 50% (95% CI 12-88%) and specificity of 89% (95% CI 52-100%) and 80% (95%CI 44-97%), respectively).[21] MR-NCTI has the advantage of direct thrombus visualization without the use of a contrast agent as the technique is based on the intrinsic contrast of fresh thrombus itself.[7,11-14,22-26] 3D TSE-SPAIR has some advantages over MRDTI sequences, including a higher spatial resolution of the vessel wall and less inflow artefacts in the arteries.[14] The two techniques were found to be potentially feasible for the diagnosis of UEDVT which was confirmed in this study.[14] We found a sensitivity and specificity of MR-NCTI that are comparable to that of MRDTI in the diagnosis of recurrent ipsilateral DVT of the leg, and for which the safety to exclude recurrent ipsilateral DVT of the leg was confirmed in an outcome study.[9,11] Notably, MR-NCTI missed the diagnosis of UEDVT in 2 patients in our study. In one patient, the MR-NCTI was performed after 48 hours of anticoagulant therapy and the anatomy was particular complex with a hypoplastic jugular vein, which may have contributed to a false negative reading by the experts. In the other case, no straightforward explanation was identified.

A limitation of the study is that 3D TSE-SPAIR sequence was not performed in all patients. Also, MR image quality of 8 patients was deemed insufficient to provide a definite diagnosis. Direct thrombus imaging seems more challenging in the upper arms and clavicular areas than in the lower extremities, because of the vascular orientation and image artefacts due to respiratory motion and cardiac- and vascular pulsation, limiting the image and contrast quality of the MRDTI scan. Therefore, we recommend using the combination of MRDTI and 3D TSE-

SPAIR sequences in all patients when applied in the diagnostic management of suspected UEDVT. A drawback of such practice is the longer image acquisition time (30 minutes) compared to that of performing only one of the sequences (MRDTI) in the lower extremities (10 minutes). Moreover, it is important that experience in performing and image reading of these techniques is gained before it can be used for the diagnosis of UEDVT.

Strengths of this study include its prospective design. The MR-NCTI scans were performed in different centers across different countries and using MR scanners of different manufactures. This, together with the excellent interobserver agreement, supports the wide applicability of this technique. We were able to prove its accuracy for the diagnosis of UEDVT in an adequate patient sample and also included the subgroup of patients with inconclusive ultrasound, for which the use of MR-NCTI may be particularly relevant. As MRI is associated with higher costs compared to ultrasonography, it should not be used as first line imaging test. Instead, we suggest that MR-NCTI could potentially serve as a second-line imaging test in patients with high clinical suspicion for UEDVT but inconclusive ultrasound. Since it was not the aim of the current study to assess the accuracy of MR-NCTI in this particular setting, future studies to the safety of this technique to exclude UEDVT in case of an inconclusive ultrasound are needed.

In conclusion, MR-NCTI was accurate for the diagnosis of UEDVT and had an excellent interobserver agreement. Future studies should determine whether this technique can replace venography as the second-line imaging test in patients with an inconclusive CUS.

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6

CHAPTER

Magnetic resonance thrombus imaging to differentiate acute from chronic portal vein thrombosis

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ABSTRACT

Background and aim: Timely diagnosis and treatment of portal vein thrombosis (PVT) is crucial to prevent morbidity and mortality. However, current imaging tests cannot always accurately differentiate acute from chronic (non-occlusive) PVT. Magnetic resonance non-contrast thrombus imaging (MR-NCTI) has been shown to accurately differentiate acute from chronic venous thrombosis at other locations and may also be of value in the diagnostic management of PVT. This study describes the first phase of the Rhea study (NTR 7061). Our aim was to select and optimize MR-NCTI sequences that would be accurate for differentiation of acute from chronic PVT.

Methods: The literature was searched for different MRI sequences for portal vein and acute thrombosis imaging. The most promising sequences were tested in a healthy volunteer, followed by one patient with acute PVT and two patients with chronic PVT, all diagnosed on (repetitive) contrast enhanced computed tomography venography, to optimize the MR-NCTI sequences. All images were evaluated by an expert panel.

Results: Several MR-NCTI sequences were identified and tested. Differentiation of acute from chronic PVT was achieved with 3-dimensional T1 Turbo Field Echo (3D T1-TFE) and 3D T1 Fast Field Echo (3D T1 Dixon FFE) sequences with best image-quality. The expert panel was able to confirm the diagnosis of acute PVT on the combined two MR-NCTI sequences and to exclude acute PVT in the two patients with chronic PVT.

Conclusion: Using 3D T1-TFE and 3D T1 Dixon FFE sequences we were able to distinguish acute from chronic PVT. This clinical relevant finding will be elucidated in clinical studies to establish their test performance.

INTRODUCTION

Acute portal vein thrombosis (PVT) has a poor short- and long-term prognosis[1] and a higher mortality rate than the 'usual site' venous thromboembolism, i.e. acute pulmonary embolism and deep vein thrombosis (DVT). Therefore, timely diagnosis and anticoagulant treatment are crucial for the patients' prognosis.[2-4] Distinguishing between a fresh thrombus, in which anticoagulant treatment is indicated, and a chronic (organized, non-resolvable) thrombus is of paramount importance for treatment decision.[5] However, currently available imaging tests are not always able to accurately differentiate acute from chronic PVT, especially when it concerns an organized non-occlusive chronic thrombus without signs of cicatrization of the affected vessel.

Magnetic resonance non-contrast thrombus imaging (MR-NCTI), also referred to as Magnetic Resonance Direct Thrombus Imaging (MRDTI) in previous publications, is a non-contrast-enhanced magnetic resonance imaging (MRI) technique which allows for direct visualization of acute thrombi.[6] This technique is based on the formation of methemoglobin in a fresh thrombus which appears as high signal intensity on a T1 weighted MRI sequence by shortening the T1 relaxation time.[6] This increased signal intensity fades when the thrombus ages over a period of 3-6 months.[7] MR-NCTI has been shown to accurately differentiate acute from chronic DVT and to safely exclude acute recurrent ipsilateral DVT of the legs.[7-9] The diagnostic accuracy of MR-NCTI has not yet been evaluated for the diagnosis of PVT. Because imaging of abdominal veins differs in many ways from imaging of veins in the extremities, e.g. artefacts from ascites and intestinal movement and gas, the MR-NCTI sequences used in the extremities need to be adjusted for optimal visualization of PVT. We set out to select and optimize MR-NCTI sequences for differentiation between acute and chronic portal vein thrombosis.

MATERIAL & METHODS

This study is the first phase of the Rhea study (NTR 7061), a prospective diagnostic study to evaluate the diagnostic accuracy of MR-NCTI for distinguishing acute from chronic PVT. In the Rhea study our aim is to include 70 PVT patients, including 35 patients with confirmed acute PVT (partial or occlusive), i.e. acute symptoms (<2 weeks) characteristic for PVT, diagnosed with doppler ultrasound (Doppler US),

computed tomography (CT) venography or MRI and 35 patients with confirmed non-symptomatic chronic PVT (partial or occlusive), i.e. unchanged chronic thrombi on 2 serial imaging tests with an at least 3-month interval. The study protocol and its amendments were approved by the institutional review board of the Leiden University Medical Center, Leiden, the Netherlands, and the University of Insubria, Varese, Italy. All patients will be asked for written informed consent.

For this first phase of the Rhea study, we aimed to select and develop MR-NCTI sequences that would be accurate for differentiation of acute from chronic PVT. First, a literature search for different MRI sequences for portal vein and acute thrombosis imaging was performed. The literature search was conducted in PubMed for papers published in English and in humans on December 16th 2019 (search strategy detailed in **Appendix A**). Because imaging of the abdomen is hampered by intestinal movements and gas, search terms included techniques with correction for respiratory motion artefacts, good spatial and contrast resolution and fat suppression.

The most promising sequences were adjusted for abdominal imaging and tested in a healthy volunteer using a MRI 3.0 Tesla unit (Philips Ingenia, Philips Medical Systems, Best, The Netherlands). A 55 cm receive-only body multi coil (combination of posterior and anterior coil) was used. Image assessment involved acquiring images in the coronal and axial plane with standard image reconstruction techniques. To gain knowledge of the performance of the sequence to detect fresh blood clots in addition to the visualisation of the venous anatomy, two tests coagulation tubes were attached to the abdomen of the volunteer; one was filled with water (control) and one with clotted blood of a healthy volunteer, prepared and stored at room temperature at least 48 hours before each scanning session. The test sequence scan parameters were adjusted until adequate image quality of the veins with high signal intensity for thrombus in the coagulation tube was achieved.

MR-NCTI sequences showing the best image quality and contrast resolution were tested in three patients with confirmed PVT, including one patient with acute PVT and two patients with chronic PVT. Scan optimization was performed until a clear distinct signal intensity was achieved between acute and chronic PVT.

Finally, the MRI images of the three PVT patients were evaluated by an expert panel, consisting of two radiologists with over 20 years of experience with vascular MRI (LK and MW), one radiology technician with over 20 years of experience with vascular MRI acquisition (GH), one internist with 6 years (FK) and one researcher with 2 years (LD) of experience with vascular MRI interpretation. The evaluation

of the scans was performed and compared with the clinical presentation and the results of other imaging (Doppler US, CT venography or MRI). The scan results were assessed for image quality, venous location, and either presence or absence of acute thrombosis.

RESULTS

Literature search

We identified the following MRI sequences: 3-dimensional T1 Turbo Field Echo (3D T1 TFE), 3D Turbo Spin Echo with Spectral Attenuated Inversion Recovery (3D TSE SPAIR) and T1 high-resolution isotropic volume excitation (THRIVE) and techniques: black-blood, Dixon and Principle of Selective Excitation Technique (ProSET) which could be suitable for portal vein imaging.

A 3D T1 TFE sequence was shown to be highly accurate for the diagnosis of first deep vein thrombosis and the differentiation of acute deep vein thrombosis from chronic residual vascular abnormalities in the leg.[8-10] Hence, this sequence seemed promising for the differentiation of acute from chronic PVT. Furthermore, in a pilot study 3D T1 TFE and 3D TSE SPAIR sequences successfully confirmed the diagnosis of arm vein thrombosis when compared to ultrasonography or contrast venography.[11] The advantages of 3D TSE-SPAIR over 3D T1 TFE were a higher spatial resolution of the vessel wall and less high signal artefacts in arteries caused by inflow effects. Therefore, both 3D T1 TFE and 3D TSE SPAIR may be suitable for portal vein imaging.

THRIVE sequences may also be a promising MR-NCTI technique in PVT with potential good contrast resolution between high signal intensity of an acute thrombus and low signal intensity intravascular.[12]

The black-blood technique was successfully used to identify deep vein thrombosis of the leg and in cerebral vein thrombosis.[13,14] With this technique the signal from flowing blood is nullified and highlights static anatomy including thrombi.[15] Because of known good contrast resolution between thrombus and flowing blood, we hypothesized that combining the black-blood technique with 3D TSE SPAIR may be suitable for portal vein imaging.

Since it can be difficult to distinguish an acute thrombus from other tissues with a short T1 relaxation time, e.g. fat-tissue which is present in the liver, adding a fat-suppression technique that suppresses the fat signal may help depicting thrombosis. With this technique, selective pulses cause signal from fat to be nulled (saturated) while the water signal is relatively unaffected. The Dixon technique is an often-used fat suppression technique that can be used with several sequences such as T1- and T2-weighted imaging, and gradient echo MRI [16,17]. An alternative to fat suppression methods is water excitation by means of a spectral spatial pulse. With this technique, only water is excited by using section-selective composite pulses, while lipid spins are left in equilibrium, thereby producing no signal.[18] ProSET, a water excitation technique, was successfully used in a pregnant patient with proximal iliac vein thrombosis[19] and may therefore be applicable in portal vein imaging as well.

Sequence testing and optimization

All three selected imaging sequences (3D T1 TFE, 3D TSE SPAIR and THRIVE) and black-blood, Dixon and ProSET techniques were tested in a healthy volunteer.

Table 1. 3D T1 TFE and T1 Dixon FFE scan parameters

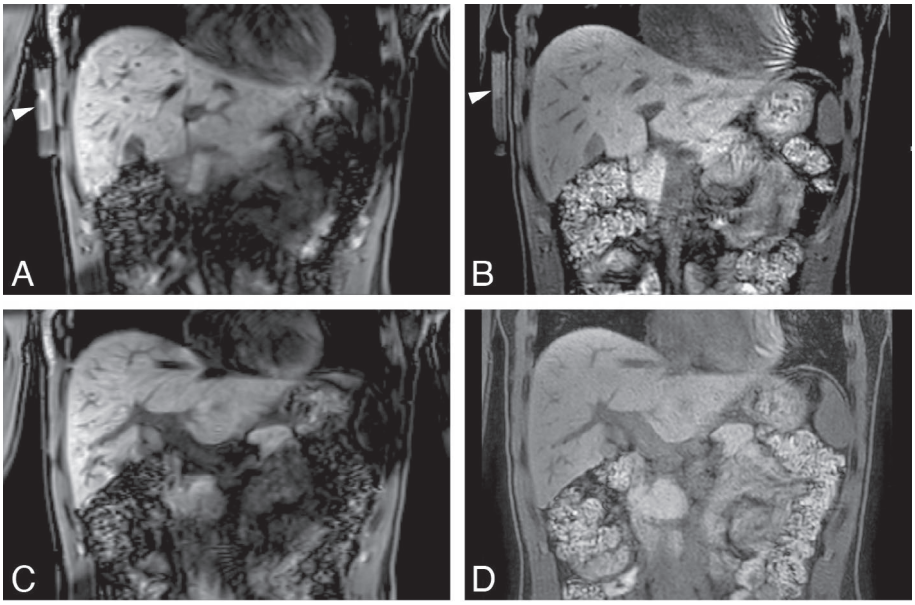
	3D T1 TFE	**3D T1 Dixon FFE**
Technique	T1 TFE	T1 FFE
Orientation	Coronal	Coronal/Transversal
Respiratory motion suppression	Respiratory gating	Breath hold
Slices	80	160
Slice thickness (mm)	4.0	3.0
Slice distance (mm)	2.0	1.5
FOV	400	400
Voxel size (mm)	1.56 x 2.24 x 4	1.7 x 1.7 x 3.5
Scan time (ms)	02:36	00:19
Echo time (ms)	3.73	-
Repetition time (ms)	7.41	3.75
Flip angle	10	15

3D T1 Dixon FFE, three-dimensional T1 fast field echo sequence; 3D T1 TFE, three-dimensional T1 turbo field echo; FOV, field of view.

3D T1 TFE sequence combined with ProSET technique and the Dixon technique added to a 3D T1 Fast Field Echo sequence (3D T1 Dixon FFE) showed good contrast resolution between the liver parenchyma and intrahepatic veins. Moreover, a high signal intensity was acquired from the coagulation tube (**Figure 1**). These two sequences were thus the most promising for portal vein imaging and were evaluated in three PVT patients (**Table 1**).

3D TSE SPAIR, with and without the black-blood technique, and THRIVE sequence were shown to be suboptimal for abdominal direct thrombus imaging, because of a high signal intensity from blood flow in splanchnic veins and intestines despite saturation slab and low image quality due to motion artifacts. These sequences were excluded for further analysis.

Figure 1A-D. MR images of the abdomen in coronal view of a healthy volunteer with a coagulation tube attached to the abdomen; A and C. 3D T1 TFE images at two levels showing a low signal intensity in intrahepatic veins and good contrast resolution between the liver parenchyma and veins. High signal intensity is present in the coagulation tube with clotted blood (arrow). B. and D. 3D T1 Dixon FFE (water-only) images at two levels showing a low signal intensity in the intrahepatic veins and intermediate signal intensity in the coagulation tube (arrow).



MR-NCTI optimization in PVT patients

3D T1 TFE and 3D T1 Dixon FFE sequences were used to evaluate the patient with acute PVT and two patients with chronic PVT (**Table 2**). 3D T1 TFE and 3D T1 Dixon FFE showed a high signal intensity in all abdominal vein segments with acute thrombosis diagnosed on CT venography (**Figure 2**). In the two patients with chronic PVT both sequences showed no increased signal intensity in the portal or mesenteric veins (**Figure 3**). The expert panel was able to confirm the diagnosis of acute PVT on the combined two MR-NCTI sequences and to exclude acute PVT in the two patients with chronic thrombosis. The combination of 3D T1 TFE and 3D T1 Dixon FF was thus judged optimal for locating and differentiating acute from chronic PVT with good image quality and short scanning time (10-15 minutes).

Figure 2A-F. Coronal computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen of a patient diagnosed with acute thrombosis in portal and mesenteric veins; A. CT image after intravenous contrast administration in portal-venous contrast phase shows a large luminal filling defect in the portal vein (arrow). B. MRI, 3D T1 TFE image shows a high signal intensity in the portal vein compatible with acute thrombus (arrow). C. MRI, 3D T1 Dixon FFE (water-only) image shows a high signal intensity in the portal vein (arrow). D. CT image after intravenous contrast administration shows extensive filling defects in mesenteric veins (arrow) with increased attenuation of the surrounding mesenteric fat (encircled). E. MRI, 3D T1 TFE image shows a high signal intensity in the mesenteric veins compatible with acute thrombus (encircled). F. MRI, 3D T1 Dixon FFE (water-only) image shows a high signal intensity in the mesenteric veins (encircled).

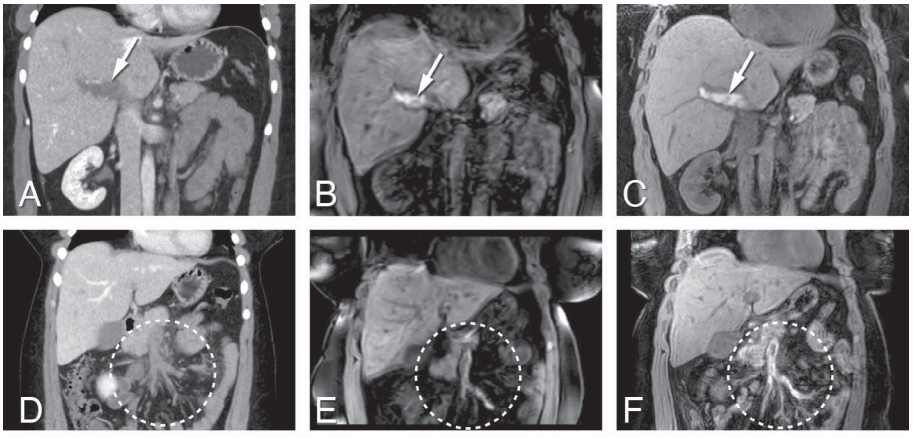
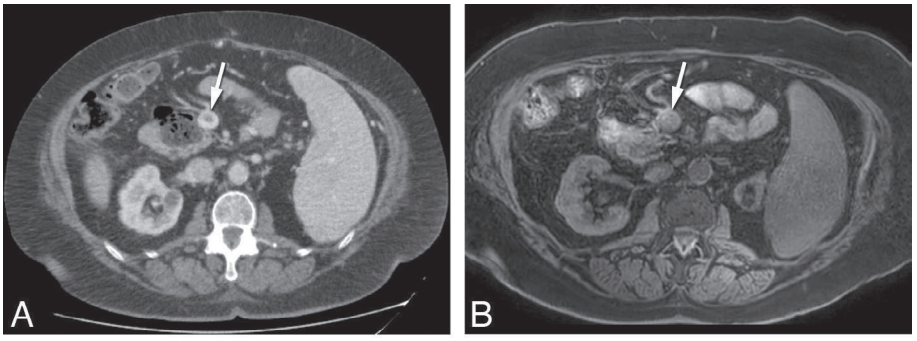


Table 2. Patient characteristics of the three patients diagnosed with portal vein thrombosis

	Diagnosis at inclusion	*Sex*	*Age (years)*	*Relevant patient history*	*Previous venous thromboembolism (VTE)*	*Anticoagulants at inclusion*	*Risk factors for VTE*
Patient 1	Acute PVT	Female	35	None	No	No	Hormonal contraception use
Patient 2	Chronic PVT	Male	29	Myeloproliferative neoplasia complicated by thrombosis of mesenteric veins, portal and splenic vein. Portal hypertension with esophageal varices.	Yes	No	Myeloproliferative neoplasia (JAK2 mutation)
Patient 3	Chronic PVT	Female	67	Non-alcoholic steatohepatitis (NASH) liver cirrhosis for which liver transplantation. Thrombosis of superior mesenteric vein with ischemic small bowel for which ileum resection.	Yes	Yes	NASH liver cirrhosis

NASH, nonalcoholic steatohepatitis; PVT, portal vein thrombosis; VTE, venous thromboembolism; JAK2, janus kinase 2.

Figure 3. A. Computed tomography, axial image of the abdomen in portal-venous contrast phase after intravenous contrast administration, showing a central luminal contrast defect caused by chronic thrombus in the mesenteric vein (arrow). B. Magnetic resonance imaging (MRI), axial 3D T1 Dixon FFE image of the same patient showing isointense signal intensity in the mesenteric vein (arrow). On MRI, the signal intensity of the filling defect in the mesenteric vein is not increased, indicating chronic thrombus.



DISCUSSION

In this first phase of the Rhea study the combination of 3D T1 TFE and 3D T1 Dixon FFE sequences was found to be the most optimal for diagnosing and differentiating acute from chronic PVT. Differentiation between acute and chronic PVT is essential as current guidelines recommend different anticoagulant strategies in patients with acute or chronic PVT, though based on (very) low level of evidence.[5] However, with currently available imaging tests, Doppler US, CT venography, and MRI, it is not always possible to accurately differentiate acute from chronic thrombosis. The diagnosis of chronic PVT can be made in cases of morphologic changes such as an atretic portal vein, inflow branches and cavernous transformation of the portal vein, also called portal cavernoma.[20,21] However, it may be impossible to differentiate acute from chronic PVT in the presence of an organized non-occlusive chronic PVT, without these morphologic changes. Furthermore, up to 30% of the PVT cases are detected incidentally in imaging studies performed for other indications in which it is very challenging to determine whether the incidentally observed thrombosis is acute, chronic or even an imaging artefact.[22]

MR-NCTI has been shown to be a valuable diagnostic test for the diagnosis of upper extremity DVT, pelvic vein and cerebral vein thrombosis [11,19,23] and was shown to be an accurate, simple, feasible and reproducible diagnostic test in suspected recurrent ipsilateral DVT of the leg.[9] There are some important differences between

venous thrombosis of the portal vein and at other locations. For instance, portal vein imaging is different from imaging of veins in the extremities and brain, due to the presence of ascites, gas and bowel movements which can hamper abdominal vein imaging. Furthermore, PVT occurs in different clinical circumstances (i.e. portal hypertension, cirrhosis) that are less relevant to typical VTE.[24]

There are only a few case-reports available on non-contrast-enhanced MRI for the diagnosis of PVT, using different techniques and without results on the diagnostic accuracy of MRI for PVT.[25,26] In a study from Zirinsky et al, T1- and T2 weighted MR images of 14 patients with acute and chronic PVT on CT or ultrasonography and of 8 patients with portal hypertension but without evidence of PVT were evaluated. With MRI (sub-)acute (<5 weeks old) thrombi appeared hyperintense relative to liver and muscle on both T1- and T2 weighted sequences and older thrombi (2-18 months old) appeared hypertense in some patients, but only on T2-weighted images. Therefore, it was suggested that chronic thrombosis may lose their relative hyperintensity on T1-weighted images and thus may be used for detecting and classification of PVT.[25] In a case-series from Haddad et al, thrombosis on non-contrast-enhanced T1-weighted images appeared different depending on the age of the thrombus, with a high signal intensity in subacute splanchnic vein thrombosis (<6 weeks) and low signal intensity in more chronic (> 2 months old) thrombosis.[26]

There are some limitations of the current study. First, this study includes only three patients and therefore, the validity of the results must be evaluated in a large cohort before we can proceed to an outcome study. Such an accuracy study is currently ongoing. Furthermore, the evaluation of MR-NTCI images by the expert panel was not blinded for other imaging studies including ultrasound and CT images. Additionally, due to the small number of patients the interobserver agreement could not be established.

In conclusion, we were able to identify two MR-NTCI sequences, 3D T1 TFE and 3D T1 Dixon FFE, that were able to diagnose and differentiate acute from chronic PVT. With our previous experience based on imaging of DVT in the lower and upper extremities [9,11,19], we believe that the image quality is sufficient to be of clinical value and initiate the clinical part of the Rhea study (NTR 7061) to establish the diagnostic accuracy of MR-NCTI for the differentiation of acute from chronic PVT. Furthermore, the interobserver agreement of these sequences for PVT imaging will be assessed.

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Appendix A: Pubmed search string

(((“Venous Thrombosis”[mesh]) OR “splanchnic vein thrombosis”[tw] OR “splanchnic vein thromboses”[tw] OR “splanchnic venous thrombosis”[tw] OR “mesenteric vein thrombosis”[tw] OR “mesenteric vein thromboses”[tw] OR “mesenteric venous thrombosis”[tw] OR “mesenteric venous thromboses”[tw] OR “portosplenomesenteric venous thrombosis”[tw] OR “splanchnic”[ti] OR “mesenteric”[ti] OR “portosplenomesenteric”[ti]) OR “vein”[ti] OR “venous”[ti] OR (“abdominal”[ti] AND “imaging”[ti]) OR (“thrombosis”[ti] OR “thromboses”[ti] OR “embolism”[ti] OR “thrombus”[ti] OR “occlusion”[ti]))) AND (“MRDTI”[tw] OR MR-DTI[tw] OR “magnetic resonance direct thrombus imaging”[tw] OR “magnetic resonance”[tw] OR “Magnetic Resonance Imaging”[mesh] OR “Magnetic Resonance Imaging”[tw] OR “MRI”[tw] OR mr imag*[tw] OR “thrombus imaging”[tw]) OR (“Fat”[All Fields] AND “Suppression”[All Fields]) AND (“methods”[All Fields] OR “techniques”[All Fields] OR “methods”[mesh] OR “techniques”[All Fields])).

For online supplementary material, please scan this QR code:


7

CHAPTER

Current imaging modalities for diagnosing cerebral vein thrombosis – a critical review

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ABSTRACT

Cerebral vein thrombosis (CVT) is a rare presentation of venous thromboembolism. Prompt and accurate diagnosis is essential as delayed recognition and treatment may lead to permanent disability or even death. Since no validated diagnostic algorithms exist, the diagnosis of CVT mainly relies on neuroimaging. Digital subtraction angiography (DSA) is the historical diagnostic standard for CVT but is rarely used nowadays and replaced by computed tomography (CT) and magnetic resonance imaging (MRI). High quality studies to evaluate the diagnostic test characteristics of state-of-the-art imaging modalities are however unavailable to date. This review provides an overview of the best available evidence regarding the diagnostic performance of CT and MRI for the diagnosis of CVT. Notably, available studies are observational, mostly small, outdated, and with a high risk of bias. Therefore, direct comparison between studies is difficult due to large diversity in study design, imaging method, reference standard, patient selection and sample size. In general, contrast-enhanced techniques are more accurate for the diagnosis of CVT then non-contrast-enhanced techniques. CT venography and MRI have been both reported to be adequate for establishing a final diagnosis of CVT, but choice of modality as used in clinical practice depends on availability, local preference and experience, as well as patient characteristics. Our review underlines the need for high-quality diagnostic studies comparing CT venography and MRI in specific settings, to improve clinical care and standardize clinical trials.

INTRODUCTION

Cerebral vein thrombosis (CVT) refers to dural sinus as well as cerebral vein (cortical and deep vein) thrombosis, and is a rare but potentially life threatening presentation of venous thromboembolism.[1] It accounts for 0.5-1% of all strokes in the adult population with an incidence of 1.32 per 100 000 person-years.[2,3] The clinical presentation of CVT is highly variable and nonspecific. Since there are no validated diagnostic algorithms incorporating decision rules or D-dimer tests, the diagnosis of CVT mainly relies on neuroimaging.[2,4] Neuroimaging is also the main method for evaluation of CVT related complications relevant for prognosis and therapeutic management.[2,5] Therefore, knowledge of the diagnostic performance of available imaging modalities is of great importance for optimal management of the individual patient.

Different imaging modalities and techniques can be used for the diagnosis of CVT in adults. Digital subtraction angiography (DSA) once was the diagnostic standard for CVT but is rarely used nowadays due to its invasive nature which harbours a small risk for serious complications, including neurologic complications (i.e. neurologic sign or symptom or worsening of a preexisting neurologic deficit that occurred during the procedure or within 24 hours).[6,7] Neurologic complications are reported to occur in around 1.3% of patients undergoing DSA; with permanent deficits in 0.5% of patients.[7] Additional disadvantages of DSA include radiation exposure, and allergic or nephrotoxic effects of iodinated contrast agent.[8] In current clinical practice, DSA is reserved for exceptional cases, often when reperfusion therapy (such as thrombosuction) is considered.[4,9] Computed tomography (CT)/CT venography and magnetic resonance imaging (MRI) are presently the first line tests used in clinical practice [5,10-12], but each modality and technique has its advantages and disadvantages.[13] Randomized controlled diagnostic trials comparing these imaging modalities are absent, probably because of the low incidence of the disease. Therefore, knowledge of the diagnostic performance of each of these modalities is based on small observational studies. Results on diagnostic accuracy of the different imaging modalities from available studies must be interpreted with caution and cannot directly be compared nor translated into daily clinical practice, due to heterogeneity in study design, patient population (clinical presentation), imaging methods and used reference standard. Consequently, the diagnostic approach for the diagnosis of CVT differs considerably per country and even per hospital.[5]

We aimed to provide an overview of published literature and applied extensive literature searches to identify all relevant papers regarding the diagnostic performance of CT/CT venography and MRI for the diagnosis of CVT (search strategy detailed in **Appendix 1**). Papers were chosen if written in Dutch or English and evaluating the diagnostic accuracy of CT/CT venography and MRI in cerebral vein thrombosis. We only excluded case-reports and reviews. Notably, in previous publications various terminology has been used for CVT. In this review isolated thrombosis of the dural sinuses is referred to as cerebral sinus thrombosis and thrombosis of both dural sinus and cerebral veins as CVT.

Computed tomography

In the emergency setting, CT is often the imaging test of choice for patients presenting with acute focal neurological symptoms [5,10], since it's widely available, cost-effective and useful to rule out common neurological diagnoses.[14] CVT may present variable on CT (**Table 1**). A direct sign of CVT on non-contrast CT (NCCT) is direct visualization of a thrombus which is predominantly caused by the protein factor of haemoglobin within red blood cells, often called the "dense clot sign" or "dense vessel sign" (**Figure 1A**).[15] After the administration of a contrast agent the thrombus can directly be visualized as a filling defect within a dural sinus also called "empty delta sign", which is specific for thrombosis of the superior sagittal sinus.[2,9] On CT indirect signs of CVT are often seen and may occur in 60-80% of cases.[14] Common indirect signs on CT that are highly evocative of CVT are multiple bilateral lesions (e.g. bilateral parasagittal hemispheric lesions are suggestive of superior sagittal sinus thrombosis), bilateral thalamic edema (can be found in deep cerebral vein thrombosis) and temporo-occipital lesions (suggestive for transverse sinus thrombosis).[14,16,17] Cerebral hemorrhage is also a common finding in patients with CVT, present in approximately 40% of patients.[18] Juxtacortical hemorrhages, small hemorrhages with limited or no edema, localized at the junction between the superficial and deep venous drainage system, are seen in up to 12% of CVT patients and are very specific for CVT and almost exclusively occur in superior sagittal sinus thrombosis.[18]

There are several studies that evaluated the diagnostic accuracy of direct and indirect signs on NCCT. These studies (with sample sizes ranging between 7 and 588 patients), which were all retrospective, mostly small and using different reference standards (CT venography, MRI, DSA and/or multiple imaging and

follow up), found a sensitivity 41-100% and specificity of 77-100%.(**Appendix 2**) [19-26] The best reported diagnostic accuracy of the attenuated vein sign on NCCT for the diagnosis of deep cerebral vein thrombosis was a sensitivity of 100% and specificity of 99%.[20] It is important to note that this was found in a small single center retrospective study, including only 8 patients diagnosed with deep cerebral vein thrombosis.[20] The reported accuracy for cerebral sinus thrombosis is a sensitivity of 50-100% and a specificity of 83-100%.[20-22,24,25] An explanation for these wide ranges may be the different scan technologies and acquisition measures used, with a generally lower sensitivity in older studies.[23] Poor interrater variability of the evaluation of direct and indirect signs on NCCT may also play a role.[26] In the specific setting of isolated cortical vein thrombosis, the reported sensitivity and specificity are 25% (95%CI 18-25%) and 100% (95%CI 92-100%), respectively.[21] In these studies, a thrombus was often missed since the "cord sign" or "string sign", a direct sign of cortical vein thrombosis on CT, is difficult to detect due to its location next to the skull.[21]

Because of the linear association between the attenuation of blood and haematocrit levels [27], high haematocrit values can result in a false positive CVT diagnosis.[15] On the other hand anaemia may result in false negative diagnosis. Moreover, subacute thrombosis may also result in false negative diagnoses since the density of thrombi attenuated over time and becomes isodense or even hypodense after approximately 7-14 days.[15,28] Therefore, studies have evaluated whether quantitative assessment of the attenuation and attenuation values compared to haematocrit (H:H ratio) improved the diagnostic accuracy of NCCT for the diagnosis of CVT, but did not find superior sensitivity (64-95%) or superior specificity (54-100%).[13,15,24-26,29-31] Notably, after the administration of a contrast agent, direct/indirect signs on CT scan can still be absent in up to 30% of the CVT cases (**Appendix 2**).[9,32-39]

Recently, a meta-analysis summarizing the diagnostic accuracy of CT (non-contrast- and contrast-enhanced) for CVT has been published.[40] Twenty-four eligible publications, including 48 studies with varying study designs and diagnostic standards were included, for a total of 4595 individual patients. Overall, CT was found to have a reasonable diagnostic accuracy with a pooled sensitivity of 79% (95%CI 76-82%) and a pooled specificity of 90% (95%CI 89%-91%). For the diagnosis of cerebral sinus thrombosis, the pooled sensitivity and specificity of CT were 81% (95%CI 78-84%) and 89% (95%CI 88-91%), respectively. Subgroup analyses showed no significant difference of the diagnostic accuracy in suspected acute, sub-acute

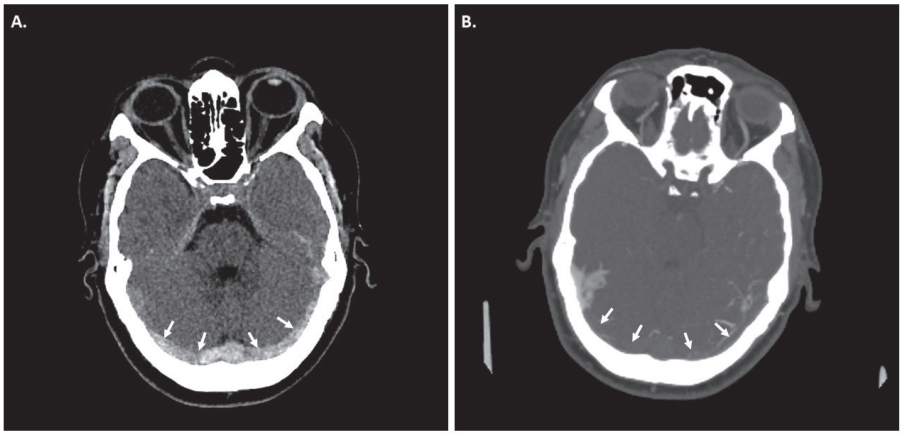
or chronic CVT. The authors also found that visual assessment (evaluation of direct/indirect signs) was more accurate than quantitative assessment (attenuation evaluation).[40]

In summary, while CT is useful as primary imaging modality in patients with suspected acute CVT, additional imaging is generally required to diagnose and rule out CVT with more certainty.[2,5,15,26,41]

Table 1: (Non-)contrast-enhanced computed tomography (CT) findings in cerebral vein thrombosis.

	Direct signs	**Indirect signs**
Non-contrast CT (NCCT)	Dense clot sign: direct visualization of the thrombus in the cerebral sinus and veins	Haemorrhagic infarction
		Brain oedema
	Cord or string sign (dense vessel sign): linear or cord-like density of a thrombosed cortical vein	Mass effect
		Subarachnoid haemorrhage
Contrast-enhanced CT (CECT)	Empty delta sign: thrombosed sinus seen as triangular area of enhancement with relatively low attenuation center	Same findings as on NCCT

Figure 1. Axial CT images of a patient with acute sinus thrombosis; A. Non-contrast CT image shows a hyperdense aspect of both transverse sinus (arrows) and B. CT venography after administration of iodinated contrast agent shows a filling defect in both transverse sinus (arrows).



CT venography

CT venography is one of the most often used imaging modalities for the diagnosis of CVT because of its widespread availability and cost-effectiveness.[5] CT venography is a contrast-enhanced helical CT examination performed with a time-optimized contrast bolus in order to enhance the cerebral venous system.[17,42] The diagnosis of CVT can be made by evaluation of the axial thin-section contrast-enhanced source images of a helical CT scan. However, two- and three-dimensional (2D and 3D) reformation techniques (e.g. maximum intensity projection, integral display, and volume rendering) can be used to provide detailed anatomic images of the deep and superficial cerebral veins free from overprojecting bones and brain parenchyma.[17,43] On CT venography, a thrombosed cerebral vein can be visualized as a filling defect (**Figure 1B**).[5,9] Also indirect signs of CVT such as brain edema and subarachnoid haemorrhage can contribute to the diagnosis of CVT.[2,5]

In the most relevant studies available, CT venography was found to be a reliable alternative to DSA for diagnosing CVT [41,44,45] with a sensitivity and specificity of both 100%.[44] However, quality of this evidence is low, since individual studies included less than 100 patients, were observational and suffered from a high risk of bias.[41]

Other studies used consensus reading of multiple imaging modalities and final clinical outcome as reference standard rather than DSA (**Appendix 3**).[10,21,46] In these studies, CT venography was found to be accurate for diagnosing cerebral sinus thrombosis as well, with a sensitivity of 100% (95%CI 88-100%) and specificity of 100% (95%CI 95-100%).[10,21,46] However, these studies were also small ($n<34$) and retrospective. Notably, CT venography has been shown to be of limited diagnostic value for diagnosing cortical vein thrombosis with a reported sensitivity of 6-75%.[21,46] This is explained by the fact that the 'missing vein', i.e. contrast filling defect, is difficult to distinguish from physiological variations in venous anatomy.[21]

Thus, available literature supports the use of CT venography for diagnosing cerebral sinus thrombosis, but less so for cortical vein thrombosis.[21]

Emerging CT techniques

In past years new CT techniques have been developed that may allow better diagnosis of CTV. With the emerge of multidetector row CT (MDCT), thin slices are obtained with the use of less contrast and shorter scanning time allowing better

image quality without significantly increasing overall radiation dose.[46,47] Currently 320-MDCT techniques are used that may acquire brain volumes within a single second.

Several techniques can be used for removing unwanted overlying (bone) structures from the vascular (venous) structures to improve the diagnostic accuracy of CT venography, which is especially needed for 3D interpretation. Previous studies have used the 'graded subtraction' technique, a non-automated post-processing technique which is time-consuming and operator dependent.[42,43,48] State of the art techniques include mask-subtraction and dual-energy. With mask-subtraction a low-dose non-enhanced CT is subtracted from the contrast-enhanced vascular (CT venography) acquisition.[48,49] With dual-energy techniques bone removal is obtained by postprocessing a dual-energy CT data set that is simultaneously acquired with a low- and a high kilovoltage, where difference in x-ray absorption of different materials depend on x-ray energy.[50] New spectral CT techniques such as photon-counting CT hold promise for further improved visualization of CVT.[51,52]

Magnetic resonance imaging

Various MR techniques are available to visualize cerebral vascular structures and/or thrombosis. The MRI techniques can be divided into three groups based on how the thrombosis is depicted: 1) non-contrast-enhanced flow related MRI, 2) native contrast thrombus MRI and 3) contrast-enhanced MRI (**Table 2**). Non-contrast-enhanced flow related MRI, often called non-contrast-enhanced magnetic resonance venography (MRV), includes time-of-flight (TOF) MRV and phase-contrast (PC) MRV (**Table 3**). With this MR technique a thrombus can be depicted by absence of normal flow patterns (**Figure 2**). A thrombus can also be directly visualized with native contrast thrombus MRI techniques. These sequences are used to visualize thrombus by presence of paramagnetic deoxyhaemoglobin, methaemoglobin, or hemosiderin.[53] Moreover, MRI after the administration of an intravenous gadolinium-based agent can be used (contrast-enhanced MRI), which allows direct luminal visualization that is comparable to that of CT venography, where a thrombus can be identified as a filling defect.[5] Compared to CT venography, MRI is more sensitive for the detection of small parenchymal lesions and cerebral edema and has the advantage of not exposing the patient to ionizing radiation.[5,12,54] On the other hand, advantages of CT venography over MRI are the fast acquisition times and the possibility to scan more patients, since many MRI contraindications exist.

Table 2: Different MRI techniques

Type	Sequences
Non-contrast-enhanced flow related MRI	*Gradient echo:* 2D TOF MRV, 3D TOF MRV, 2D PC MRV, 3D PC MRV
Native contrast thrombus MRI	*Spin echo:* T1-WI FSE/TSE, T2-WI FSE/TSE, FLAIR, PDw, MR Black Blood Imaging (MRBTI: T1-WI 3D SPACE), 3DT1 TSE SPAIR
	Gradient echo: DWI, MR Direct Thrombus Imaging (MRDTI: T1-WI magnetization prepared 3D gradient TFE)
	Gradient echo susceptibility weighted: T2*WI, T2*WI SE EPI, T2*SW, T2*GRE, GRE
Contrast-enhanced (T1 SE or GRE) MRI	*Spin echo:* CE T1-WI SE/FSE
	Gradient echo: 3D T1 GRE/MP-RAGE, CE T1 GRE, CE MRV (including combo 4D MRV, 3D EC MRV, CE TOF MRV)

TOF MRV: dimensional time-of-flight magnetic resonance venography, PC MRV: phase-contrast magnetic resonance venography, T1/T2-WI: T1/T2-weighted imaging, FSE: fast spin-echo, TSE: turbo spin-echo, FLAIR: Fluid Attenuated Inversion Recovery, PDw: proton density weighted, SPACE: variable-flip-angle-turbo spin echo, SPAIR: Spectral Attenuated Inversion Recovery *DWI: diffusion weighted imaging, TFE: turbo field echo, SE: spin-echo, EPI: echo-planar imaging, SW: susceptibility weighted, GRE: gradient-echo, CE: contrast-enhanced, MP-RAGE: magnetization-prepared rapid gradient-echo*

Figure 2. Coronal Phase Contrast (PC) MR venography (MRV) image of a patient with acute sinus thrombosis of the left transverse and sigmoid sinus; A. Coronal PC MRV image and B. PC MRV maximum intensity projection (MIP) with absence of flow in the left transverse and sigmoid sinus (arrows).

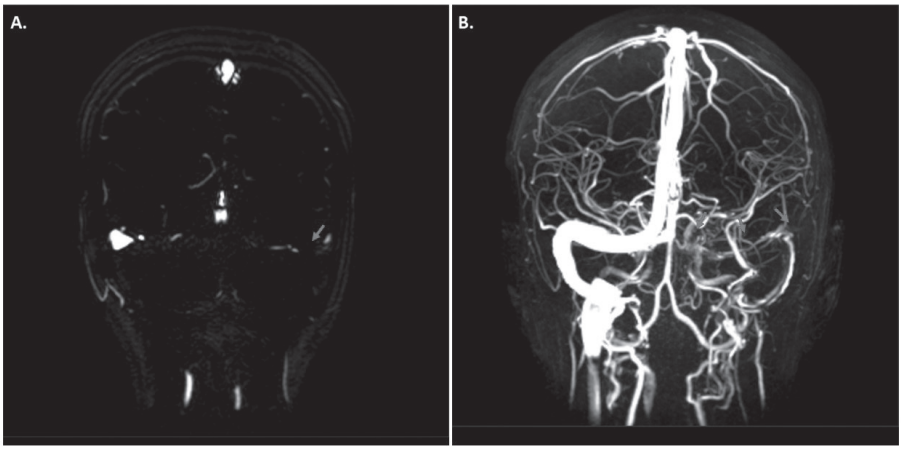


Table 3: Overview of different contrast-enhanced and non-contrast-enhanced magnetic resonance venography (MRV) techniques with advantages and disadvantages.

	Technique	Mechanism	Advantages	Disadvantages
Non-contrast-enhanced (non-CE) MRV	Time-of-flight (TOF) MRV (2D (dimensional) or 3D)	Flow-related enhancement	• Sensitive to slow flow (especially 2D TOF) • Does not require use of a contrast agent • Relatively short acquisition times (5–8 min)	• False positives: loss of signal due to in-plane saturation • False negatives: high signal from background tissue with short T1 values that can mimic flowing blood
	Phase-contrast (PC) MRV (2D or 3D)	Velocity-induced phase shift of spins	• Great suppression of background (stationary) tissues • No false negatives due to methaemoglobin • Can detect flow in 3 orthogonal planes • Ability to quantify flow and determine flow direction	• Sensitive to motion artefacts and turbulent flow • Relatively long acquisition times (>15 min) • Need to predict optimal velocity encoding variable (VENC) • Easily affected by the velocity of blood flow and turbulence
Contrast-enhanced (CE) MRV	3D CE MRV (Static)	T1 shortening of Gadolinium	• Great suppression of background signal • No in-plane saturation effects that are often problematic with the TOF technique • Relatively fast acquisition time • Able to assess (partial) recanalization	• Need for a contrast agent • False negatives: the clot may enhance, simulating an open sinus
	4D CE MRV (Dynamic)	Same as 3D CE MRV	• Same advantages as 3D CE MRV • No need for sophisticated triggering system for contrast injection compared to 3D CE MRV	• Same disadvantages as 3D CE MRV

Non-contrast-enhanced flow related MRI

Most studies that evaluated the diagnostic accuracy of non-contrast-enhanced flow related MRI techniques compared to DSA found an adequate sensitivity and specificity for CVT (**Appendix 4**).[13,55-58] Two studies evaluating non-contrast-enhanced PC MRV found that this technique is sensitive for diagnosing CVT with a sensitivity of 100% and specificity of 71%.[13,57] Notably, DSA was not performed in all study participants.[13,57] The non-contrast-enhanced TOF MRV technique also seems highly reliable for CVT in larger cerebral veins and sinuses. However, this technique was not sensitive for assessing smaller veins (i.e. in branches of cortical veins).[56,58,59]

Most studies evaluated the diagnostic accuracy of non-contrast-enhanced flow related MRI techniques compared to the combination of multiple imaging modalities and final clinical outcome or contrast-enhanced MRV (**Appendix 5**)[21,32,60-69], were adequate sensitivity and specificity for CVT were found too. Non-contrast-enhanced TOF MRV and PC MRV had a sensitivity of 64-100% and 48-100%, respectively, although with wide 95% confidence intervals. Moreover, non-contrast-enhanced flow related MRI was confirmed to be less accurate for identifying cortical vein thrombosis.[21,65]

Native contrast thrombus MRI

With native contrast thrombus MRI techniques, a thrombus is directly visualized (**Figure 3**). In the first 5 days after clot formation, the signal may be isointense on T1-weighted images (T1WI) and hypointense on T2-weighted images (T2WI) as the acute thrombus has a high deoxyhaemoglobin concentration.[2,5,14] Between 6 and 15 days, the clot may appear hyperintense on T1WI and T2WI due to a high methaemoglobin concentration.[2,5] After 15 days the thrombus may appear iso- to hyperintense on T2WI and isointense on T1WI.[2,5] On gradient-recalled echo (GRE) susceptibility weighted (SW) images, deposited blood breakdown products (i.e. methaemoglobin, deoxyhaemoglobin) can cause exaggerated signal drop-out (**Figure 4**) so that intraluminal thrombi can be depicted in stages where the clot may be subtle in other sequences.[5]

Figure 3. Coronal 3DT1 TSE SPAIR images: A. with a high signal intensity of the left transverse sinus (arrows) in a patient with acute sinus thrombosis (6-15 days old) and B. with high signal intensity in two cortical veins (arrows) in another patient indicative of acute cortical vein thrombosis (6-15 days old).

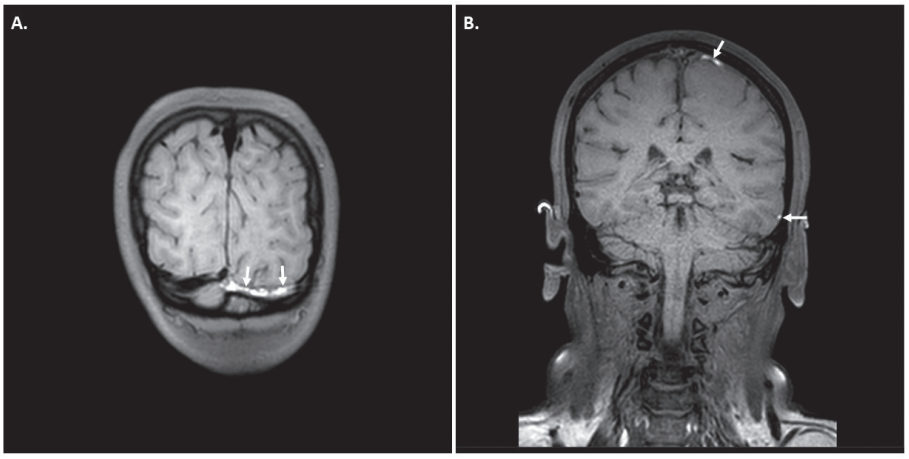
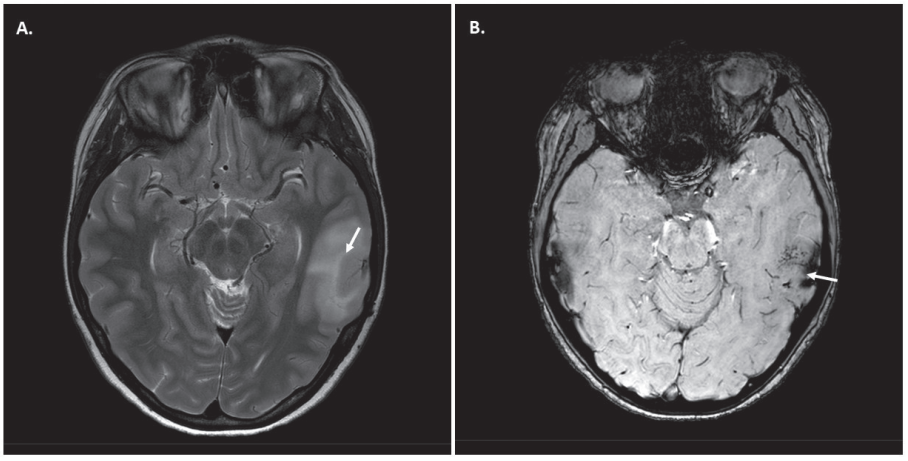


Figure 4. Transversal native contrast thrombus MR images of a patient with left temporal cortical vein thrombosis with venous haemorrhagic infarction: A. T2 weighted image showing a region of increased signal intensity in the cortex and subcortical white matter in the left temporal lobe and B. Susceptibility weighted image showing multiple susceptibility artefacts indicating haemorrhagic transformation in the pathological region with pronounced blooming artefacts within the thrombosed cortical veins (arrow).



The combination of different native contrast thrombus MRI techniques had an overall sensitivity and specificity of 84-97% and 28-96%, respectively, for the diagnosis of CVT (**Appendix 4** and **5**).[32,57,62,70-76] The comparison of these studies and interpretation of their results is complicated by the inclusion of heterogeneous patient populations and different applied MRI sequences, e.g., T1 WI, T2 WI, fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI) and proton density weighted (PDw) sequences. For the diagnosis of cortical vein thrombosis however, GRE SW MRI was consistently reported to have an adequate sensitivity of 97-98% and specificity of 100%.[21,77,78]

Contrast-enhanced MRI

When DSA was used as reference standard, contrast-enhanced MRI was more accurate for diagnosing cerebral sinus thrombosis than non-contrast-enhanced flow related and native contrast thrombus MR sequences, with a sensitivity and specificity of 83% and 100% versus 8-51% and 80-93%, respectively (**Appendix 4**).[56] Other studies used the combination of multiple imaging modalities and final clinical outcome [62-64] or contrast-enhanced MRV [71] alone as reference (**Appendix 5**). In these latter studies, contrast-enhanced MRI was also more sensitive for CVT than non-contrast-enhanced MRI, with a sensitivity and specificity of 86-97% and 52-100% versus 55-97% and 28-95%, respectively.[62-64,71] Furthermore, in studies that evaluated the diagnostic accuracy of MRI for visualization of cerebral veins (not necessarily in the setting of suspected CVT), contrast-enhanced MRI was found to be superior to non-contrast-enhanced MRI as well.[67,79-84]

In a recent meta-analysis, the diagnostic accuracy of flow related MRI (MRV; contrast- and non-contrast-enhanced) for CVT was summarized.[85] Subgroup analyses of different MRV techniques confirmed that the diagnostic performance of contrast-enhanced MRV was better than that of non-contrast-enhanced TOF and PC MRV.

Magnetic resonance black-blood thrombus imaging

Recently, magnetic resonance black-blood thrombus imaging (MRBTI), a native contrast thrombus MR technique, has been evaluated in the setting of suspected CVT.[14,86,87] MRBTI yielded a sensitivity of 100% and specificity of 96%, even up to the level of individual venous segments, using CT and MRI in combination with clinical and outcome assessments -but not DSA- as diagnostic standard.[86] A very similar native contrast thrombus MR technique, MR Direct Thrombus Imaging (MRDTI), has been shown to be highly accurate for the diagnosis of deep vein thrombosis and for the differentiation of acute versus chronic deep vein thrombosis in the legs.[88-93] Thus, this technique may be of great value for diagnosing CVT as well, especially in complex cases such as in suspected recurrent CVT. Further research is however needed before MRBTI can be used for the diagnosis of CVT in daily clinical practice.

MRI versus CT venography

When CT venography was compared to MRI, CT venography had a sensitivity of 100% and specificity of 100% for the diagnosis of cerebral sinus thrombosis (**Appendix 6**).[42,94,95] Two of these studies even found that CT venography was better for the evaluation of small vessel anatomy with fewer artefacts than MRI.[42,94] It is important to note that these studies were small (n=24-36), included patients with suspected CVT but also patients without the suspicion for CVT (follow-up after acute CVT or pre-operative screening), and did not perform the same MR sequences in all included patients.

CONCLUSION

Contrast-enhanced MRI is more accurate than non-contrast-enhanced MRI for diagnosing CVT, as CT venography is more accurate than CT. Both CT venography and contrast-enhanced MRI seem adequate for establishing a CVT diagnosis. Solid evidence to choose one over the other is however unavailable. In practice therefore, clinical availability, local preference and experience mainly determine which modality is used. Large high-quality diagnostic studies are needed to improve clinical care and standardize clinical trials.

For Appendix 1-6, please scan this QR code:

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8

CHAPTER

Magnetic resonance thrombus imaging for the differentiation of chronic versus (sub)acute cerebral vein thrombosis: a Case Report

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ABSTRACT

The diagnosis of cerebral vein thrombosis (CVT) can be difficult. Patients with suspected CVT, in whom venous sinuses are affected by intracranial tumours or after intracranial surgery constitutes a particular challenging setting. Magnetic resonance non-contrast thrombus imaging (MR-NCTI) is a new magnetic resonance imaging (MRI) technique that has previously been shown to be accurate in the diagnosis of a first CVT and difficult-to-diagnose venous thrombosis in other anatomical locations. In this case report, a patient with a medical history of craniotomy for parieto-occipital meningioma was suspected of an acute CVT but had an inconclusive computed tomography (CT) and MRI venography. MR-NCTI showed no abnormalities diagnostic for (sub)acute CVT and thus cerebral sinus occlusion was most likely a chronic thrombus or a result of residual meningioma tissue. Anticoagulant treatment was discontinued, and she was discharged from hospital in good health. This case shows that MR-NCTI may be a valuable additional imaging test in complex cases in whom CT and MRI venography could not exclude acute CVT.

BACKGROUND

Cerebral vein thrombosis (CVT) includes thrombosis of the dural sinuses and cerebral veins and is an uncommon presentation of venous thrombosis.[1] The imaging test of choice for diagnosing CVT is computed tomography (CT) or magnetic resonance imaging (MRI) venography.[2] Even though CT and MRI venography have a high sensitivity and specificity for CVT [3], the diagnosis can be challenging due to complex anatomic variation of cerebral veins and sinuses [2] and also in patients in whom venous sinuses are affected by brain tumours or after intracranial surgery. Magnetic resonance non-contrast thrombus imaging (MR-NCTI) has been shown to be sensitive and specific for the diagnosis of CVT [4,5] as well as difficult-to-diagnose venous thrombosis in other locations, including suspected recurrent ipsilateral deep vein thrombosis (DVT) of the leg or isolated pelvic vein thrombosis in pregnant patients.[6-10] In our view, MR-NCTI therefore has potential added value in the diagnostic management of suspected CVT.

CASE PRESENTATION

We present a 52-year-old patient in whom acute CVT could not be excluded on CT and MRI venography due to post-surgical changes of venous sinuses and in whom the final treatment decision was based on MR-NCTI. She presented at the emergency department with a mild, pressing headache with concomitant nausea that had started three weeks before presentation. In the week before presentation, she had experienced three episodes of acute and intense worsening of the headache, all of which occurred during exercise. Except for blurry vison, she reported no other symptoms. Her medical history included a craniotomy for right sided parieto-occipital meningioma five years ago. She smoked 30 cigarettes per day and was treated with simvastatin because of hypercholesteremia. She did not use oral contraceptives. On physical examination, her blood pressure was 149/87 mmHg, and the heartrate was 84 bpm. The Glasgow Coma Scale was 15/15. Further neurologic examination revealed no abnormalities, in particular no papilledema.

Non-contrast brain CT showed a tissue defect in the right parieto-occipital region, compatible with the postoperative status. CT venography showed no opacification of the posterior part of the superior sagittal sinus and both transverse sinuses

(**Figure 1A**). As prior MRI scans already showed increased signal intensities on fluid-attenuated inversion recovery (FLAIR) and restricted diffusion on diffusion weighted MR images at the same anatomical location, it was initially concluded that the lack of opacification of these sinuses on CT venography could well represent post-surgical changes or chronic thrombosis (**Figure 1B**). Even so, acute CVT could not be excluded with certainty and anticoagulant treatment was therefore started empirically. The next day, a MRI scan was performed including MR-NCTI sequences to evaluate these sinuses in more detail. MR-NCTI scan included three dimensional (3D) T1 weighted turbo field-echo (T1 TFE) and 3D Turbo Spin-echo Spectral Attenuated Inversion Recovery (TSE-SPAIR) sequences performed on a 3.0 Tesla unit (**Table 1**).

MRI venography confirmed the absence of flow in the posterior part of the superior sagittal sinus and in both transversal sinuses (**Figure 1C** and **D**), with concomitant (heterogenous) increased signal intensity on T2 weighted MR images. However, on MR-NCTI images no increased signal intensity was present at these locations, making the diagnosis of an (sub)acute CVT highly unlikely (**Figure 1E** and **F**). The final diagnosis therefore was changed into a cerebral sinus occlusion either due to chronic CVT or as a result of residual meningioma tissue. Anticoagulant treatment was discontinued, and she was discharged from hospital in good health. She was kept under outpatient surveillance at the department of Neurosurgery for regular follow-up after the meningioma resection. She had persistent headache which was diagnosed as tension type- and medication overuse headache. A 12-months follow-up MRI showed no new abnormalities and no new adverse events.

DISCUSSION AND CONCLUSIONS

The diagnosis of CVT is based on the positive findings of intraluminal thrombus on either CT or MRI, or a filling defect in a cerebral vein or sinus.[2,11] Excluding acute CVT with non-invasive conventional imaging techniques can be challenging.[2] MR-NCTI is a new technique based on the visualization of methemoglobin in a fresh thrombus which appears as a high signal intensity (bright signal).[12] This allows for the direct visualization of (sub)acute thrombi and the differentiation between acute and chronic thrombosis.[6,13,14] MR-NCTI has previously been shown to be accurate in the diagnosis of a first CVT and is likely to be valuable in the diagnostic management of complex cases in whom CT and MRI venography could not exclude

acute CVT, such as patients with changes in venous sinuses due to brain tumours or after intracranial surgery. Application of this technique may avoid overdiagnosis and subsequently potential bleeding events. Larger diagnostic studies are needed to confirm the value of MR-NCTI in the diagnostic management of suspected CVT.

Figure 1. Computed tomography (CT) (A) and magnetic resonance images (MRI) (B-F) in a patient with suspected acute cerebral vein thrombosis: A. Sagittal CT venography image showing no opacification of the posterior part of the superior sagittal sinus (arrows) B. Transverse FLAIR MR image showing a parenchymal defect in the right parietal region, surrounded by increased signal intensity (indicative of gliosis), adjacent to the falx cerebri at the location of the superior sagittal sinus. C. and D. Sagittal and coronal MRI venography images showing absence of flow in posterior and caudal part of the superior sagittal sinus and both transversal sinuses (arrows). E. and F. Sagittal and coronal magnetic resonance non-contrast thrombus images (3D T1 TSE SPAIR sequence) showing no high signal intensity at the location of superior sagittal sinus or both transversal sinuses (arrows), making the diagnosis of (sub)acute thrombosis highly unlikely.

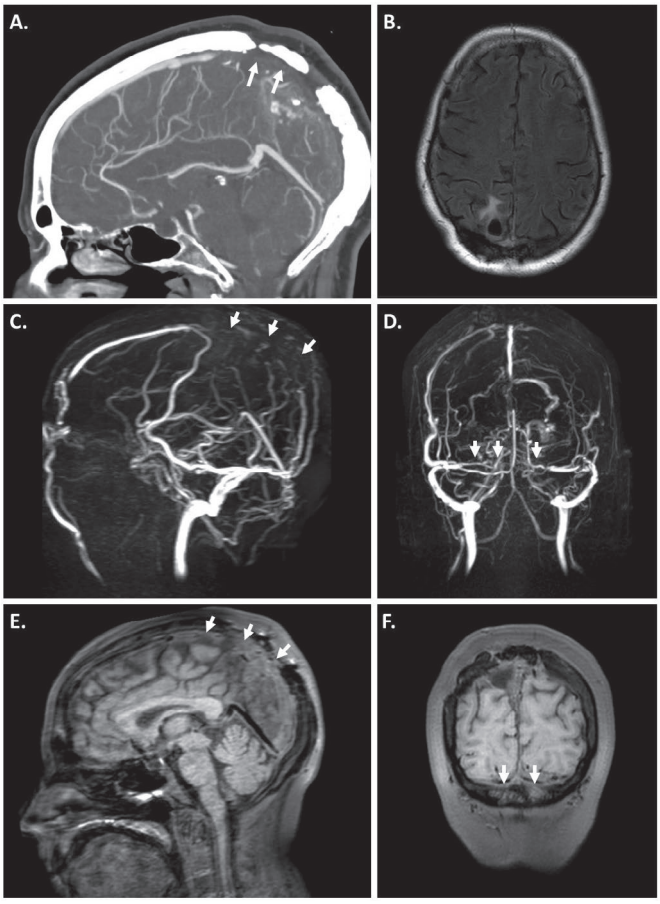

Table 1. Three dimensional T1 weighted turbo field-echo (3D T1 TFE) and three dimensional Turbo Spin-echo Spectral Attenuated Inversion Recovery (3D TSE-SPAIR) MRI scan parameters

	3D T1 TFE	**3D TSE-SPAIR**
Technique	T1 TFE	TSE
Orientation	Coronal	Coronal
Slices	160	209
Slice thickness (mm)	3	1.1
Slice distance (mm)	1.5	0
FOV	250 x 200	250 x 180
Voxel size (mm)	1.0 x 1.0 x 1.5	1.1 x 1.1 x 1.1
Scan time (min)	4.23	5.46
Echo time (ms)	Shortest (5.2)	Shortest (30)
Repetition time (ms)	Shortest (10)	400
Flip angle	15	90

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9

CHAPTER

Magnetic resonance direct thrombus imaging can distinguish between old and new thrombosis in the abdominal aorta: a Case Report

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ABSTRACT

A 43-year-old man with abdominal angina for several months showed a large suprarenal aneurysm with extensive circumferential wall thrombosis of the abdominal aorta on CT angiography, with complete occlusion of the right renal artery and critically stenosed left renal artery. He suffered from severe hypertension and renal failure. A percutaneous transluminal angioplasty (PTA) was planned. After complicated PTA leading to occlusion of the left renal artery, successful rescue revascularization surgery was performed. Hesitant to start anticoagulant treatment because of a high bleeding risk, magnetic direct thrombus imaging (MRDTI) to assess the age of the extensive arterial thrombosis was done. The MRDTI scan showed a low signal intensity of the aortic thrombus indicative of chronic thrombosis rather than acute thrombosis. Oral anticoagulant treatment was therefore not started. The patient recovered without major complications.

INTRODUCTION

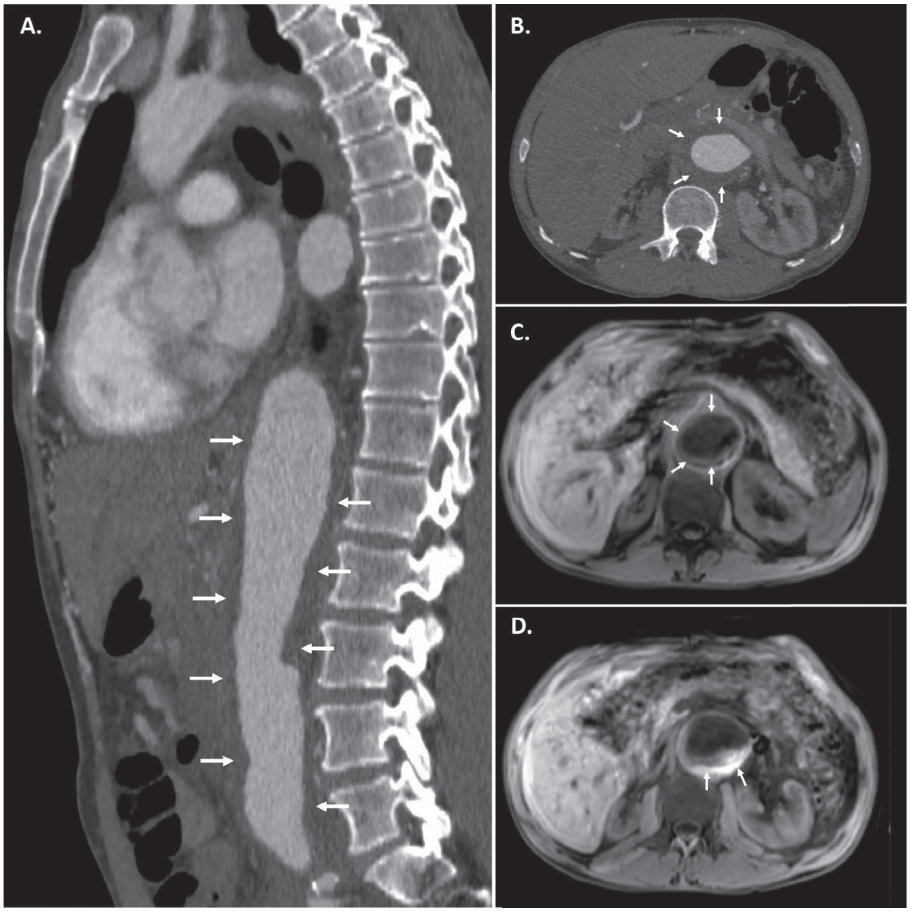
Aortic intraluminal thrombosis (ILT) commonly occurs in the presence of aortic pathology, such as aneurysmal disease, atherosclerotic plaque and/or dissection. Approximately 70-80% of patients with an abdominal aortic aneurysm (AAA) develop a non-occlusive aortic ILT.[1] Accurate diagnosis and treatment of ILT are of utmost importance to prevent serious complications such as (peripheral) arterial embolic occlusion with resultant ischemia.[2] To the best of our knowledge, we present the first report of a patient in whom the non-invasive magnetic resonance direct thrombus imaging (MRDTI) technique was used to determine whether an abdominal aortic thrombus was acute or chronic to guide antithrombotic management.

CASE DESCRIPTION

A 43-year-old man was referred to our hospital with abdominal discomfort for several months. He was a heavy smoker with 30 pack/years. His medical history included an ischemic stroke, helicobacter pylori gastritis and severe hypertension complicated by cardiac hypertrophy. He was prescribed chlorthalidone, barnidipine, lisinopril, nebivolol, clopidogrel, simvastatin and ranitidine. His family history was remarkable for multiple aortic aneurysms and coronary artery disease in his father, who died at a young age of a ruptured aneurysm. His mother had been treated for systemic hypertension. On physical examination he was hypertensive with a blood pressure of 211/130 mmHg and a heart rate of 55 bpm. During auscultation of the abdomen a murmur was recognized. Palpitation of the abdomen was not painful. Peripheral pulsations were present in both arms and legs. Neurologic examination was normal.

Laboratory results showed severe renal insufficiency with an estimated glomerular filtration rate (eGRF) of 14mL/min and a creatinine level of 418 µmol/L. A CT angiography was performed showing a large suprarenal aortic aneurysm with diffuse circular atherosclerosis and extensive circumferential aortic wall thrombosis (**Figure 1A** and **1B**). The celiac trunk, superior mesenteric artery and right renal artery were occluded with an atrophic right kidney. The left renal artery was critically stenosed. The patient was subjected to PTA of the left renal artery, which was complicated by complete occlusion. To rescue the left kidney

Figure 1. CT images after IV iodinated contrast and MRDTI images without contrast agent. Figure 1A and 1B: Sagittal and axial CT image after IV contrast showing extensive wall thrombosis of the abdominal aorta (arrows) which cannot be distinguished from the aortic wall. Figure 1C: Axial MRDTI image showing chronic thrombosis (low signal intensity) in the aortic wall (arrows). Figure 1D: Axial MRDTI image showing high signal intensity representing recent thrombus in the aortic wall near the location of the PTA and rescue revascularization (arrows).



and treat abdominal angina a bifurcated Dacron bypass was made from the right external iliac to the left renal artery and common hepatic artery. Collateral flow via a well-developed gastroduodenal artery ensured adequate perfusion of the superior mesenteric arterial network. We hesitated initiating anticoagulant treatment because of a high bleeding risk due to the recent major surgery, severe hypertension and renal insufficiency. Therefore, a MRDTI scan was performed

to assess the age of the thrombus, which showed a low signal intensity of the aortic thrombus indicative of chronic rather than acute thrombosis (**Figure 1C**). A high signal intensity was only found in the aortic wall at the level of the left renal artery where the PTA had caused acute occlusion and bypass surgery had been performed (**Figure 1D**).

Because no acute thrombosis was identified, anticoagulant treatment was not started, and antiplatelet therapy continued. Abdominal ultrasonography after the bypass surgery showed open bypasses. The renal function gradually improved, and the patient could be discharged from hospital in good health. Genetic testing was performed because of the premature aortic thrombosis in presence of an AAA but was negative for connective tissue disorders or chromosomal syndromic thoracic aortic aneurysm. The patient was kept under close outpatient surveillance because of chronic persistent renal insufficiency with an eGFR of 60mL/min. In the first year after presentation, there were no thrombotic or bleeding complications.

DISCUSSION

Aortic ILT may lead to peripheral embolism resulting in occlusion of the distal arteries.[3] Importantly, an acute aortic thrombosis (AAT) is a rare life-threatening event and may be caused by in-situ thrombosis of an atherosclerotic aorta, large saddle embolus to the aortic bifurcation or occlusion of previous surgical reconstruction.[4] Prompt management is indicated in case of an AAT or an acute ischemic event caused by distal embolization [4] and may be considered in an unstable thrombus.[1] However, current imaging modalities do not allow for accurate distinction between acute versus chronic thrombosis. It is therefore challenging to differentiate between stable and unstable thrombi.

MRDTI is a technique in which a thrombus can directly be visualized without the use of a potential toxic contrast agent. This method is based on the formation of methemoglobin in a fresh thrombus leading to shortening of the T1 signal on MRI.[5] It has been shown to accurately diagnose a first deep vein thrombosis (DVT) and distinguish chronic thrombotic remains from acute recurrent DVT with a sensitivity of 95-100% and specificity of 100%.[6,7] Current studies are evaluating its diagnostic accuracy for unusual site venous thromboembolism, including upper extremity DVT and splanchnic vein thrombosis (NTR 5738 and NTR 7061), where current imaging tests often cannot provide a definite diagnosis.

MRDTI may prove useful to overcome diagnostic challenges in the arterial system too, but the technique has not been extensively studied in this setting. In a preliminary study, 14 patients with acute limb ischemia were evaluated with MR angiography and MRDTI. MRDTI showed a positive signal in 11 (79%) patients. In 6 patients MRDTI findings were discrepant in thrombus length and occlusion compared to MR angiography. Since recanalization with thrombolysis in these 6 patients was not achieved, it was suggested that the discrepancy reflected a difference between chronic arterial disease and superimposed acute thrombosis.[8] MRDTI was also suggested to be useful in identifying complicated plaques in the carotid arteries and upper thoracic aorta in patients with cerebral vascular disease.[9,10] MRDTI has not yet been evaluated as a tool to guide anticoagulant treatment in abdominal aortic thrombosis. Because of the associated morbidity and mortality of complicated aortic ILT, accurate diagnosis of an unstable thrombus or differentiation between acute versus chronic thrombosis remains very relevant for selected patients.

We present the case of a patient who was diagnosed with AAA and extensive wall thrombosis in whom acute and unstable thrombosis could be excluded with MRDTI. MRDTI may therefore be a valuable additional imaging test to establish a definitive diagnosis and treatment in patients with abdominal aortic thrombosis with or without co-existing aortic pathology. More diagnostic studies are needed to support our findings.

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10

CHAPTER

Computed tomography pulmonary perfusion for prediction of short-term clinical outcome in acute pulmonary embolism

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ABSTRACT

Background: Computed tomography pulmonary angiography (CTPA) is the imaging modality of choice for the diagnosis of acute pulmonary embolism (PE). With computed tomography pulmonary perfusion (CTPP) additional information on lung perfusion can be assessed, but its value in PE risk stratification is unknown. We aimed to evaluate the correlation between CTPP-assessed perfusion defect score (PDS) and clinical presentation and its predictive value for adverse short-term outcome of acute PE.

Methods: This was an exploratory, observational study in 100 hemodynamically stable patients with CTPA-confirmed acute PE in whom CTPP was performed as part of routine clinical practice. We calculated the difference between the mean PDS in patients with versus without chest pain, dyspnoea and haemoptysis and 7-day adverse outcome. Multivariable logistic regression analysis and likelihood-ratio test were used to assess the added predictive value of PDS to CTPA parameters of right ventricle dysfunction and total thrombus load, for intensive care unit admission, reperfusion therapy and PE-related death.

Results: We found no correlation between PDS and clinical symptoms. PDS was correlated to reperfusion therapy (n=4 with 16% higher PDS, 95%CI 3.5-28%) and PE-related mortality (n=2 with 22% higher PDS, 95%CI 4.9-38). Moreover, PDS had an added predictive value to CTPA assessment for PE-related mortality (from Chi-square 14 to 19, p=0.02).

Conclusion: CTPP-assessed PDS was not correlated to clinical presentation of acute PE. However, PDS was correlated to reperfusion therapy and PE-related mortality and had an added predictive value to CTPA-reading for PE-related mortality; this added value needs to be demonstrated in larger studies.

INTRODUCTION

Computed tomography pulmonary angiography (CTPA) is the current imaging modality of choice for the diagnosis of pulmonary embolism (PE).[1] In recent years technical advances have been made in the diagnostic management of PE including the introduction of computed tomography pulmonary perfusion (CTPP) imaging. With CTPP additional information of hemodynamic and functional impact of the PE as expressed by measures of pulmonary perfusion can be assessed.[2]

Available studies using CTPP have mostly focused on its diagnostic performance for acute PE. The addition of CTPP to CTPA has been reported to improve the specificity for a PE diagnosis [3] and to improve the detection rate of small, subsegmental emboli.[4,5] Also, perfusion defects on CTPP were found to be correlated to PE thrombus load and signs of right ventricular dysfunction on CTPA.[6-10] Therefore, perfusion defects on CTPP may be relevant for prognostication of PE patients as well, although this is less well studied. For instance, the quantification of perfusion defects may predict PE-related death, hemodynamic collapse or need for oxygen therapy. This information is relevant for initial risk stratification and treatment or to consider home treatment in patients with good prognosis.[11]

In this study, we aimed to evaluate the correlation between perfusion defects on CTPP and clinical symptoms at presentation and its predictive value for adverse short-term outcome of acute PE.

METHODS

Study design and population

This was a prospective observational study in a convenience sample of 100 consecutive hemodynamically stable adult patients (≥18 years) with CTPA-confirmed acute symptomatic PE, diagnosed between July 2017 and October 2019 in the Leiden University Medical Center (LUMC) in whom CTPP was performed as part of routine clinical practice. Patients were excluded in case of non-assessable CTPP scan due to imaging artefacts. The diagnostic management of patients with suspected acute PE started with assessment of the clinical pre-test probability in

combination with D-dimer testing, following the YEARS algorithm.[12,13] In patients with CTPA-confirmed acute PE, anticoagulant treatment was started or modified in patients already on anticoagulant treatment according to international standards. The Hestia rule, consisting of 11 clinical criteria, was used to identify low risk PE patients for outpatient treatment.[11,14,15] This study was approved by the institutional review board of the LUMC, and informed consent requirement was waived due to its observational nature.

Primary and secondary aim

The primary aim was to investigate the correlation between quantification of CTPP-measured perfusion defects with clinical symptoms at presentation, and its predictive value for adverse short-term 7-day outcome. The secondary aim was to investigate the added value of CTPP reading to right ventricle to left ventricle diameter ratio (RV/LV ratio), pulmonary artery trunk diameter and total thrombus load on CTPA for prediction of intensive care unit (ICU) admission, reperfusion therapy and PE-related mortality. Furthermore, the correlation between perfusion defect score on CTPP and total thrombus load on CTPA was evaluated.

Outcomes

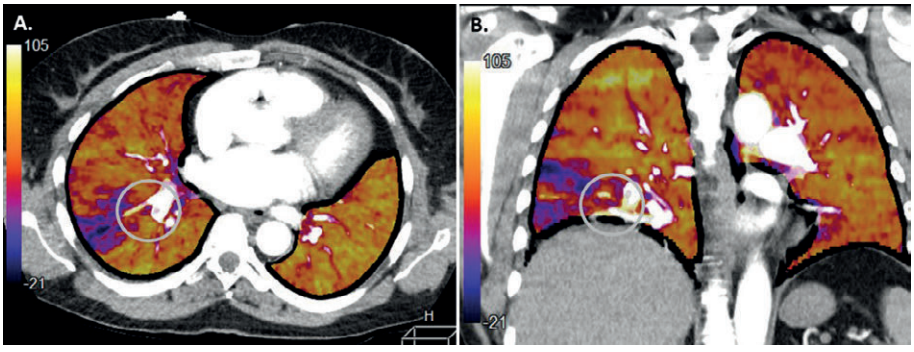
For the primary outcome, clinical symptoms at presentation and adverse short-term outcome were evaluated. Clinical symptoms included (non-)pleural chest pain, dyspnoea and haemoptysis. Adverse short-term outcome included hospital or ICU admission, need for supplemental oxygen therapy or intravenous pain medication >24 hours, reperfusion therapy, vasopressor or inotropic therapy and PE-related death within 7-day follow-up. All symptoms and outcomes were assessed from digital patient files.

For the secondary outcome, we assessed prognostic imaging signs on CTPA including RV/LV ratio, pulmonary artery trunk diameter and total thrombus load. The predictive capacity of these CTPA clinical imaging signs and of PDS for the outcome of ICU admission, reperfusion therapy and PE-related mortality was evaluated.

Image acquisition and analysis

Since June 2017, CTPP is part of the standard CT angiography protocol in adult patients with suspected PE at our hospital. CT examinations were performed on a 320-multislice detector row CT scan (Canon). CTPP images were acquired using subtraction technique, in which the pre-contrast image is subtracted from the contrast-enhanced image. The subtraction image is then colour coded and fused with the CTPA images; normal perfusion: yellow to orange, moderately decreased perfusion: red to pink, severely decreased or absent perfusion: purple to dark blue/black (**Figure 1**).

Figure 1. A. Fused parametric perfusion map with CTPA, axial and B. coronal image in a patient with an acute thrombus in the right lower lobe pulmonary artery (encircled) with subsegmental reduced lung perfusion in the laterodorsal segment of the right lower lobe.



For this analysis, CTPP and CTPA image reading was performed independently by two different readers, who were unaware of presenting symptoms and occurrence of adverse events. CTPP assessment was performed by a researcher (L.F.V.D.) trained by an expert thoracic radiologist (L.J.M.K.). Perfusion defects were quantified per segment using the score proposed by Chae et al and expressed as mean PDS in percentage.[10] To assess the interobserver agreement for PDS reading CTPP images of 25 consecutive patients were independently evaluated by a second reviewer (L.K.). RV/LV ratio, pulmonary artery trunk diameter and total thrombus load on CTPA were evaluated by one expert thoracic radiologist (L.J.M.K.) with over 20 years of experience in pulmonary CTPA-reading. The maximum diameters of both the right and left ventricle were measured in the standard axial view with measurement of the maximal distance between the ventricular endocardium and the interventricular septum. The pulmonary artery trunk was measured at its

largest transverse diameter. The total thrombus load was assessed by using the CT obstruction index according Qanadli et al.[16]

Definitions

Acute PE was defined as at least one filling defect in the pulmonary artery tree on CTPA.[17-19] Pleural chest pain was defined as sharp chest pain that worsens during breathing. Non-pleural chest pain was defined as pressure on or squeezing sensation in the chest. PE-related death was defined as objectively confirmed clinically severe PE before death in the absence of an alternative diagnosis.[20]

Statistical analysis

Baseline characteristics are described as mean with standard deviation (SD) or median with interquartile range (IQR). To evaluate the correlation between PDS to clinical symptoms and adverse outcomes, the difference between the mean PDS with corresponding 95% confidence interval (95%CI) in patients with versus without chest pain, dyspnoea and haemoptysis and adverse short-term outcome was calculated. To evaluate the agreement in PDS scoring between the two reviewers the mean difference between PDS assessed by reviewer 1 and 2 was calculated.

The added predictive value of PDS to CTPA assessment for ICU admission, reperfusion therapy and PE-related death was assessed by comparing two prediction models. In the first prediction model CTPA parameters including RV/LV ratio, pulmonary artery trunk diameter and total thrombus load were included. In the second prediction model PDS assessment was added to these CTPA parameters. Multivariable logistic regression analysis and the likelihood-ratio test were performed to assess the predictive value of the two models for ICU admission, reperfusion therapy and PE-related death and whether PDS assessment significantly improved the predictive value of the model. Additionally, to quantify the performance of the prediction models, we determined the discrimination and calibration. Discrimination refers to the ability to discriminate between those with and those without the outcome and calibration to the agreement between observed outcomes and predictions. Discrimination was expressed with the concordance (c) statistic, by calculating the area under the receiver operating characteristic curve (AUC) with a 95%CI, with discrimination considered perfect if AUC=1, good if AUC>0.8, moderate if AUC 0.6–0.8, poor if AUC<0.6, and no better

than chance if AUC=0.5. Calibration was assessed using the Brier score, which ranges from 0 to 0.25, with a score of zero signifies a perfect prediction model and a score of 0.25 a non-informative model.[21]

The correlation between PDS and total thrombus load was evaluated using the Pearson's correlation test. A two-sided p-value of $p<0.05$ was considered as statistically significant. All statistical analyses were performed in SPSS version 25 (IBM, Armonk, NY, USA).

RESULTS

Study population

A total of 100 patients with CTPA proven acute PE were eligible for analysis. The baseline characteristics of the 100 included patients are shown in **Table 1**. Four patients were transferred to another hospital within 48 hours because of logistical reasons. Results for adverse short-term outcome were thus available for 96 patients. The mean PDS of all included patients was 27% (SD 13%) and mean Qanadli score was 30% (SD 23%). Fourty-nine patients (49%) had a RV/LV ratio>1 (**Table 1**). The agreement in PDS scoring between the two reviewers was good with a mean difference in PDS of 4.2% (SD 6.9%).

Table 1. Baseline characteristics of 100 patients with acute pulmonary embolism (PE)

Mean age (+/- SD) – years	62 (16)
Male – no (%)	53 (53)
Median duration of complaints (IQR) – days	2.0 (1-7)
Recurrent VTE – no (%)	17 (17)
Active malignancy – no (%)	27 (27)
Immobility for > 3 days or recent long travel >6 hours in the past 4 weeks – no (%)	24 (24)
Trauma/surgery during the past 4 weeks – no (%)	22 (22)
Active inflammation/infection	3 (3)
Hormone (replacement) therapy – no (%)	7 (7)
Known genetic thrombophilia – no (%)	0 (0)
Outpatient	80 (80)
Mean PDS score (+/- SD) – percentage	27 (13)
Mean Qanadli score (+/- SD) – percentage	30 (23)
RV/LV ratio>1 – no (%)	49 (49)

IQR, interquartile range; PDS, perfusion defect score; RV/LV ratio, right ventricle to left ventricle diameter ratio; SD, standard deviation; VTE, venous thromboembolism.

Primary outcome

The prevalence of symptoms at presentation and adverse short-term outcome with associated mean PDS are presented in **Table 2**. Of the 100 patients, dyspnea was present in 84 (84%), pleural chest pain in 55 (55%), non-pleural chest pain in 25 (25%), and hemoptysis in 6 patients (6.0%). A total of 60 patients (60%) were admitted to the hospital, of whom 7 patients (7.3%) were admitted to the ICU. Twenty-five patients (26%) were treated with oxygen >24 hours, 6 patients (6.3%) received intravenous pain medication >24 hours, 4 patients (4.2%) received reperfusion therapy, and 3 patients (3.1%) needed vasopressor/inotropic therapy. We did not find a relevant correlation between PDS and clinical presentation (**Table 2**). The PDS was associated with reperfusion therapy (16% higher PDS, 95%CI 3.5-28%) and PE-related mortality (22% higher PDS, 95%CI 4.9-39%; **Table 2)**. The PDS was not associated with the need for oxygen therapy, pain medication or vasopressor/inotropic therapy nor with ICU admission.

Table 2. Perfusion defect score (PDS) in 100 acute pulmonary embolism (PE) patients and correlation to presenting symptoms and short-term adverse outcome

	Prevalence (%)	Mean (SD) PDS in % in patients with:	Mean (SD) PDS in % in patients without:	Difference (95% CI)
Symptoms at presentation (n = 100) and 7-day outcome (n = 96)				
Pleural chest pain†	55 (55)	28 (14)	27 (12)	1.5 (-3.7 to 6.7)
Non-pleural chest pain†	25 (25)	32 (12)	26 (13)	5.5 (-0.41 to 11)
Dyspnea	84 (84)	28 (13)	25 (13)	3.4 (-3.7 to 11)
Hemoptysis	6 (6.0)	27 (14)	27 (13)	-0.74 (-12 to 10)
Hospital admission	60 (60)	28 (14)	27 (11)	0.92 (-4.4 to 6.2)
ICU admission	7 (7.3)	32 (19)	26 (12)	5.7 (-3.9 to 15)
Oxygen therapy > 24 hours	25 (26)	28 (15)	26 (12)	1.4 (-4.3 to 7.2)
IV pain medication > 24 hours	6 (6.3)	23 (12)	27 (12)	-4.6 (-15 to 5.7)
Reperfusion therapy	4 (4.2)	42 (14)	26 (12)	16 (3.5 to 28)*
Need for vasopressor therapy	3 (3.1)	34 (32)	27 (12)	7.6 (-6.8 to 22)
PE related death	2 (2.1)	49 (19)	27 (12)	22 (4.9 to 39)*

*† Patients could have either pleural chest pain or non-pleural chest pain, or both at the same time.*symptoms/outcome correlated to PDS on CTPP*

ICU, intensive care unit

Secondary outcome

The results from logistic regression and likelihood-ratio test are shown in **Table 3**. The first model including CTPA parameters alone was correlated to ICU admission (χ^2 = 17.1, degrees if freedin (d.f.) =3, p=0.001). Model 2 was also correlated to ICU admission (χ^2 = 17.9, d.f.=4, p=0.001), but the predictive capacity hardly improved when PDS was added to CTPA parameters (χ^2 = 0.799, d.f.=1, p=0.371). Model 1 including CTPA parameters and model 2 with addition of PDS assessment were both able to predict reperfusion therapy (χ^2 = 20.9, d.f.=3, p<0.001 and χ^2 =24.1, d.f.=4, p<0.001, respectively). However, the predictive capacity of the model did not improve when PDS was added to CPTA parameters (χ^2 = 3.22, d.f.=1, p=0.073). Model 1 including CTPA parameters alone was able to predict PE-related mortality (χ^2 = 13.8, d.f.=3, p=0.003). Model 2 was also able to predict PE-related mortality (χ^2 = 19.3, d.f.=4, p=0.001) and the addition of PDS scoring also increased the predictive capacity of the model (χ^2 = 5.44, d.f.=1, p=0.020). The odds ratios including 95%CI of each CTPA parameter and PDS within prediction model 2 for each adverse outcome are provided in **Table 3**.

The AUC for CTPA parameters to predict ICU admission was 0.852 (95%CI 0.647-1.00), 0.976 (95%CI 0.938-1.00) for reperfusion therapy and 0.989 (95%CI 0.965-1.00) for PE-related mortality. When PDS was added to the prediction model these AUCs were 0.876 (95%CI 0.725-1.00), 0.984 (95%CI 0.951-1.00) and 1.00 (95%CI 1.00-1.00), respectively (**Table 3**). The prediction model including CTPA parameters had a Brier score of 0.042 for ICU admission, 0.021 for reperfusion therapy and 0.010 for PE-related mortality. Prediction model 2 had a Brier score of 0.043 for predicting ICU admission, 0.013 for reperfusion therapy and <0.001 for PE-related mortality (**Table 3**).

With the use of the Pearson correlation test, a positive correlation between the total PDS and CTPA-assessed total thrombus load was found (r = 0.523, p<0.001).

Table 3. Predictive value, area under the receiver operating characteristic curve (AUC) and Brier score of model 1 (CTPA parameters including RV/LV ratio, pulmonary artery trunk diameter and total thrombus obstruction score) and model 2 (CTPA parameters and perfusion defect score) and odds ratios for each parameter within model 2 for ICU admission, reperfusion therapy and PE-related mortality

	χ^2	d.f.	Sign.	AUC (95%CI)	Brier score	Odds ratio (95%CI)
ICU admission						
Model 1	17.1	3	0.001	0.852 (0.647-1.00)	0.042	
Model 2	17.9	4	0.001	0.876 (0.725-1.00)	0.043	
• RV/LV ratio						6.27 (0.880-44.6)
• Pulmonary artery trunk diameter						1.03 (0.832-1.28)
• Total thrombus obstruction score						1.07 (0.999-1.15)
• Perfusion defect score						0.955 (0.859-1.06)
Difference between model 1 and 2	0.799	1	0.371	-	-	
Reperfusion therapy						
Model 1	20.9	3	<0.001	0.976 (0.938-1.00)	0.021	
Model 2	24.1	4	<0.001	0.984 (0.951-1.00)	0.013	
• RV/LV ratio						65.4 (0.243-1.76^{E}+4)
• Pulmonary artery trunk diameter						1.51 (0.866-2.63)
• Total thrombus obstruction score						1.21 (0.975-1.49)
• Perfusion defect score						1.19 (0.947-1.49)
Difference between model 1 and 2	3.22	1	0.073	-	-	
PE-related mortality						
Model 1	13.8	3	0.003	0.989 (0.965-1.00)	0.010	
Model 2	19.3	4	0.001	1.00 (1.00-1.00)	< 0.001	
• RV/LV ratio						Not applicable due to low number of events
• Pulmonary artery trunk diameter						
• Total thrombus obstruction score						
• Perfusion defect score						
Difference between model 1 and 2	5.44	1	0.020	-	-	

D.f., degrees of freedom; AUC, area under the receiver operating characteristic curve, CI, confidence interval, ICU, intensive care unit

DISCUSSION

We showed that perfusion defects on CTPP are correlated to reperfusion therapy and PE-related mortality and that the addition of PDS assessment to CTPA assessment of RV/LV ratio, pulmonary artery trunk diameter and total thrombus load improved the predictive value of the model to predict PE-related mortality, but not ICU admission nor reperfusion therapy. Moreover, perfusion defects on CTPP did not correlate to clinical symptoms at presentation.

Risk stratification of patients with acute PE is crucial for deciding on the optimal treatment, including hospitalization, close hemodynamic monitoring and reperfusion therapy.[1,22,23] Previous studies found that right ventricle enlargement (RV/LV ratio>1.0) is associated with an increased risk for PE-related mortality.[24-26] Current European guidelines therefore recommend assessment of right ventricular dimensions or function as part of initial risk stratification.[22] As previous publications have shown that CTPP-assessed PDS is correlated to RV/LV ratio and total thrombus load [6-10], perfusion imaging may play a role in this risk stratification. Although our results showed an improvement in the predictive capacity for PE-related mortality when PDS was added to CTPA-reading, the improvement in AUC was only marginally. Furthermore, we could not confirm an added value of PDS over CTPA assessment to predict ICU admission nor reperfusion therapy. A possible explanation may be the low incidence of these adverse outcomes (range between 2 to 7 patients).

We also evaluated whether perfusion defects on CTPP were correlated to clinical symptoms at presentation. This is relevant, as pain and dyspnea for which treatment with intravenous pain medication and oxygen therapy may be needed are also relevant for the decision for hospitalization or home-treatment.[27,28] However, an association between PDS and presenting symptoms could not be established. Of note, as the generation of dyspnea and chest pain involve multiple underlying (complex and not fully understood) mechanisms, a discrepancy between chest pain and dyspnea and extent of perfusion defects in acute PE is possible.[29] PDS was also not correlated to hospital admission. However, the decision to admit a patient to the hospital is often based on multiple variables, some not included in this analysis, including pregnancy, active bleeding and the presence of a social reason for treatment in hospital.

In current literature, the addition of CTPP to CTPA was found to improve the specificity in the PE detection from 94% (95%CI 89-97%) to 100% (95%CI 100-100%)

and the detection of occlusive (sub)segmental pulmonary emboli.[30] CTPP was also evaluated for PE prognostication and was shown to be correlated to adverse clinical outcome including ICU admission, all-cause and PE-related mortality [7,31], but had no added value to RV/LV ratio to predict mortality.[32,33] Hence, based on our results and available literature, the application of CTPP seems to be mostly relevant for the diagnostic management of acute PE, rather than for prognostication.

Limitations of the study are its observational design and the use of a convenience cohort without a specific sample size calculation. This latter may have resulted that the study was underpowered to detect a correlation between PDS and clinical symptoms and some adverse outcomes. On the other hand, the predictive value of perfusion defects for reperfusion therapy and PE-related mortality may be overestimated due to the low incidence of these adverse events and should therefore be interpreted with caution. Furthermore, the presence of clinical symptoms was self-reported and not assessed in a standardized manner, what may have introduced relevant bias. Bias may also be present in the perfusion defect quantification as perfusion defects may not only be the result of a pulmonary embolism but also of other pathology such as a pneumonia. The strengths of this study are its prospective design and the inclusion of all-comers, which supports the external validity of our findings. Also, CTPA and CTPP assessment was performed by independent readers who were unaware of the clinical presentation and course.

In conclusion, PDS was not associated with clinical presentation of acute PE. However, our data showed that CTPP-assessed PDS was correlated to reperfusion therapy and PE-related mortality and improved the predictive value of CTPA-reading for PE-related mortality, but not for ICU admission or reperfusion therapy. Due to the limited number of adverse events and the design or our study, our observations should be considered hypothesis generating. Future larger studies including an upfront determined sample size calculation are needed to determine the clinical relevance of PDS quantification on top of CTPA assessment of right ventricle dysfunction in risk stratification of acute PE.

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11

CHAPTER

Computed tomography pulmonary perfusion imaging and 3-months clinical outcomes after acute pulmonary embolism

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INTRODUCTION

In recent years new imaging techniques have been developed for the diagnosis of acute pulmonary embolism (PE). With the introduction of computed tomography pulmonary perfusion (CTPP), functional images of PE can be obtained with the use of perfusion images.[1] Previous studies haves shown that the addition of CTPP to routine computed tomography pulmonary angiography (CTPA), which is the current imaging test of choice for the diagnosis of PE, improves the diagnosis of acute PE and could be of value in initial risk stratification as well.[1,2] Moreover, perfusion imaging may also play a role in the long-term prognosis of acute PE: extensive clot burden and perfusion defects at the moment of a PE diagnosis have been associated with persistent perfusion defects after 6 months of treatment occurring in up to 50% of PE patients despite anticoagulant treatment.[3-6] This poor recanalization of occluded pulmonary arteries may in turn lead to increased dead-space ventilation and/or abnormal cardiopulmonary response to exercise, or in worst case scenario to chronic thromboembolic pulmonary disease (CTEPD) or pulmonary hypertension (CTEPH).[7] Therefore, extensive perfusion defects on the initial CTPA scan at the time of PE diagnosis may correlate with a future diagnosis of CTEPH, CTEPD and/or functional limitations.[6-8] In this study, we aimed to evaluate the predictive value of CTPP-assessed perfusion defects at initial PE diagnosis for persistent symptoms and adverse outcomes at 3-month follow-up.

METHODS

This was an exploratory study in which we studied a convenience cohort of 100 consecutive adult patients (≥18 years old) with hemodynamically stable CTPA-confirmed acute PE in whom CTPP was performed as part of routine clinical practice in the Leiden University Medical Center (LUMC) in Leiden, the Netherlands between July 2017 and October 2019. Patients with clinically suspected acute PE were managed according to the YEARS algorithm, including clinical pre-test probability assessment and D-dimer testing.[9] Anticoagulant treatment was started in patients with CTPA-confirmed acute PE. All patients were followed for three months as part of routine clinical practice. The study protocol was approved by the institutional review board of the LUMC, and informed consent requirement was waived due to its observational nature.

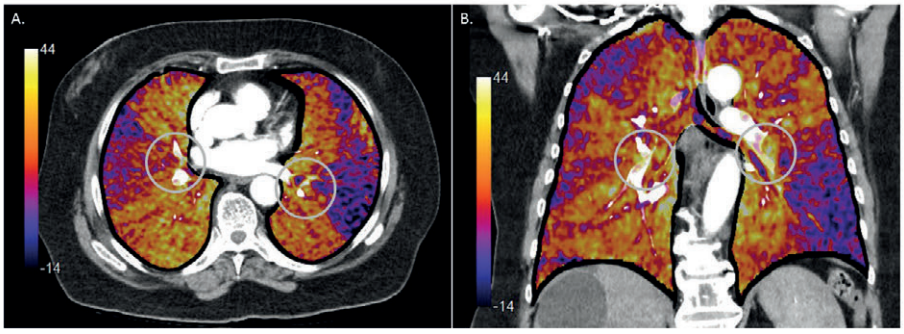
The aim of this analysis was to investigate the predictive value of CTPP-assessed perfusion defects at initial PE diagnosis for persistent symptoms and adverse outcomes at 3-month follow-up. Persistent symptoms included self-reported: 1) dyspnea; 2) chest pain; or 3) post-PE functional impairment. Adverse outcomes included: 1) recurrent venous thromboembolism (VTE); 2) PE-related readmission or; 3) all-cause mortality.

Post-PE functional impairment was defined as new/progressive dyspnea, exercise intolerance and/or diminished functional status following PE adequately treated with anticoagulation for at least 3 months, without an apparent non-PE alternative explanation.[10] PE-related readmission was defined as readmission to hospital due to PE-related complications, such as dyspnea, chest pain, major bleeding or (suspected) recurrent VTE.

CT examinations were performed on a 320-multislice detector row CT scanner (Canon). Perfusion images were obtained with subtraction CT technique in which pre-contrast images are subtracted from contrast-enhanced images. Subsequently, a colour-coded parametric map is produced representing iodine distribution within the lungs, that is fused with the CTPA image. Display settings can be set for normal perfusion: yellow to orange, moderately decreased perfusion: red to purple, severely decreased or absent perfusion: purple to dark blue/black (**Figure 1**). The evaluation of CTPP images was performed by a researcher (L.D.) trained by an expert thoracic radiologist (L.K.) with over 20 years of experience in pulmonary CT reading, and was blinded for symptoms and adverse outcomes. Perfusion defect score (PDS) on CTPP was assessed by using the score proposed by Chae et al. and was expressed as mean PDS in percentages.[2] Additionally, the CTPP images of 24 consecutive patients were independently evaluated by a second reviewer (L.K.) to assess the interobserver agreement for perfusion defect measurement.

Baseline characteristics are described as mean with standard deviation (SD). To assess the correlation between PDS on CTPP and both persistent symptoms and adverse outcomes, differences between mean PDS with corresponding 95% confidence interval (95%CI) in patients with and without persistent symptoms and adverse outcomes were calculated. All statistical analyses were performed in SPSS version 25 (IBM, Armonk, NY, USA).

Figure 1. Colour-coded parametric CT pulmonary perfusion images fused with CT pulmonary angiography images, axial (A) and coronal (B) views of a 68-year-old female patient with an acute pulmonary embolism in the left and right pulmonary arteries (encircled). Several wedge-like dark-coloured areas in both lungs represent hypoperfusion



RESULTS

Of the 100 patients, 7 patients were transferred to another hospital because of logistical reasons. These patients were therefore not taken into account in the following analyses. The mean age of the 93 study patients was 62 years (SD 17), 50 patients (54%) were male, 17 patients (18%) had one or more previous episode(s) of VTE, 25 patients (27%) had an active malignancy and 3 patients (3.2%) had an active infection (urinary tract infection, abdominal infection after complicated pancreaticoduodenectomy and post lumbar laminectomy wound infection) at time of inclusion, 21 patients (23%) had been immobilized for >3 days or had travelled for more than 6 hours by plane or car, and 19 patients (20%) presented with a trauma or surgery in the four weeks before presentation. Mean PDS of the study population was 27% (SD 12). The interobserver agreement of PDS assessment was good with a mean difference in PDS of 4.4% (SD 7.0) between reviewers.

The prevalence of persistent symptoms and adverse outcomes at 3-month follow-up with associated mean PDS are presented in **Table 1**. At 3-months, persistent dyspnea was present in 22 patients (24%), chest pain in 11 (12%) and post-PE functional impairment in 22 patients (24%). None of the patients had been diagnosed with CTEPH at 3-month follow-up. During 3-months of follow-up, 9 patients (9.7%) were readmitted to hospital, of whom 4 patients were readmitted due to pain or dyspnea related to the PE and 5 patients because of major bleeding. Six patients (6.5%) were investigated for suspected recurrent VTE: one patient

(1.1%) was diagnosed with deep vein thrombosis of the leg and recurrent VTE was excluded in the other 5 patients. A total of 6 patients (6.5%) died during the follow-up period, of whom 2 patients as result of the index PE.

PDS was not correlated to persistent dyspnea (mean difference -3.7%; 95%CI -9.7% to 2.3%), chest pain (mean difference -0.70%; 95%CI -8.7% to 7.3%) or post-PE functional impairment (mean difference -4.7%; 95%CI -11% to 1.3%, **Table 1**). Moreover, CTPP-assessed PDS could not predict PE-related readmission (mean difference of 3.3%; 95%CI -5.4% to 12%) or all-cause mortality (mean difference 0.1%; 95%CI -10% to 11%, **Table 1**).

Table 1. Perfusion defect score (PDS) in 93 acute pulmonary embolism (PE) patients and its correlation with persistent symptoms and adverse outcome at 3-month follow-up

	Prevalence (%)	Mean (SD) PDS in % in patients with:	Mean (SD) PDS in % in patients without:	Mean difference (95% CI)
Persistent symptoms at 3 months				
Dyspnea	22 (24)	24 (11)	28 (13)	-3.7 (-9.7 to 2.3)
Chest pain	11 (12)	26 (11)	27 (13)	-0.70 (-8.7 to 7.3)
Post-PE functional impairment	22 (24)	23 (11)	28 (13)	-4.7 (-11 to 1.3)
Adverse outcomes at 3 months				
Recurrent VTE	1 (1.1)	30 (-)	27 (13)	3 (-)
PE-related readmission	9 (9.7)	31 (12)	27 (12)	3.3 (-5.4 to 12)
All-cause mortality	6 (6.5)	27 (21)	27 (12)	0.1 (-10 to 11)

DISCUSSION

In this analysis, we did not find clinically relevant correlations between PDS at initial PE diagnosis and persistent symptoms nor between PDS and any of the evaluated adverse outcomes at 3-month follow-up.

Multiple studies have shown that incomplete thrombus resolution occurs in around 50% of patients after acute PE episode despite adequate anticoagulant treatment.[3,4,6] At least two studies have demonstrated that pulmonary vascular obstruction (PVO) on initial CTPA and ventilation/perfusion scan (V/Q scan) were

independent predictors of residual PVO assessed by V/Q scan.[3,4] These persistent pulmonary perfusion defects have been associated with functional limitations during long-term follow-up and CTEPH.[3,6] In a study of 647 PE patients, 3.4% of patients with residual PVO after 6 months of the initial PE diagnosis were diagnosed with CTEPH versus none of the patients without residual PVO.[6] We therefore hypothesized that the extend of perfusion defects at initial PE diagnosis could be of value for predicting persistent symptoms and adverse events at 3-month follow-up. However, we had to reject our hypothesis: the extent of perfusion defects on CTPP did not show a trend towards an association with persistent dyspnea or pain. Of note, discrepancy between the extent of perfusion defects and symptoms including dyspnea and pain may exist as the generation of dyspnea and pain involve multiple underlying complex (and not fully understood) mechanisms.[11] Moreover, as the study represents a case mix of patients from the LUMC including patients with a history of VTE and active malignancy, it cannot be ruled out that the predictive value of PDS for persistent symptoms and adverse outcomes is different in other settings or hospitals.

We also assessed whether PDS on CTPP at PE diagnosis could predict recurrent VTE, PE-related readmission and all-cause mortality. In the current literature, there is evidence that the extend of baseline perfusion defects is associated with persistent perfusion defects on V/Q scans, the latter predicting recurrent VTE.[6,12] In the recent PADIS-PE trial, including 371 patients with first unprovoked PE treated with anticoagulants for 6 months, persistent perfusion defects of more than 5% determined by V/Q scan was associated with increased risk for recurrent VTE (hazard ratio of 2.06, 95%CI 1.14-3.72).[12] Since only one recurrent VTE event occurred during 3-month follow-up in our study cohort, we were not able to assess whether the extent of perfusion defects at initial PE diagnosis could predict recurrent VTE.

Our study has limitations. First, the presence of dyspnea and functional limitations was self-reported, which may have introduced bias [8], rather than assessed with a validated instrument such as the Post-VTE Functional Status (PVFS) scale. Further, this was an exploratory study in which we focused on a convenience cohort of 100 patients without a specific sample size calculation and followed patients for 3 months without taking longer follow-up into account. However, since our data did not even show a trend towards an association between perfusion defects and persistent symptoms or adverse outcomes, we expect that a larger sample size would not make a difference and show the same results. Furthermore,

we were not able to assess whether PDS was associated to CTEPH/CTEPD since these conditions are rather rare complications of acute PE [13,14] which can usually only be diagnosed beyond the initial 3-month treatment period with adequate anticoagulation.

In conclusion, in our cohort, CTPP-assessed PDS at initial PE diagnosis was not correlated to persistent symptoms nor with 3-month adverse outcomes in patients diagnosed with acute PE. Large prospective studies with longer follow-up are needed to more definitively determine whether CTPP imaging can be used to predict long-term outcomes after acute PE.

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CHAPTER

Clinical and computed tomography characteristics of COVID-19 associated acute pulmonary embolism: A different phenotype of thrombotic disease?

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ABSTRACT

Introduction: COVID-19 infections are associated with a high prevalence of venous thromboembolism, particularly pulmonary embolism (PE). It is suggested that COVID-19 associated PE represents in situ immunothrombosis rather than venous thromboembolism, although the origin of thrombotic lesions in COVID-19 patients remains largely unknown.

Methods: In this study, we assessed the clinical and computed tomography (CT) characteristics of PE in 23 consecutive patients with COVID-19 pneumonia and compared these to those of 100 consecutive control patients diagnosed with acute PE before the COVID-19 outbreak. Specifically, RV/LV diameter ratio, pulmonary artery trunk diameter and total thrombus load (according to Qanadli) were measured and compared.

Results: We observed that all thrombotic lesions in COVID-19 patients were found to be in lung parenchyma affected by COVID-19. Also, the thrombus load was lower in COVID-19 patients (Qanadli score -8%, 95% confidence interval [95%CI] -16 to -0.36%) as was the prevalence of the most proximal PE in the main/lobar pulmonary artery (17% versus 47%; -30%, 95%CI -44% to -8.2). Moreover, the mean RV/LV ratio (mean difference -0.23, 95%CI -0.39 to -0.07) and the prevalence of RV/LV ratio >1.0 (prevalence difference -23%, 95%CI -41 to -0.86%) were lower in the COVID-19 patients.

Conclusion: Our findings therefore suggest that the phenotype of COVID-19 associated PE indeed differs from PE in patients without COVID-19, fuelling the discussion on its pathophysiology.

INTRODUCTION

COVID-19 infections are associated with frequent activation of the coagulation system. This so-called COVID-19 coagulopathy has been shown to be predictive of poor outcome and excess mortality.[1-6] Moreover, COVID-19 illness is associated with high rates of venous thromboembolism, particularly acute pulmonary embolism (PE).[7-14] This high rate of venous thromboembolic complications is likely related to the COVID-19 coagulopathy, in combination with well-known strong thrombotic risk factors including inflammation, hypoxia and immobilisation, which all become more pronounced in critically ill patients. Based on autopsy studies, it has been proposed that the inflammatory process in the microcirculation of the lung may cause in situ immunothrombosis.[15,16] This suggests an alternative explanation to the conventional thromboembolic pathomechanism of PE.[17] To investigate this hypothesis, we set out to determine the clinical and computed tomography (CT) characteristics of acute PE in COVID-19 patients and compare these to the characteristics of acute PE in patients without COVID-19 pneumonia.

METHODS

Patients and design

We included all adult patients admitted to the Leiden University Medical Center (LUMC) with polymerase chain reaction (PCR) proven COVID-19 infection and computed tomography pulmonary angiography (CTPA) proven acute PE between March 19th and April 14th. Additionally, we studied a convenience control cohort, in whom all radiological parameters had been assessed as part of an ongoing observational study. This control group consisted of 100 consecutive adult patients with CTPA confirmed PE, diagnosed between July 2017 and October 2019 in the LUMC, before the COVID-19 outbreak. In both cases and controls, CTPA was ordered only upon clinically suspected PE. In patients not admitted to the intensive care unit (ICU) and with suspected acute PE, the YEARS algorithm was applied and CTPA was performed only if the D-dimer level was above the threshold.[18] In patients admitted to the ICU and with suspected acute PE, CTPA was directly ordered without prior clinical probability scoring and/or D-dimer testing. This study was approved by the Institutional Review Board of the LUMC for observational studies.

Aims of the study

We aimed to determine the clinical and CT parameters of patients with COVID-19 associated PE, i.e. the reasons for clinical suspicion of PE, the location of the pulmonary emboli in the pulmonary artery tree in general and in relation to COVID-19 affected pulmonary segments, total thrombus load, right to left ventricular diameter ratio (RV/LV ratio) and pulmonary artery trunk diameter. We compared the CT characteristics of acute PE in COVID-19 patients to those assessed in the control cohort.

Image acquisition and analysis

CTPA examinations were performed on a 320-multislice detector row CT scanner (Canon) after iodinated contrast administration. RV/LV ratio, pulmonary artery trunk diameter and total thrombus load for both COVID-19 cases and controls were evaluated by an expert thoracic radiologist (LK) with over 20 years of experience in CTPA reading. The maximum diameters of both the RV and LV were measured in the standard axial view in which the maximal distance between the ventricular endocardium and the interventricular septum perpendicular to the long axis of the heart were assessed. The pulmonary artery trunk was measured at its largest transverse diameter. The thrombus load was assessed by using the Qanadli CT pulmonary artery obstruction index, including 10 lung segments for each lung.[19] For each PE location, ground glass opacities or consolidations were reported as being present or not present for each affected lung segment. Also, the extent of COVID-19 lung lesions by ground-glass opacities and consolidations was visually assessed as percentage of affected lung volume.

Clinical and CT characteristics of PE are described as mean with standard deviation (SD) or median with interquartile range (IQR). We calculated absolute differences in these characteristics between COVID-19 patients and controls with corresponding 95% confidence interval (95%CI). All statistical analyses were performed in SPSS version 25 (IBM, Armonk, NY, USA).

RESULTS

A total of 23 patients with proven COVID-19 pneumonia and symptomatic CTPA proven PE were included in the study. Their baseline characteristics are shown in **Table 1**. All received pharmacological thromboprophylaxis. The main reason for PE suspicion was lack of clinical improvement in ventilated patients (n=13, 57%), sudden unexpected respiratory deterioration (n=7, 30%), hemodynamic collapse (n=2, 8.7%) and persistent fever of unknown origin (n=1, 4.3%).

In the COVID-19 cohort, the most proximal PE was located in the main/lobar pulmonary artery in 4 (17%) patients, and the most proximal PE was in a segmental artery in 16 (70%) (**Figure 1**). In 3 patients (13%), the PE was limited to subsegmental arteries, and 1 patient had a single subsegmental PE (4.3%). The mean total Qanadli score was 23% (SD 18%). Overall, 426/460 (93%) of the anatomical lung segments in the 23 patients were affected by COVID-19 and the mean percentage of affected lung was 58% (SD 22%). A total of 178/460 (39%) pulmonary artery segments were affected by PE; all pulmonary artery segments with PE were in lung parenchyma with radiological signs of COVID-19 pneumonia. The mean RV/LV ratio was 0.97 (SD 0.15) and the mean pulmonary trunk diameter was 29mm (SD 4.6mm). Six patients had a RV/LV ratio >1.0 (26%).

The control cohort consisted of 100 patients (**Table 1**). The location of the most proximal PE in the COVID-19 patients was less often the main/lobar pulmonary artery than in the control patients (17% versus 47%; -30%, 95%CI -44 to -8.2%). The Qanadli score was lower in the COVID-19 patients (mean difference -8%, 95%CI -16 to -0.13) as was the mean RV/LV ratio (mean difference -0.23, 95%CI -0.39 to -0.07) and the prevalence of RV/LV ratio >1.0 (26% versus 49%; -23%, 95%CI -41 to -0.86%). The mean pulmonary trunk diameter was comparable between cases and controls.

DISCUSSION

Our findings suggest that the PE phenotype in patients with COVID-19 is different from PE patients without COVID-19 pneumonia. Specifically, in COVID-19 patients, the thrombotic lesions were more distributed in the peripheral arteries of the lung, total clot burden was lower and the mean RV/LV ratio and prevalence of RV/LV ratio > 1 were lower.

Differences between patients with COVID-19 associated PE and the control patients related to thrombosis risk (e.g. sex or BMI) may explain our observations. The relatively small sample size did not allow performing multivariate analyses to adjust for these differences. Nevertheless, sex and BMI have been shown not to be associated with clot burden or distribution in previous studies so we feel this explanation is less likely.[20] It is however possible that prophylactic anticoagulation, which was prescribed in all COVID-19 patients, and a shorter diagnostic delay may have influenced the radiological parameters of the PE. An alternative explanation is that in situ immunothrombosis indeed plays a role in the pathophysiology of COVID-19 associated PE. Alveolar injury and the inflammatory storm caused by COVID-19 pneumonia as well as disruption of the thrombo-protective state of the pulmonary vascular endothelial cells contribute to profound small vessel thrombus formation.[15,16,20] Even so, since 93% of lung segments was affected by infection, a 'true' association between location of the thrombotic and COVID-19 lesions could not be established, simply because unaffected segments were hardly present. The markedly higher D-dimer levels in COVID-19 patients with PE nonetheless underline the extreme coagulopathy and pro-thrombotic state associated with COVID-19 infection. The absence of clinical signs of deep vein thrombosis (DVT) in the COVID-19 patients may also support the concept of in situ immunothrombosis, although the prevalence of clinical signs of DVT was equally low in the control group. Importantly, the fact that the majority of PEs was located in the segmental arteries and 17% even centrally in the pulmonary artery tree is strongly compatible with the conventional thromboembolic origin of PE. This was also seen in previous publications in which COVID-19 associated PE was located in the central/lobar pulmonary artery in 44-56% of the cases.[22,23] Our findings are in line with histologic findings in autopsy studies were multiple thrombi in small to mid-sized pulmonary arteries were observed supporting the concept of immunothrombosis.[21,24] The observation by others that the incidence of DVT in COVID-19 patients was high upon screening also suggests that the conventional thromboembolic origin of PE plays indeed a role in COVID-19 associated PE.[9, 25] Of note, increased prevalence of PE and not of DVT has been described before in pulmonary conditions such as COPD and pneumonia.[26]

The main limitations of our study include the relatively small sample size and the lack of screening ultrasonograms of the leg veins. Furthermore, selection bias may have occurred as the threshold for PE screening may have been lower in COVID-19 patients than in the control group resulting in less extensive PE in the COVID-19 patients. Another limitation may be that blinded CT assessment by the

radiologist was not possible as typical COVID-19 lesions can be seen in patients with COVID-19 infection.

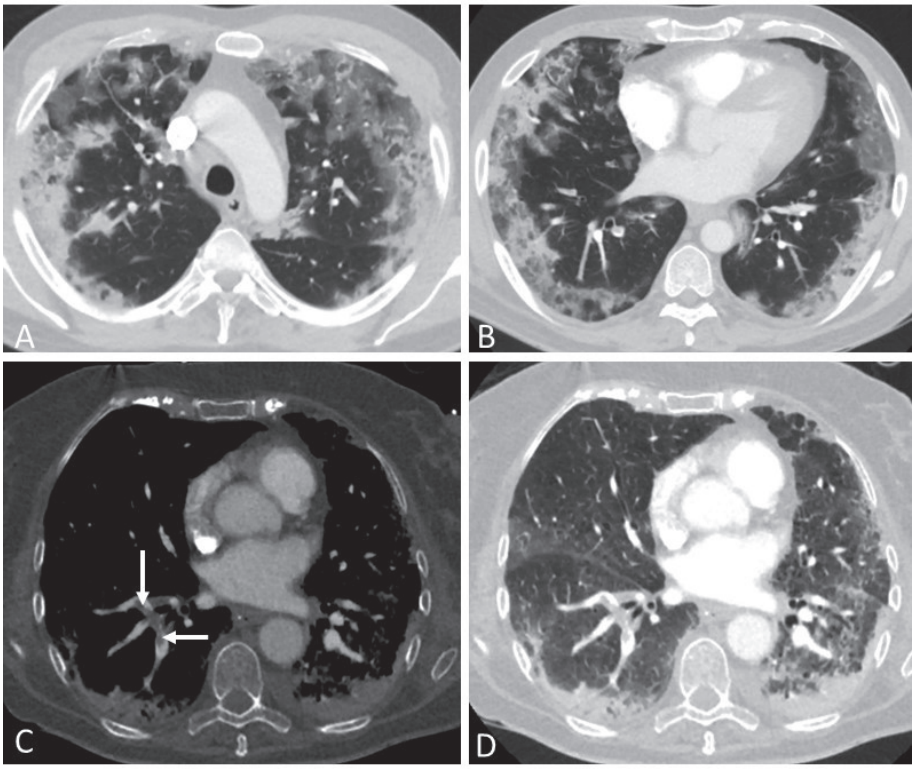
Our data suggest that the phenotype of PE in COVID-19 patients may be different from the PE phenotype in patients without COVID-19 pneumonia. Since pulmonary emboli in COVID-19 associated PE patients are more located in the peripheral lung segments and are less extensive compared to PE in patients without COVID-19, COVID-19 associated PE more likely represents a combination of thromboembolic disease and in situ thrombosis. Further investigations, including laboratory studies, are needed to explore the true causal relation between COVID-19 pneumonia and PE or in situ immunothrombosis. Exact knowledge of the origin of PE in COVID-19 patients has important therapeutic consequences since the effect of (prophylactic) anticoagulation on in situ thrombosis is largely unknown.

Table 1. Characteristics of pulmonary embolism (PE) patients with and without COVID-19

	PE patients *with* COVID-19 (n = 23)	PE patients *without* COVID-19 (n = 100)
Characteristics and venous thromboembolism (VTE) risk factors		
Mean age (±SD) – years	63 (6.4)	62 (16)
Male sex – n (%)	16 (70)	53 (53)
Previous VTE – n (%)	1 (4)	17 (17)
Active malignancy – n (%)	1 (4)	27 (27)
Trauma/surgery during the past 4 weeks – n (%)	0 (0)	22 (22)
Clinical presentation		
Chest tightness – n (%)	0/4 (0)*	25 (25)
Pleural pain – n (%)	0/4 (0)*	55 (55)
Dyspnea – n (%)	3/4 (75)*	82 (82)
Hemoptysis – n (%)	0 (0)	6 (6.0)
Clinical signs of deep vein thrombosis	0 (0)	6 (6.0)
D-dimer results (ng/mL) – median (IQR)	7551 (3852-10,005)	2637 (3345-4998)
Hemodynamic unstable at diagnosis – n (%)	2 (8.7)	6 (6.0)
Reperfusion therapy – n (%)	1 (4.3)	5 (5.0)
>24 hours supplemental oxygen therapy– no (%)	23 (100)	25 (25)
Intensive care admission – no (%)	20 (87)	8 (8.0)
Radiological presentation		
Most proximal anatomic location		
Main/lobar	4 (17)	38 (38)
Segmental	16 (70)	41 (41)
Subsegmental	3 (13)	11 (11)
Qanadli score (%) – mean (SD)	23 (18)	31 (17)
Right ventricle diameter (mm) – mean (SD)	43 (8.0)	45 (9.9)
Left ventricle diameter (mm) – mean (SD)	44 (7.0)	41 (8.9)
RV/LV ratio – mean (SD)	0.97 (0.15)	1.2 (0.38)
Pulmonary artery trunk diameter (mm) – mean (%)	29 (4.6)	28 (4.7)

**Only for non-sedated non-intubated patients.*

Figure 1: CT-pulmonary angiography: A and B: 54-year-old male patient with COVID-19 pneumonia, axial CT images in 3 mm reconstructions at upper and lower lung levels showing typical COVID-19 lesions with bilateral patchy ground-glass opacities and consolidations in predominantly peripheral distribution. The pulmonary involvement of COVID-19 lesions was 50% of lung volume. C and D: 69-year-old female patient with COVID-19 pneumonia, axial CT images in 1 mm reconstructions. Soft tissue setting showing thrombus in the right lower lobe segmental pulmonary arteries (arrows, C). Lung setting showing extensive pulmonary interstitial- and subpleural consolidation in both lungs (D), predominantly in the dependent areas but not related with presence (right lung) or absence (left lung) of visible pulmonary thrombus



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CHAPTER

General discussion and summary

In this thesis, we described studies that aimed to overcome diagnostic challenges in venous thromboembolism (VTE) using novel imaging techniques. **Chapter 1** provides a general introduction of the diagnosis of pulmonary embolism (PE) and deep vein thrombosis (DVT) at different anatomic locations and an overview of the presented studies.

The diagnostic management of suspected VTE can be complex, especially in certain settings such as in suspected recurrent VTE. An adequate diagnosis in this patientgroup is of great importance because most patients diagnosed with a recurrence are treated with lifelong anticoagulant treatment. In suspected recurrent PE, the YEARS algorithm incorporating 3 clinical items and a D-dimer test with a pre-test probability dependent threshold, followed by computed tomography pulmonary angiography (CTPA) is the current favored diagnostic strategy. Although persistent thrombi can be present after a previous PE, these are hardly relevant in the diagnostic management of suspected recurrent PE. In most patients the PE will completely resolve over time and when persistent thrombi in the pulmonary artery are present these are often of limited size.

The diagnostic management in suspected recurrent DVT proves more of a challenge. First, the safety of the commonly used Wells score in combination with a D-dimer test in this setting has not been proven beyond doubt. Second, up to 50% of patients with a previous DVT have persistent thrombi after one year, despite adequate anticoagulant treatment. The differentiation between acute recurrent DVT and chronic residual thrombosis with compression ultrasonography (CUS) is difficult and sometimes impossible. As a result, CUS is not able to provide a definite diagnosis in 30% of patients with suspected recurrent ipsilateral DVT. Magnetic Resonance Non-Contrast Thrombus Imaging (MR-NCTI) is a magnetic resonance imaging (MRI) technique that can directly visualize the metabolism of a fresh thrombus by imaging methemoglobin, which is formed in a fresh blood clot by the oxidation of hemoglobin. This technique can thus be used to differentiate acute from chronic thrombosis and to accurately visualize notorious difficult to image VTE. Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a MR-NCTI sequence that has been shown to accurately diagnosis a first DVT and to differentiate acute from chronic DVT in the legs. Before MRDTI could be implemented in the diagnostic management of suspected recurrent ipsilateral DVT in clinical practice an outcome study needed to be performed.

In **Chapter 2**, we described the Theia study in which the safety of MRDTI to exclude acute recurrent ipsilateral DVT was assessed. We showed that the 3-month

incidence of recurrent VTE was low in patients with MRDTI negative for DVT (1.1%; 95% confidence interval (95%CI) 0.13-3.8) and in patients with MRDTI negative for DVT and thrombophlebitis, who were not treated with any anticoagulant during follow-up (1.7%; 95%CI 0.20-5.9). Moreover, with an excellent interobserver agreement and MRDTI not being available in only 3.6% of patients, this technique was proven to be a feasible and reproducible diagnostic test. Additionally, the use of MRDTI possibly resulted in 19% fewer false positive diagnoses. However, as a MRI scan is more expensive than a CUS examination, the cost-effectiveness of the addition of MRDTI to the diagnostic management of suspected recurrent DVT needed to be proven before this technique can be widely implemented. In **Chapter 3**, the one-year healthcare costs of 10 diagnostic strategies including the Wells score in combination with a D-dimer test, CUS and/or MRDTI in suspected recurrent DVT was assessed and compared. We showed that the healthcare costs of strategies with MRDTI were generally lower than of strategies without MRDTI, due to superior specificity resulting in less false-positive diagnosis and overtreatment. Therefore, it was concluded that application of MRDTI to the diagnostic management of suspected recurrent ipsilateral DVT will not increase healthcare costs.

Healthcare costs can also be reduced with the use of diagnostic algorithms in which VTE can be ruled out without additional imaging tests, i.e. in case of a low clinical probability in combination with a negative D-dimer test. As discussed, the safety of these algorithms has not yet been proven in large prospective studies exclusively in patients with suspected recurrent DVT. In **Chapter 4**, we therefore evaluated the diagnostic accuracy of the combination of the (modified) Wells rule for DVT and D-dimer for suspected recurrent ipsilateral DVT in the prospective Theia study. We showed that excluding recurrent DVT based on a low clinical probability according the (modified) Wells rule in combination with a negative D-dimer test would have resulted in an unacceptable high failure-rate (6.1-11%). Our data therefore suggest not to routinely apply assessment of a clinical decision rule and D-dimer in the diagnostic workup of suspected recurrent DVT, but to directly perform a CUS to exclude or diagnose recurrent DVT. In patients with a suspected recurrent ipsilateral DVT and inconclusive CUS, MRDTI should be performed to provide a definitive diagnosis.

The diagnostic management of upper extremity deep vein thrombosis (UEDVT) is also very challenging due to the anatomic location of the deep veins. Adequate visualization is difficult as the upper extremity deep veins lies partly within the

thoracic cavity. Moreover, CUS examination is hindered due to overlying bone structures, such as the claviculae. We hypothesized that MR-NCTI would be an accurate diagnostic test without the invasive characteristics of (CT) venography imaging. MRDTI and T1-weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery, which is another MR-NCTI sequence, were previously shown to successfully visualize acute thrombosis in three patients with UEDVT proven by conventional imaging. In **Chapter 5**, the results of the Selene study were described in which the diagnostic accuracy of MR-NCTI for the diagnosis of UEDVT was evaluated. We showed that MR-NCTI was accurate with a sensitivity of 93% (95%CI 78-99%) and specificity of 100% (95%CI 88-100%) and had an excellent interobserver agreement. This technique may therefore be useful in patients with suspected UEDVT but with inconclusive CUS.

Differentiation between acute and chronic thrombosis is also important in the diagnostic management of portal vein thrombosis (PVT), as current guidelines recommend different anticoagulant strategies in patients with acute or chronic PVT. With currently available imaging tests including doppler ultrasonography, CT venography and MRI, this is not always possible, especially in case of an organized non-occlusive chronic PVT without signs of cavernous transformation of the portal vein. We hypothesized that MR-NCTI could accurately differentiate acute from chronic PVT. In **Chapter 6**, the first phase of the Rhea study was described, in which we evaluated the most optimal MR-NCTI sequences for the setting of PVT. We found that three-dimensional (3D) T1 Turbo Field Echo and 3D T1 Dixon Fast Field Echo were both able to diagnose and differentiate acute from chronic PVT. These MR-NCTI sequences will therefore be evaluated in the second phase of the Rhea study to assess its diagnostic accuracy for distinguishing acute from chronic PVT.

The diagnosis of cerebral vein thrombosis (CVT) can also be challenging due to the complex anatomic variation of cerebral veins and sinuses. Digital subtraction angiography was previously the diagnostic standard for CVT but is now rarely used due to its invasive nature. In **Chapter 7**, an overview of all relevant papers regarding the diagnostic performance of the current available imaging techniques including CT, CT venography and MRI for the diagnosis of CVT is presented. Although large high-quality diagnostic studies are absent, we showed that contrast-enhanced imaging techniques are more accurate than non-contrast-enhanced techniques. We also described that CT venography and contrast-enhanced MRI both seem adequate for the diagnosis of CVT. MR-NCTI was previously shown to be accurate for the diagnosis of CVT too. Therefore, MR-NCTI could possibly be of value in

establishing a final diagnosis in complex cases, such as in patients with suspected recurrent CVT and in patients in whom venous sinuses are affected by brain tumours or after intracranial surgery. In **Chapter 8**, we described a 52-year-old female patient who presented at the Emergency Department with a mild headache and blurry vision and was suspected of an acute CVT. Her medical history included a craniotomy for right sided parieto-occipital meningioma. Imaging with CT and MR venography showed no opacification of the superior sagittal sinus and both transverse sinuses suspected of thrombosis, but of unknown age. However, as MR-NCTI showed no high signal intensity, acute CVT was excluded and anticoagulant treatment discontinued. The cerebral sinus occlusion was most likely due to chronic CVT or as a result of residual meningioma tissue and follow-up MRI showed no new abnormalities, nor had the patient new adverse events during 12 months of follow-up. MRDTI also excluded an acute thrombus in a patient with aortic thrombosis. This case was described in **Chapter 9**. It concerned a 43-year-old male patient known with severe hypertension and renal failure, who presented with abdominal pain for several months. CT angiography showed a large extensive circumferential wall thrombosis in an abdominal aortic aneurysm. The patient was referred for MRDTI scan, since it was unknown whether the thrombus concerned an acute or chronic thrombosis, and the treating doctors were hesitant to start anticoagulant treatment because of the high bleeding risk. MRDTI excluded an acute thrombus, and anticoagulant treatment was not started. These two case reports represent the first cases in which MR-NCTI techniques were used to guide anticoagulant treatment in suspected acute CVT and aortic thrombosis.

CTPA is the diagnostic test of choice for the diagnosis of acute PE. Moreover, CTPA parameters of right heart dysfunction, including right ventricle to left ventricle diameter ratio (RV/LV ratio) and pulmonary artery trunk diameter, can be used in the initial risk stratification of acute PE patients. A novel CT technique, called CT pulmonary perfusion (CTPP), has an added value to CTPA reading as it shows the pulmonary perfusion and thus possible functional impact of an acute PE. CTPP has previously be shown to improve the diagnosis of PE when added to CTPA. We hypothesized that CTPP could also improve the prediction of adverse outcomes of PE. In **Chapter 10,** we evaluated the correlation between perfusion defect score (PDS) on CTPP and both clinical presentation and adverse short-term outcomes in hemodynamically stable PE patients. In this analysis, we were not able to show an association between PDS and clinical presentation such as chest pain, dyspnea and haemoptysis. We did show that PDS was correlated to the need for reperfusion therapy and PE-related mortality.

Perfusion defect quantification may not only be clinically relevant for initial risk stratification of acute PE, but possibly also for prediction of long-term adverse outcomes. Extensive clot burden and perfusion defects at the moment of a PE diagnosis have been associated with residual perfusion defects and with persistent symptoms. Therefore, we hypothesized that the extent of perfusion defects as measured by CTPP at PE diagnosis would predict persistent symptoms and 3-month adverse outcomes, including recurrent PE, PE-related readmission and all-cause mortality. In **Chapter 11**, we showed that PDS on CTPP at initial PE diagnosis was not associated to persistent symptoms nor to any of the three adverse outcomes. Future larger studies are needed to determine the value of CTPP to CTPA for the prognostic management of acute PE patients.

The year 2020 was characterized by the coronavirus disease 19 (COVID-19) outbreak which has led to worldwide spreading of a highly infectious respiratory disease caused by a new coronavirus known as SARS-CoV-2. COVID-19 infection has been associated with an increased incidence of VTE and in particular PE. However, the pathogenesis of COVID-19 associated PE is currently not fully understood. It has been suggested that these pulmonary emboli may be the result of in-situ immunothrombosis rather than conventional VTE. This hypothesis was based on the results of autopsy studies in patients with COVID-19 pneumonia showing multiple small thrombi in the alveolar capillaries. To test this hypothesis, we assessed the clinical and CT characteristics of PE in patients with COVID-19 and compared these to the characteristics of PE in patients without COVID-19. In **Chapter 12**, we showed that the PE in patients with COVID-19 was less extensive and more located in the peripheral lung segments. Also, the mean RV/LV ratio was lower in COVID-19 patients, as was the prevalence of RV/LV ratio >1. We therefore concluded that COVID-19 associated PE is indeed different from conventional PE, a finding that could support the in-situ immunothrombosis theory. This also suggests a possible different (prophylactic) anticoagulant strategy in this patient group then the conventional VTE treatment. Future studies to the exact pathophysiology of COVID-19 associated PE and most optimal anticoagulant treatment are needed.

FUTURE PERSPECTIVES

Major technical advances have been made in the diagnostic imaging of VTE. This has led to an increase in the detection of very small and/or incidental thrombi. The

clinical relevance and most optimal treatment of these thrombi is often not known. With the introduction of MR-NCTI, we are able to directly visualize thrombosis and differentiate acute from chronic thrombosis, and with that determine the need for anticoagulant treatment. In suspected recurrent ipsilateral DVT, MR-NCTI is now increasingly used when a recurrence cannot be diagnosed or excluded with CUS. Formally a diagnostic outcome study on the safety of MR-NCTI for excluding UEDVT and CVT is needed before this technique can be implemented in these settings as well. Of note, when translating the findings of the Theia study to suspected UEDVT and CVT, MR-NCTI may be applied in complex clinical cases in which non-invasive diagnostic tests do not provide a definitive diagnosis, even in the absence of such a study.

In splanchnic vein thrombosis (SVT), MR-NCTI could be used to guide the treatment decision in patients with suspected chronic SVT as current guidelines suggest no anticoagulation in patients with chronic rather than acute SVT. Therefore, when the accuracy of MR-NCTI for the differentiation between acute and chronic SVT has been proven in the Rhea study, an outcome study should be performed, ideally in a randomized controlled trial (RCT), in which patients with suspected chronic SVT and normal MR-NCTI will be randomized between therapeutic anticoagulant treatment and no anticoagulation to compare clinical outcome, i.e. the occurrence of recurrent or progressive SVT, major bleeding and death. This will be particularly relevant for patients with incidental SVT, a group of patients comprising 30% of all SVTs, even when conventional imaging tests do not indicate signs of chronicity.

Before MR-NCTI can be widely implemented in daily clinical practice when its safety has been proven in diagnostic outcome studies, implementation challenges in real-world practice need to be assessed and addressed. Among those are the lower availability of and less experience with MR-NCTI compared to conventional VTE imaging techniques. Moreover, MRI is associated with higher imaging costs. Therefore, implementation studies are needed to develop the most optimal strategies to include MR-NCTI in daily clinical practice. These studies should among others focus on the exact indications of MR-NCTI imaging, the training of MR technicians and radiologist, the latter who have to learn to interpret MR-NCTI images.

In the diagnostic management of suspected PE, CTPP and ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scintigraphy can both provide lung perfusion images, however their place in the diagnostic and prognostic management of PE is still yet to be determined. Indeed, while MR-

NCTI is close to implementation in practice, this is not the case for CTPP. For instance, as manual perfusion defect quantification is time-consuming and current literature does not unambiguously support the added value of perfusion imaging on top of CTPA, its applicability in daily clinical practice is still unknown. With the development and validation of artificial intelligence-based (AI) software it may be possible to more accurately and reproducible quantify perfusion defects. Automatically quantification of perfusion defects, if shown more reliably associated with prognosis, could in turn facilitate implementation of CTPP in daily practice, allowing for precision management with regard to initial treatment, duration of hospitalization and patient tailored follow-up. Studies to achieve this are currently ongoing.

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CHAPTER

Nederlandse samenvatting

In dit proefschrift worden studies beschreven, die gericht zijn op het verbeteren van de diagnostiek van veneuze trombo-embolieën (VTE) met behulp van nieuwe beeldvormende technieken. In **Hoofdstuk 1** wordt een algemeen overzicht van de diagnostiek van de acute longembolie en diepe veneuze trombose (DVT) op verschillende anatomische locaties, en daarnaast een overzicht van de beschreven studies in dit proefschrift gegeven.

De diagnostiek van VTE is onder bepaalde omstandigheden zeer complex, zoals bij verdenking op een recidief VTE. Het accuraat vaststellen van een recidief VTE is van groot belang, omdat patiënten met een recidief vaak levenslang met antistolling worden behandeld. Bij verdenking op een acuut recidief longembolie gebruikt men het YEARS-algoritme, bestaande uit drie klinische items en een D-dimeerbepaling met een afkapwaarde welke afhankelijk is van de klinische voorafkans, gevolgd door een computer tomografie (CT)-angiografie van de longen. Hoewel er na een longembolie reststolsels aanwezig kunnen blijven, zijn deze nauwelijks relevant in de diagnostiek van een recidief longembolie, omdat in de meeste patiënten de longembolieën na verloop van tijd volledig resorberen en wanneer er restafwijkingen in de longarterie aanwezig zijn deze vaak van geringe omvang zijn.

De diagnostiek bij verdenking op een acuut recidief DVT is een grotere uitdaging om de volgende redenen. Allereerst is niet eenduidig bewezen dat het gebruik van de Wells score in combinatie met een D-dimeerbepaling veilig is voor het uitsluiten van een recidief DVT. Daarnaast blijkt dat bijna 50 % van de patiënten met een eerdere DVT-episode een jaar later nog steeds reststolsels heeft, ondanks adequate antistollingsbehandeling. Vervolgens is het ook lastig en soms zelfs onmogelijk om met compressie-echografie onderscheid te maken tussen een acuut recidief DVT en reststolsels. Dit heeft tot gevolg dat bij 30% van de patiënten met verdenking op een ipsilateraal recidief DVT geen definitieve diagnose kan worden vastgesteld door middel van echografie. *Magnetic Resonance Non-Contrast Thrombus Imaging* (MR-NCTI) is een *magnetic resonance imaging* (MRI) techniek waarmee een trombus direct in beeld kan worden gebracht door de aanwezigheid van methemoglobine, dat ontstaat door oxidatie van hemoglobine tijdens de stolselvorming. Hierdoor is het mogelijk om acute trombose van chronische trombose te onderscheiden, en moeilijk vast te stellen VTE in beeld te brengen. *Magnetic Resonance Direct Thrombus Imaging* (MRDTI) is een MR-NCTI sequentie die accuraat is voor het vaststellen van een eerste DVT en om acute van chronische DVT in het been te onderscheiden. Voordat MRDTI in de klinische praktijk kan worden geïmplementeerd, moet een uitkomststudie worden verricht.

In **Hoofdstuk 2** worden de resultaten van de Theia studie beschreven, waarin de veiligheid van de MRDTI-scan voor het uitsluiten van een acuut ipsilateraal recidief DVT werd onderzocht. Deze studie liet zien dat onder patiënten met een negatieve MRDTI-uitslag en onder patiënten met een negatieve MRDTI-uitslag, die geen enkele vorm van antistollingsbehandeling kregen, de incidentie van een recidief VTE gedurende een *follow-up*periode van drie maanden laag was (1,1%; 95% betrouwbaarheidsinterval (95%-BI); 0,12-3,8 en 1,7%; 95%-BI 0,20-5,9). Daarnaast bleek de MRDTI een reproduceerbare diagnostische test te zijn, met een goede overeenkomst tussen de diagnostische uitslag van de lokale radioloog en de posthoc-evaluatie door experts. Slechts bij 3,6% van de patiënten kon de MRDTI-scan niet worden verricht. Bovendien zou de toepassing van de MRDTI-scan tot 19% minder fout-positieve diagnoses hebben geleid. Daar staat tegenover dat, voorafgaand aan de implementatie van MRDTI-onderzoeken in de praktijk van recidief DVT-diagnostiek, de kosteneffectiviteit onderzocht moet worden, omdat een MRI-scan duurder is dan een echografisch onderzoek. In **Hoofdstuk 3** worden de totale zorgkosten in één jaar tussen tien verschillende diagnostische strategieën vergeleken, bestaande uit de Wellsscore in combinatie met een D-dimeerbepaling, echografie en/of MRDTI-scan, bij vermoeden van een recidief DVT. Hieruit bleek dat de totale zorgkosten van strategieën met MRDTI-onderzoek gelijk of lager zijn dan strategieën zonder MRDTI-onderzoek, als direct gevolg van minder fout-positieve diagnoses door MRDTI-onderzoek. De conclusie was dat aanvullend MRDTI-onderzoek in de klinische praktijk niet leidt tot hogere zorgkosten.

De zorgkosten kunnen ook worden beperkt door de toepassing van diagnostische algoritmes, waarbij een (recidief) VTE kan worden uitgesloten zonder beeldvorming, wanneer sprake is van een lage klinische voorafkans in combinatie met een negatieve D-dimeertest. De veiligheid van deze algoritmes is echter nog niet bewezen in grote prospectieve studies bij patiënten die een verdenking op recidief DVT hebben. Daarom is in **Hoofdstuk 4** de sensitiviteit en specificiteit van de (aangepaste) Wells-beslisregel in combinatie met de D-dimeertest bij verdenking op ipsilateraal recidief DVT in de populatie van de prospectieve Theia studie onderzocht. Hieruit bleek dat het uitsluiten van een recidief DVT, gebaseerd op een lage klinische voorafkans volgens de (aangepaste) Wells-beslisregel in combinatie met een negatieve D-dimeertest, mogelijk leidt tot een onacceptabel hoog aantal fout-positieve diagnoses (6,1-11%). Derhalve wordt op basis van deze resultaten het routinematig gebruik van een klinische beslisregel en D-dimeertest in de diagnostiek van recidief DVT afgeraden. Bij voorkeur wordt direct compressie-

echografie verricht om een recidief uit te sluiten of aan te tonen, gevolgd door MRDTI-onderzoek als echografie geen uitsluitsel geeft.

De diagnostiek van armvene trombose wordt bemoeilijkt door de anatomische ligging van de armvenen, onder meer doordat een deel van de diepe venen in de thoraxholte ligt. Daarnaast is een goede diagnose met compressie-echografie vaak niet mogelijk door overliggende anatomische structuren in de schouder, zoals de clavicula. MR-NCTI is mogelijk een accuraat diagnostisch onderzoek in deze situatie zonder de invasieve eigenschappen van (CT-)venografie. Uit een eerdere analyse is gebleken dat zowel MRDTI als *T1-weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery*, dat ook een MR-NCTI sequentie betreft, acute trombose in drie patiënten met armvene trombose heeft kunnen vaststellen. In **Hoofdstuk 5** zijn de resultaten van de Selene studie beschreven, waarin de diagnostische accuratesse van MR-NCTI voor de diagnose van armvene trombose is onderzocht. Deze studie liet zien dat MR-NCTI een sensitiviteit van 93% (95%-BI: 78-99%) en specificiteit van 100% (95%-BI: 88-100%) heeft, met daarbij een goede overeenstemming tussen onafhankelijke beoordelaars. Deze techniek lijkt daardoor een waardevol beeldvormend onderzoek bij verdenking op armvene trombose als echografie geen uitsluitsel geeft.

Differentiatie tussen acute en chronische trombose is ook van groot belang in de diagnostiek van vena portae trombose (VPT), omdat huidige richtlijnen een verschillend antistollingsbeleid adviseren voor patiënten met een acute of chronische trombose. Dit is echter niet altijd mogelijk met de huidige beeldvormende technieken, waaronder doppler echografie, CT-venografie en MRI; dit geldt vooral in het geval van een georganiseerde non-occlusieve chronische trombose zonder tekenen van caverneuze transformatie in de levervenen. Omdat met MR-NCTI onderscheid kan worden gemaakt tussen acute en chronische trombose bij een DVT in het been, was de hypothese dat dit ook mogelijk zou moeten zijn bij een DVT in de buikvenen. In **Hoofdstuk 6** wordt de eerste fase van de Rhea studie beschreven, waarin de meest optimale MR-NCTI sequenties voor de diagnostiek van VPT worden geëvalueerd. Resultaten van deze studie lieten zien dat een VPT met driedimensionale (3D) *T1 Turbo Field Echo* en *3D T1 Dixon Fast Field Echo* kan worden vastgesteld en dat onderscheid kan worden gemaakt tussen acute en chronische VPT. Deze twee MR-NCTI sequenties zullen daarom in de tweede fase van de Rhea studie worden onderzocht voor het differentiëren tussen acute en chronische VPT.

De diagnostiek van cerebrale vene trombose (CVT) kan lastig zijn door de complexe anatomische variatie van de diepe cerebrale venen en veneuze sinussen. Digitale substractie-angiografie was vroeger de diagnostische standaard voor CVT, maar wordt tegenwoordig zelden toegepast omdat dit een invasief onderzoek is. In **Hoofdstuk 7** wordt een overzicht getoond van de relevante publicaties over de diagnostische waarde van de beschikbare beeldvormende technieken voor de diagnostiek van CVT, inclusief CT, CT-venografie en MRI. Hoewel grote diagnostische studies van hoge kwalitatieve waarde ontbreken, is gebleken dat beeldvorming na toediening van intraveneus contrast nauwkeuriger is dan beeldvorming zonder contrastvloeistoftoediening. Daarnaast bleek dat zowel CT-venografie als MRI na contrastvloeistoftoediening beide adequaat zijn voor de diagnostiek van CVT. Uit eerdere studies bleek dat MR-NCTI ook accuraat is voor het vaststellen van CVT. Daarmee lijkt MR-NCTI mogelijk van toegevoegde waarde voor de diagnostiek van CVT in complexe omstandigheden, zoals bij een vermoeden van een recidief CVT of bij patiënten bij wie de veneuze sinussen zijn aangetast door hersentumoren of na intracraniële chirurgie. In **Hoofdstuk 8** wordt een casus beschreven van een 52-jarige vrouw die zich met milde hoofdpijnklachten en wazig zicht presenteerde op de Spoedeisende hulp, en bij wie een acute CVT aanwezig werd vermoed. In de voorgeschiedenis had zij een craniotomie gehad voor het verwijderen van een rechtszijdig pariëto-occipitaal meningioom. CT en MR-venografie toonden contrastuitsparingen in de superior sagittale sinus en beide transversale sinussen, verdacht voor trombose, maar hieruit bleef onbekend of dit een acute of chronische trombose betrof. Een acute CVT werd vervolgens uitgesloten, omdat geen hoog signaal, passend bij acute trombose, te zien was op de MR-NCTI. Hierop werd de antistollingsbehandeling gestaakt en geconcludeerd dat de contrastuitsparing hoogstwaarschijnlijk een chronische CVT of restafwijking van meningioomweefsel betrof. De MRI-scan in het vervolgonderzoek vertoonde geen nieuwe afwijkingen en er vonden geen complicaties plaats gedurende de volgende 12 maanden. In **Hoofstuk 9** wordt een casus beschreven waarin acute trombose in een patiënt met een aorta trombose werd uitgesloten door middel van MRDTI. Het betrof een 43-jarige man, bekend met ernstige hypertensie en nierfalen, die al maanden buikpijnklachten had. CT-angiografie liet een uitgebreide wandtrombose in een abdominaal aorta aneurysma zien. Aangezien het onduidelijk was of het ging om een acute of chronische trombose en de artsen terughoudend waren om antistollingsbehandeling te starten gezien het hoge bloedingsrisico, werd de patiënt verwezen voor een MRDTI-scan. Deze scan sloot een acute trombose uit, waarop werd besloten geen behandeling met antistolling te starten. Dit zijn de

eerste casus waarin de MR-NCTI techniek is gebruikt in de behandelbeslissing bij verdenking op een acute CVT en aorta trombose.

Bij verdenking op een acute longembolie heeft CT-angiografie van de longen de voorkeur als beeldvormend onderzoek. Daarnaast kan op de CT-angiografie naar tekenen van rechtsoverbelasting worden gekeken door de rechter ventrikel tot linker ventrikel diameter ratio (RV/LV ratio) en diameter van de longslagader te bepalen. Beide zijn bruikbaar voor de risicoclassificatie van patiënten met een acute longembolie. Een nieuwe CT-techniek, CT-pulmonale perfusie (CTPP), is daarbij van toegevoegde waarde, omdat hiermee de longperfusie in beeld kan worden gebracht en daarmee de mogelijke functionele gevolgen van een acute longembolie. Eerdere studies toonden aan dat de toevoeging van CTPP aan CT-angiografie de diagnostiek van longembolieën verbeterde. Onze hypothese was dat met de toevoeging van CTPP aan CT-angiografie mogelijk ook de klinische uitkomst van een longembolie beter kan worden voorspeld. In **Hoofdstuk 10** werd de correlatie tussen de perfusie-defectscore (PDS) op CTPP en zowel de klinische presentatie als de uitkomst bij hemodynamisch stabiele patiënten met een acute longembolie onderzocht. In deze analyse kon geen relatie tussen de PDS en klinische presentatie zoals pijn op de borst, dyspnoe of hemoptoe worden gevonden. Wel werd een correlatie gevonden tussen de PDS en noodzaak tot trombolyse/trombectomie en longembolie-geassocieerde sterfte.

Het bepalen van de mate van perfusiedefecten is niet alleen mogelijk klinisch relevant in de initiële risicoclassificatie, ook kan het een rol spelen bij de voorspelling van lange termijngevolgen van een longembolie. Eerder is aangetoond dat uitgebreide longembolieën en perfusiedefecten ten tijde van de diagnose van een longembolie gerelateerd zijn aan persisterende perfusiedefecten en klinische symptomen op de lange termijn. De hypothese was dat de mate van perfusiedefecten op CTPP op het moment van de longemboliediagnose de aanwezigheid van persisterende symptomen en uitkomsten - inclusief recidief longembolie, PE-gerelateerde heropnames en mortaliteit - op drie maanden *follow-up* zou kunnen voorspellen. De uitkomsten van deze analyse werden beschreven in **Hoofdstuk 11**. Hieruit volgt dat de PDS ten tijde van de longemboliediagnose geen verband hield met persisterende symptomen of één van de drie lange termijn uitkomsten. Voor de voorspelling van de toegevoegde waarde van CTPP aan CT-angiografie van de prognose van een longembolie zijn grotere studies benodigd.

De uitbraak van het '*coronavirus disease 19*' (COVID-19) in 2020 heeft geleid tot een wereldwijde verspreiding van een zeer besmettelijke longinfectieziekte ten gevolge van een nieuw coronavirus; SARS-CoV-2. De uitbraak van COVID-19 houdt verband met een toename van de incidentie van VTE en met name longembolieën. Echter, de precieze pathofysiologie van deze COVID-19 geassocieerde longembolieën is nog onbekend. Er wordt verondersteld dat de trombose ontstaat door lokale immuunreacties in de longslagaders en derhalve niet zozeer een conventionele longembolie betreft. Deze hypothese is gebaseerd op de resultaten van autopsiestudies, waarbij in patiënten met een COVID-19-pneumonie meerdere kleine trombi in de alveolaire capillairen werden gevonden. Voor nader onderzoek zijn in **Hoofdstuk 12** de klinische en CT-kenmerken van longembolieën in patiënten met een COVID-19-infectie geanalyseerd en zijn deze vervolgens vergeleken met die in patiënten zonder COVID-19-infectie. Hieruit bleek dat de longembolieën in patiënten met een COVID-19-infectie minder uitgebreid waren en vaker in de perifere longsegmenten waren gelokaliseerd. Daarnaast waren zowel de gemiddelde RV/LV ratio als de prevalentie van een RV/LV ratio >1 lager in patiënten met een COVID-19-infectie. Hieruit werd geconcludeerd dat COVID-19-geassocieerde longembolieën inderdaad verschillen ten opzichte van conventionele longembolieën en dat deze resultaten mogelijk de hypothese ondersteunen dat COVID-19-geassocieerde longembolieën het gevolg zijn van een plaatselijke immuunreactie. Daarnaast kan dit betekenen dat de (profylactische) antistollingsbehandeling bij COVID-19-geassocieerde longembolieën wellicht anders zou moeten zijn dan bij een conventionele longembolie. Toekomstige studies zijn nodig naar de precieze pathofysiologie van COVID-19-geassocieerde longembolieën en naar het meest optimale antistollingsbeleid in dit ziektebeeld.

TOEKOMSTPERSPECTIEF

In de afgelopen jaren is grote technische vooruitgang geboekt in de diagnostische beeldvorming van VTE. Dit heeft ertoe geleid dat frequenter zeer kleine en/of asymptomatische trombi worden gevonden. De klinische relevantie en meest optimale behandeling van deze trombi is echter niet bekend. Met de komst van MR-NCTI is het nu mogelijk om trombose direct in beeld te brengen en om acute van chronische trombose te onderscheiden en daarmee ook de indicatie voor antistolling te bepalen. In de praktijk wordt MR-NCTI steeds vaker toegepast bij verdenking op een ipsilateraal recidief DVT waarbij de echo geen uitsluitsel kan

geven. Voordat MR-NCTI kan worden geïmplementeerd in de klinische praktijk bij verdenking op een armvene trombose en CVT moet eerst een diagnostische uitkomststudie worden verricht om de veiligheid van deze techniek vast te stellen. Echter, wanneer de resultaten van de Theia-studie worden vertaald naar patiënten met een vermoeden van een armvene trombose of CVT, kan de toepassing van MR-NCTI worden overwogen in complexe omstandigheden, waarin non-invasieve diagnostische testen geen definitieve diagnose kunnen geven, zonder de aanwezigheid van zo'n uitkomststudie.

In geval van buikvene trombose, kan MR-NCTI mogelijk worden gebruikt bij de beslissing tot het starten van antistollingsbehandeling bij patiënten met verdenking op een chronische trombose. In de huidige richtlijnen worden namelijk geen antistollingsmedicijnen bij patiënten met een chronische buikvene trombose geadviseerd in tegenstelling tot patiënten met een acute trombose. Wanneer MR-NCTI accuraat blijkt voor de differentiatie tussen acute en chronische buikvene trombose in de Rhea studie, moet er een uitkomststudie worden verricht. In de meest ideale situatie betreft dit een gerandomiseerde klinische studie, waarin patiënten met een verdenking op een chronische buikvene trombose en normale MR-NCTI worden geloot tussen therapeutische antistollingsbehandeling en geen antistollingsbehandeling. Vervolgens kan dan de klinische uitkomst - zoals de aanwezigheid van een recidief of progressieve trombose, grote bloedingen en sterfte - tussen deze twee groepen worden vergeleken. Bij ongeveer 30% van de patiënten met de diagnose buikvene trombose, wordt deze trombose per toeval gevonden. Met name voor deze groep, zal de toepassing van MR-NCTI relevant zijn. Dit geldt dan ook in de situatie waarin conventionele beeldvormende technieken geen aanwijzingen voor chroniciteit laten zien.

Nadat de veiligheid van MR-NCTI is vastgesteld in diagnostische uitkomststudies, moeten de uitdagingen van implementatie in de klinische praktijk in kaart worden gebracht voordat deze techniek ook daadwerkelijk wijdverspreid kan worden geïmplementeerd. Eén van deze uitdagingen betreft de lagere beschikbaarheid van, en beperkte ervaring met MR-NCTI ten opzichte van conventionele beeldvormende technieken. Daarnaast heeft MRI hogere kosten. Implementatiestudies zijn nodig om de meest optimale strategie te ontwikkelen voor het implementeren van MR-NCTI in de dagelijkse klinische praktijk. Deze studies moeten onder andere gericht zijn op de exacte indicatie van MR-NCTI-beeldvorming en training van MRI-laboranten en radiologen, zodat zij MR-NCTI beelden kunnen beoordelen en interpreteren.

In de diagnostiek van longembolieën kan zowel met CTPP als met ventilatie/perfusie *single-photon*-emissietomografie (V/Q SPECT) scintigrafie longperfusiebeelden worden verkregen. De rol van deze perfusiebeelden in de diagnostiek en risicoclassificatie van longembolieën is echter nog steeds onduidelijk. Waar de MR-NCTI-scan bijna in de dagelijkse praktijk is geïmplementeerd, geldt dit niet voor de CTPP-techniek. De toepassing van CTPP in de kliniek is nog onduidelijk, onder meer doordat de manuele perfusiedefectkwantificatie veel tijd kost en doordat huidige studies niet eenduidig de toegevoegde waarde van CTPP bovenop CT-angiografie hebben kunnen vaststellen. Met de ontwikkeling en validatie van artificiële intelligentie (AI) software kan het mogelijk worden om nauwkeuriger en reproduceerbaar perfusiedefecten te kwantificeren. Als toekomstige studies aantonen dat automatische kwantitatieve bepaling van perfusiedefecten met gebruik van deze software sterker gerelateerd is met de klinische prognose van longembolieën, kan dit leiden dat CTPP in de dagelijkse praktijk kan worden toegepast. Dan kan wellicht een individuele patiëntgerichte behandeling na een longembolie-diagnose worden opgesteld bij zowel de initiële behandeling als bij de bepaling van de opnameduur en het vervolg. Onderzoek naar de ontwikkeling en validatie van AI-software voor het bepalen van perfusiedefecten en naar een correlatie met de klinische uitkomst loopt nog.

LIST OF PUBLICATIONS

DANKWOORD

CURRICULUM VITAE

LIST OF PUBLICATIONS

van Dam LF, Dronkers CEA, Gautam G, Eckerbom Å, Ghanima W, Gleditsch J, van Haren GR, von Heijne A, Huisman MV, Stöger JL, Westerlund E, Kroft LJM, Klok FA. Detection of upper extremity deep vein thrombosis by magnetic resonance non-contrast thrombus imaging. J Thromb Haemost. 2021 Aug; 19(8): 1973-1980

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CURRICULUM VITAE

Lisette Florence van Dam werd geboren op 10 juli 1988 te Leusden, waar ze ook opgroeide. In 2006 behaalde ze haar atheneumdiploma aan de Amersfoortse Berg te Amersfoort. In datzelfde jaar startte ze met de studie Geneeskunde aan de Universiteit van Groningen. In 2011 begon zij met haar coschappen in Groningen en vanaf 2012 in Zwolle met onder andere keuzecoschappen op de Spoedeisende hulp en de Intensive Care in de Isala Klinieken te Zwolle. Haar wetenschapsstage deed zij op de Spoedeisende hulp in het St. Antonius ziekenhuis te Nieuwegein naar elleboogtrauma's en geïsoleerde fat pads. Lisette haalde haar artsendiploma in 2013. Het daaropvolgende jaar startte zij als arts-assistent op de Spoedeisende hulp in Ziekenhuis Rivierenland te Tiel. Zij begon als arts-assistent in vooropleiding van de Spoedeisende hulp in het HagaZiekenhuis te Den Haag in 2015, waar ze één jaar werkzaam was op de Spoedeisende hulp en zes maanden op de Intensive Care. Per januari 2017 is zij gestart met de opleiding tot Spoedeisende hulp arts in het HagaZiekenhuis (opleider mw. Drs. G. Veldhuis). Vanaf januari 2018 heeft zij haar opleiding gedurende drie jaar onderbroken om promotieonderzoek te verrichten in het Leids Universitair Medisch Centrum te Leiden onder begeleiding van Prof. dr. M.V. Huisman en Dr. F.A. Klok. De resultaten van deze werkzaamheden zijn beschreven in dit proefschrift. Tijdens het afronden van haar promotie heeft zij vanaf januari 2021 haar opleiding vervolgd in het HagaZiekenhuis.