Novel imaging strategies in venous thromboembolism

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CHAPTER

Magnetic resonance imaging for diagnosis of recurrent ipsilateral deep vein thrombosis

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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

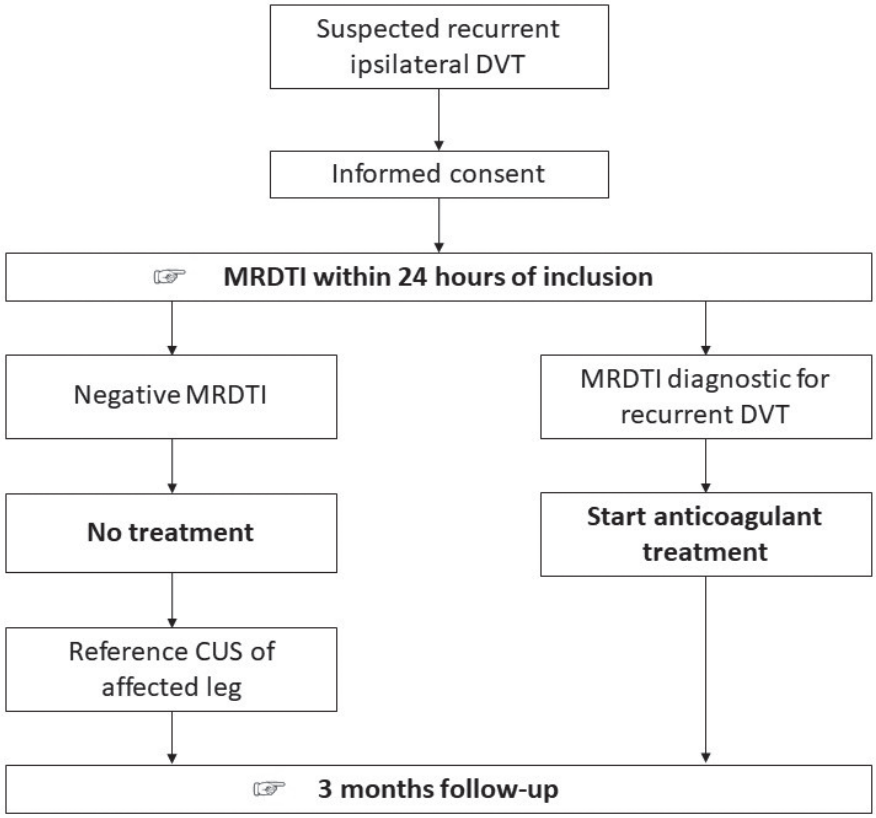
Consecutive patients who fulfilled all inclusion criteria and met none of the exclusion criteria were eligible for inclusion and managed according the study algorithm (**Figure 1**). The diagnosis and treatment decision were based solely on the result of the MRDTI of the affected leg which was performed 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

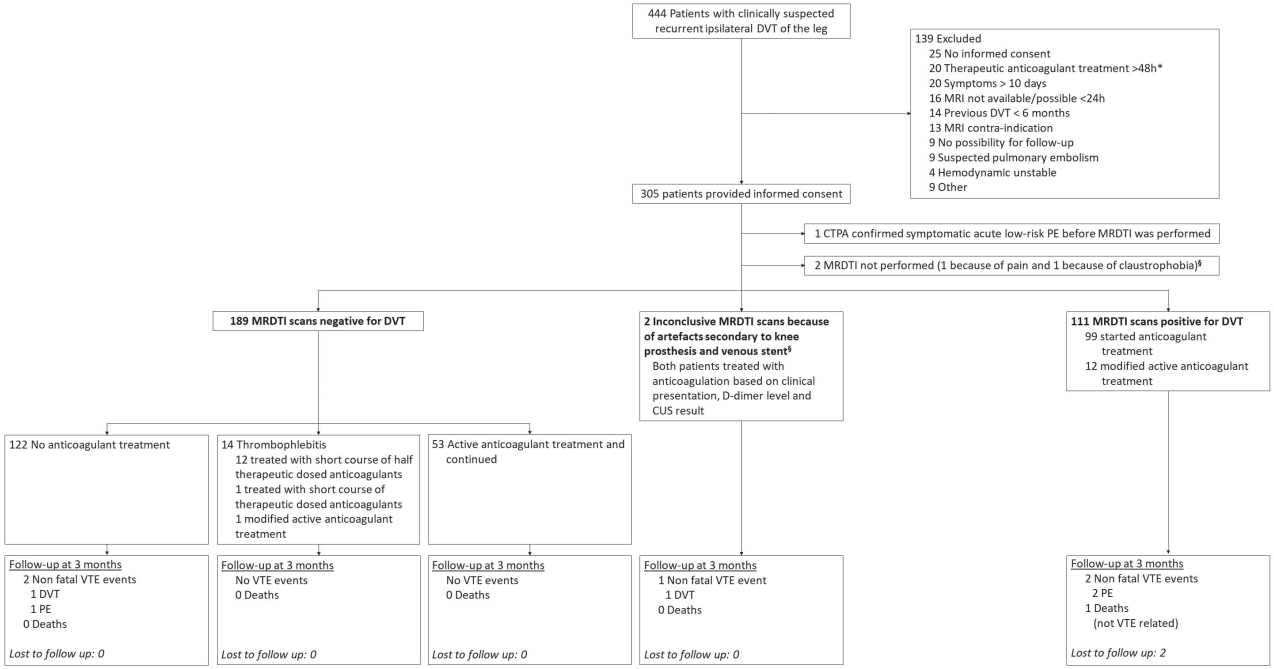
From March 2015 to March 2019, a total of 444 consecutive patients with clinically suspected acute recurrent ipsilateral DVT of the leg were screened; 139 patients (31%) were excluded for various reasons as per predefined exclusion criteria (**Figure 2**). The baseline characteristics of the 305 study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

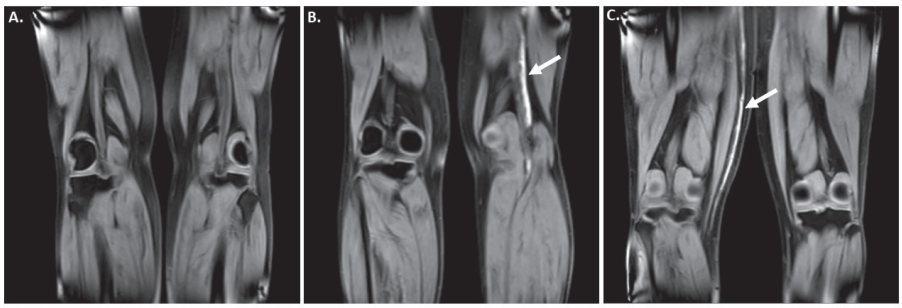
The MRDTI was negative for DVT but positive for superficial thrombophlebitis in 14 patients (7.4%). Twelve of these were treated with a short course of half-therapeutic dosed anticoagulants, while one patient was treated with short course of therapeutic dosed anticoagulants. One patient diagnosed with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