Advanced diagnostic management of suspected recurrent ipsilateral deep vein thrombosis of the leg with magnetic resonance direct thrombus imaging - The Theia study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Observational non invasive

Summary

ID

NL-OMON45235

Source
ToetsingOnline

Brief title
The Theia study

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
Deep vein thrombosis, venous thrombosis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Beurs van Nederlandse Trombose Stichting

Intervention

Keyword: Compression Ultrasonography, Magnetic resonance direct thrombus imaging, Recurrent deep vein thrombosis

Outcome measures

Primary outcome

The primary endpoint is the 3-month incidence of recurrent VTE in patients with MRDTI that is negative for the presence of DVT. The primary sensitivity analysis is restricted to patients who did not receive anticoagulants in the follow-up period. Symptomatic DVT of both the ipsilateral as contralateral leg is defined as symptoms suggestive of acute DVT, i.e. ongoing pain, swelling, tenderness, warmth and/or erythema of the leg of recent onset, and non-compressibility of the common femoral and/or popliteal vein in a new venous segment, or a pronounced increase in vein diameter (>= 4 mm) of a previously uncompressible vein as compared to the reference CUS performed at baseline. Acute PE is defined as at least one filling defect in the pulmonary artery tree on CTPA. In addition, PE is considered as the cause of any unexplained death unless autopsy will prove otherwise. All primary endpoints will be adjudicated by an independent Clinical Events Committee (see section on Monitoring).

Secondary outcome

The secondary endpoints include:

1 Post-hoc assessment of the 3-month incidence of recurrent VTE after the

baseline combination of a normal D-dimer test (for patients aged over 50 years age x 10 µg/l, for patients aged 50 years or younger 500 µg/l), and an unlikely ruling by the Wells score for DVT (Appendix B). The golden standard for a correct negative ruling by the D-dimer test and the clinical decision rule is a normal MRDTI at baseline and an uneventful 3-month follow-up period;

2 Feasibility of MRDTI as diagnostic test in daily clinical practice, i.e. the number of patients that could not be managed according to the study protocol due to logistical or technical issues and the mean time from presentation to MRDTI ruling;

3 Post-hoc assessment of the inter-observer variability of MRDTI in clinical practice: 100 MRDTI scans (first 10 scans of each study site) will be re-assessed after the study by 2 independent radiologists, who are blinded tot the clinical presentation and follow-up of the study patients. Their ruling will be compared to the ruling of the attending radiologist at the moment of clinical presentation;

4 A cost-effectiveness (KEA) and cost-utility analysis (KUA). Both will be dependent on data derived from this study as well as data from the literature. The KEA will provide en estimation of the total costs associated with diagnostic tests for one prevented false-positive diagnosis. The KUA will be additionally be based on estimated costs for patient monitoring, bleeding complications and productivity costs. Assessment of quality-adjusted life-years

(QALY) after a MRDTI based diagnostic strategy will be compared to a CUS-bases

strategy, using cost-utility models as proposed by the British National

Institute for Health and Clinical Excellence (NICE), specified for Dutch norms

Study description

Background summary

The diagnostic management of suspected ipsilateral recurrent proximal deep vein thrombosis (DVT) is complicated by critical limitations to current available diagnostic techniques, mainly caused by persistent intravascular abnormalities after a first DVT. Compression ultrasonography (CUS) is the imaging method of choice, although CUS can only diagnose ipsilateral recurrent DVT with some certainty in case of a new uncompressible venous segment, or a pronounced increase in vein diameter of a previously uncompressible vein as compared to a reference CUS, assessed after successful treatment of the first DVT. In clinical practice however, this reference CUS is seldomly available and comparisons with previous CUS examinations are subject to major inter-observer variability. Consequently, recurrent ipsilateral DVT cannot be ruled out in 20-30% of patients, who are therefore all subjected to lifelong anticoagulant therapy with associated high bleeding risk.

Magnetic resonance direct thrombus imaging (MRDTI) has been shown to accurately diagnose a first DVT episode and to reliably distinguish chronic residual thrombotic scars from acute recurrent DVT. MRDTI could therefore potentially be used as a single test in the diagnostic management of clinically suspected recurrent ipsilateral DVT. We hypothesize that MRDTI has equally high safety (sensitivity) but superior efficacy (specificity) compared to CUS in this setting.

Study objective

The primary objective of the study is to assess the safety of a normal MRDTI to rule out acute, recurrent ipsilateral proximal DVT in a prospective, multicenter, single-arm management (cohort) study.

Secondary objectives are:
1.To evaluate the safety of ruling out acute recurrent ipsilateral DVT based on a normal D-dimer test result in combination with an unlikely ruling by the Wells rule for DVT
2.To assess the health economics of a MRDTI-based diagnostic algorithm for

suspected recurrent ipsilateral DVT compared to a CUS-based algorithm.

Study design

The Theia-study is a prospective, multicenter, single-arm management (cohort) study.

Consecutive patients with clinically suspected acute, recurrent, ipsilateral, proximal DVT, who fulfil all the inclusion criteria and meet none of the exclusion criteria, are eligible for inclusion and will be managed according to the result of a MRDTI of the affected leg. The MRDTI is to be performed and adjudicated within 24 hours of study inclusion. The final treatment decision will be made based on this ruling of the MRDTI. In case of a positive MRDTI signal, patients will be treated with therapeutically dosed anticoagulants. Patients with a negative MRDTI ruling will be subjected to a standardized CUS within 48 hours after initial presentation. The latter CUS serves as a reference test in case the patient returns with symptoms of ipsilateral recurrence in the future, and will not be used for management decisions at baseline. The study flowchart can be found in Appendix A.

All patients will be followed for three months for the occurrence of acute recurrent venous thrombo-embolism (VTE). In case of suspected recurrent VTE, objective testing including either computed tomography pulmonary angiography (CTPA) for PE or CUS for DVT will be performed. Additionally, in case of a proven ipsilateral recurrent DVT during follow-up, MRDTI will be repeated.

Study burden and risks

Currently, the diagnostic management of patients with suspected acute, recurrent, ipsilateral, proximal DVT is far from accurate. Hence, relevant patients may receive a false positive CUS finding and by that, may be subjected wrongfully to indefinite therapeutic anticoagulation with its associated bleeding complications.

The very sensitive and specific MRDTI technique has been shown to be a reliable imaging modality to distinguish acute from chronic thrombi in the leg veins. This technique does not require administration of potential toxic contrast dye, or ionizing radiation, and takes only 15 minute of time. Hence, no harmful effect s of the MRDTI can be expected and on the other hand, some patients may directly benefit from this study.

The potential therapeutic advantage for the study patients comes at cost of a potential longer waiting time from moment of presentation at the outpatient clinic or emergency ward, to the definite diagnostic decision. In addition, after a negative MRDTI, an additional CUS is required for the study, which will also take some time. Even so, patients will be well informed of this before

study inclusion.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1 Ability of subject to understand the character and individual consequences of this study;
2 Signed and dated informed consent of the subject available before the start of any specific study procedures;
3 Age >=18 years;
4 Suspected acute recurrent ipsilateral DVT, as defined by a documented prior objectivated episode of DVT in the same leg as current symptoms originate from

Exclusion criteria

1 General contraindications for MRI: claustrophobia, first trimester of pregnancy, intracranial vascular clips, any ferromagnetic implants, presence of a cardiac pacemaker or defibrillator, metallic splinters in the eye, any trauma or surgery which may have left ferromagnetic material in the body;
2 CUS-proven acute symptomatic DVT within 6 months before current presentation;
3 Onset of symptoms suggestive of acute recurrent DVT more than 10 days prior to presentation;
4 Suspected acute PE;
5 Hemodynamic instability at presentation (as a consequence of concurrent acute PE or otherwise);
6 Medical or psychological condition that would not permit completion of the study or signing of informed consent, including life expectancy less than 3 months
8 Non-compliance or inability to adhere to treatment or follow-up visits.

Study design

Design

Study phase:	4
Study type:	Observational non invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-03-2015
Enrollment:	305
Type:	Actual

Ethics review

Approved WMO

Date:	12-01-2015

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	03-02-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	11-08-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	10-11-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	24-11-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	20-07-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	10-07-2017

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL50663.058.14