Safety and efficiency of the YEARS algorithm versus computed tomography pulmonary angiography alone for suspected pulmonary embolism in patients with malignancy - The Hydra Study

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20408

Source
Nationaal Trial Register

Brief title
The Hydra Study

Health condition

English keywords:
- diagnosis
- pulmonary embolism
- malignancy

Dutch keywords:
- diagnose
- longembolie
- maligniteit

Sponsors and support

Primary sponsor: Leiden University Medical Center (LUMC)
Source(s) of monetary or material Support: LUMC

Intervention

Outcome measures

Primary outcome

To prospectively validate the safety and efficiency of management according to the YEARS algorithm to safely rule out clinically suspected PE in patients with active malignancy to be compared with ‘standard’ management by CTPA alone in a randomized study. Safety is defined as the number of recurrent venous thromboembolism during three months follow-up in patients with normal initial diagnostic tests. Efficacy is defined as the number of CT scans performed at baseline.

Secondary outcome

1. To evaluate the occurrence (timing, location and severity) of recurrent symptomatic VTE during follow-up in both study arms in order to better differentiate between missed PE diagnoses and new onset VTE.
2. To compare differences in the rate of isolated sub-segmental PE, defined as CTPA demonstrating an intraluminal filling defect in a sub-segmental artery with no filling defect visualized at more proximal artery levels, in both study arms
3. To assess the occurrence of incidental VTE, defined as thromboembolism that was detected by means of imaging tests performed for reasons other than clinical suspicion of venous thromboembolism[18], during follow up in both study arms
4. To evaluate contrast material induced complications (allergic reactions and contrast material induced nephropathy) in both study arms.
5. To evaluate usage and safety of antithrombotic treatment in both study groups
6. To evaluate practice patterns of anticoagulation therapy during end-of-life care in terminally ill patients with cancer.
7. To evaluate quality of life in patients with pulmonary embolism at baseline and follow-up as measured by the Pulmonary Embolism Quality of Life (PEmb-QoL) Questionnaire.
8. To post-hoc evaluate the performance of the 4-Level Pulmonary Embolism Clinical Probability Score (4PEPS), in patients randomized for YEARS within the Hydra study.

Study description

Background summary

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent complication of malignancy[2]. Patients with malignancy were associated with a 4-fold risk of VTE compared patients without malignancy, where chemotherapy increased this risk to 6.5-fold[3]. The development of VTE is presumed to be due to the production of pro-coagulant molecules by malignant cells and to the pro-coagulant effect of these cells spread into the circulation[4]. Furthermore, many factors contribute to the thrombotic risk in malignancy patients, including classical thrombotic risk factors (i.e. age, bed-rest, history of VTE, and comorbid conditions) and risk factors typical of malignancy (i.e. type and stage of malignancy, anti-malignancy treatments)[3, 5, 6].

Diagnosing PE in patients with malignancy

Because of its diagnostic accuracy and wide availability, multi-row detector computed tomography pulmonary angiography (CTPA) is currently the imaging test of choice to confirm or exclude acute PE [7, 8]. However, this diagnostic test can yield useless or misleading test results if done without appropriate clinical indication [9]. Therefore, circulating D-dimer concentrations and clinical predictions rules were developed as complementary diagnostics steps.

The D-dimer is a biomarker that is routinely used in conjunction with clinical parameters in the initial assessment of suspected acute PE[10]. Although it is well documented that the D-dimer test is useful in the diagnostic workup of patients with suspected PE, it is thought that the D-dimer test is of less value in patients with malignancy due to often elevated levels in absence of thrombosis [11, 12]. According to previous studies, the incidence of normal D-dimer levels (cut off at 0.5µg/mL or age-adjusted) in patients with a malignancy and suspected PE may be as low as 10-15% [1, 13].

Several clinical decision rules (CDRs) have been developed for estimating the pre-test probability of PE. CDR can be combined with D-dimer testing to rule out PE in case of a non-high probability and a normal D-dimer test [14]. However, it is recognized that CDRs may not be as effective and safe in patients with malignancy. Recently, the YEARS study combined three elements of the Wells rule (i.e. clinical signs of deep vein thrombosis, hemoptysis, and whether pulmonary embolism is the most likely diagnosis) with D-dimer testing for exclusion of PE, of which the cut-off level is dependent whether YEARS items are absent or not. The study showed that CTPA could safely be avoided in an additional absolute 13% of patients compared with standard algorithms [1]. This reduction could be achieved, according to the worst case scenario, at an only 0.78% (95% CI 0.49-1.2) failure rate with regard to the 3-month incidence of recurrent venous thromboembolism. However, this algorithm showed highest failure rates (2.6%, 95%CI 1.3-5.2) in a relatively small subgroup of patients with malignancy (9.7% of the YEARS study population). Moreover, a recent meta-analysis demonstrated that the D-dimer test (cut off <0.5µg/mL), combined with the diagnostic Wells rule, resulted in a similar 2.6% (95% confidence interval (CI) 0.57-11) 3-month failure rate of diagnosing PE in patients with malignancy[13]. This was also highest among all subgroups. As a consequence of unknown safety and efficacy of CDRs in patients with malignancy and presumed futility of D-dimer as a diagnostic test, clinicians-oncologists may often directly order a CTPA when suspecting PE. However, avoidance of CTPA use results in less radiation exposure, contrast material allergy and contrast material induced nephropathy, as well as leads to a reduction of irrelevant sub-segmental emboli detection and health care costs [15-17].

Study objective

The YEARS algorithm is non-inferior to management by CTPA with regard to 3-month recurrent VTE rates and will reduce the rate of unnecessary CTPA in patients with clinically suspected PE and active malignancy.

Study design

Visit 1 (enrollment):
- Check for in- and exclusion criteria
- Obtain informed consent
- Randomization
- Medical history
- Demographic data
- Clinical examination
- Laboratory test (d dimer, renal function) (Part of clinical practice, no study proceedings)
- Decision of diagnostic method (management according to YEARS algorithm or CTPA alone)

Visit 2 (3 months follow up)
- Recording of death, adverse events, pulmonary embolism, deep vein thrombosis, major bleeding, re-hospitalization, anticoagulation therapy usage

Trial schedule:
The total duration of this study is expected to be 30 months.
Ethics approval in the primary research center is aimed to be achieved by second quarter of 2019 and by end of 2019 in the participating centers.
Subject recruitment is planned to start in June 2019 and end in February 2024.
The follow up-period will end in summer 2024, allowing for analysis of data and first assessment of results in autumn 2024.

Intervention

The Hydra-study will be a randomized controlled, multicenter international trial with a non-inferiority analysis for the main safety outcome (rate of 3-month VTE); if non-inferiority has been demonstrated at secondary stage a superiority analysis for the efficiency judgment criterion (rate of unnecessary CTPA) will be performed. The two randomized arms will exist of diagnostic management according to the YEARS algorithm and diagnostic management by CTPA alone.

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Clinically suspected PE as judged by the treating clinician
- Any type of active malignancy (other than basal-cell or squamous-cell carcinoma of the skin), defined as diagnosis within six months before the study inclusion (as confirmed histologically or high suspicion as judged by the clinician), receiving treatment for malignancy at time of inclusion or during 6 months prior to randomisation or in the presence of metastases, including recurrent or local metastatic malignancy
- Age ≥ 18 years

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Symptoms for more than 10 days
- Medical or psychological condition that would not permit completion of the study or signing of informed consent, including life
expectancy less than 3 months, or unwillingness to sign informed consent
- Treatment with full-dose therapeutically dosed anticoagulation that was initiated 24 hours or more prior to eligibility assessment
- Contraindication to CTPA
o contrast allergy
o impaired kidney function (eGFR <30 ml/min/1,73m2)
- Hemodynamic instability at presentation (as a consequence of concurrent acute PE or otherwise), indicated by at least one of the
following:
o systolic blood pressure (SBP) < 100 mm Hg, or heart rate >120 beats per minute or SBP drop by > 40 mm Hg, for > 15 min
o need for catecholamines to maintain adequate organ perfusion and a systolic blood pressure of > 100 mmHg
o need for cardiopulmonary resuscitation

- Suggestion of PE on previously performed oncologic CT scan, for which now PE-specific diagnostic testing is only performed as
means of verification
- Participating in another concurrent study on thromboprophylaxis
- Prior participation in the Hydra study

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-07-2019
Enrollment:	1566
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Plan description
/

Ethics review

Positive opinion

Date:	14-05-2019
Application type:	First submission

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
NTR-new	NL7752
Other	METC LUMC : ABR research file number NL68754.058.19

Study results

Summary results
none