Clinical Surveillance vs. Anticoagulation for Low-risk Patients with Isolated Subsegmental Pulmonary Embolism: A Multicenter Randomized Placebo-Controlled Non-Inferiority Trial

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This study has been transitioned to CTIS with ID 2023-506943-40-00 check the CTIS register for the current data. The overall objective of this trial will be to evaluate the efficacy and safety of clinical surveillance without anticoagulation in low-...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON55205

Source
ToetsingOnline

Brief title
SAFE-SSPE

Condition

- Embolism and thrombosis

Synonym
pulmonary embolism, venous thromboembolism

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Bayer,This trial is supported by the Swiss National Science Foundation (project number 33IC30_185616).

Intervention

Keyword: Pulmonary embolism, Randomized Controlled Trial, Treatment

Outcome measures

Primary outcome

The primary outcome will be the proportion of recurrent, clinically

symptomatic, objectively confirmed VTE within 90 days of randomization, defined

as recurrent fatal or nonfatal PE or lower limb deep vein thrombosis (DVT;

efficacy).

Secondary outcome

The secondary outcomes will be the proportion of clinically significant

bleeding and all-cause mortality at 90 days of randomization (safety).

The ancillary outcomes will be health-related quality of life, functional

status, and medical resource utilization at 90 days of randomization. In a

post-hoc analysis, we will also assess radiological inter-observer agreement

for SSPE

Study description

Background summary

The widespread introduction of multi-detector computed tomography pulmonary angiography (CTPA) was followed by an 80% increase in the diagnosis of acute pulmonary embolism (PE). As multi-detector CTPA allows better visualization of the peripheral pulmonary arteries, small emboli limited to the subsegmental

pulmonary arteries, so-called isolated subsegmental PE (SSPE), are increasingly detected and currently comprise 10-15% of cases with PE.
The clinical significance of isolated SSPE and whether isolated SSPE represents *true* PE, a clinically more benign form of PE, a physiologic lung clearing process, or a false positive result (artifact) is currently unclear and hence, whether patients with isolated SSPE benefit from anticoagulant treatment is uncertain. Despite growing evidence from retrospective and prospective studies that withholding anticoagulation may be a safe option in selected patients with isolated SSPE (i.e., those without concomitant deep vein thrombosis, cancer, etc.), most patients with isolated SSPE receive anticoagulant treatment and have a 90-day risk of major bleeding of up to 5%.

Study objective

This study has been transitioned to CTIS with ID 2023-506943-40-00 check the CTIS register for the current data.

The overall objective of this trial will be to evaluate the efficacy and safety of clinical surveillance without anticoagulation in low-risk patients with isolated SSPE.
Objective 1: To compare the frequency of symptomatic, recurrent venous thromboembolism (VTE) in low-risk patients with isolated SSPE randomized to receive clinical surveillance or anticoagulation.
Objective 2: To compare the frequency of clinically significant bleeding and all-cause mortality in low-risk patients with isolated SSPE randomized to receive clinical surveillance or anticoagulation.
Objective 3: To compare health-related quality of life, functional status, and medical resource utilization in low-risk patients with isolated SSPE randomized to receive clinical surveillance or anticoagulation.

Study design

This trial is designed as an international, multicenter, placebo-controlled, double-blind, parallel-group non-inferiority trial. Consenting low-risk patients with isolated SSPE without concomitant DVT will be randomly assigned in a 1:1 ratio to receive placebo (*clinical surveillance group*) or anticoagulant treatment with rivaroxaban (*anticoagulation group*). Eligible patients will be recruited at 27 high volume hospitals in Switzerland, The Netherlands, and Canada.

Intervention

Patients in the clinical surveillance group will receive a matching rivaroxaban placebo following the same schedule as patients in the control group. Clinical surveillance will be done by follow-up phone calls 2 times during the first 30 days (at 10 and 30 days) and at 90 days following randomization. Depending on

local practice, the follow-up phone calls can be substituted by in person visits. At each contact, trained study personnel will complete an assessment of symptoms and review for suspected recurrent VTE and bleeding using a checklist of pre-defined questions. Patients will also be instructed to contact study personnel or report to the ED immediately if any symptoms/signs compatible with recurrent VTE or significant bleeding occur.

Study burden and risks

Expected benefits for Patients, Society, and Research
The standard treatment for PE is anticoagulant therapy for at least 3 months.15 As outlined in section 3.1., anticoagulant treatment effectively reduces the risk of recurrent VTE,16 but comes at the cost of an increase in the risk of potentially disabling and life-threatening bleeding, which is associated with reduced quality of life and increased distress,24 medical resource utilization and costs,11 and can even result in disability or death.10,17 Therefore, the benefits of anticoagulation need to be carefully weighed against its risks. Based a growing body of evidence from observational studies indicating that withholding anticoagulation may be safe in selected patients with isolated SSPE,31,41,46-53 the latest guidelines suggest that clinical surveillance rather than anticoagulation is a management option in low-risk patients with isolated SSPE and no concomitant proximal DVT.15,55,56 However, the quality of evidence supporting these guideline recommendations is low (grade 2C). Our trial therefore addresses an important gap of knowledge, the optimal management of SSPE, and represents the first randomized, direct comparison of clinical surveillance alone vs. anticoagulant treatment for low-risk patients with isolated SSPE. Our project is important from a public health, physician, and patient perspective. First, acute PE is a common disease, with an incidence of about 112 cases per 100,000 adults.27 Currently, SSPE represents about 10-15% of cases with PE, but with the further dissemination/advancement of multi-detector CTPA technology, the number of patients with SSPE who will eventually receive anticoagulant treatment is likely to rise in the future. We expect the clinical and economic benefit of withholding anticoagulation to be primarily due to a decrease in bleeding episodes, and to a lesser extent, to a reduction in medication costs (about $500 for a 3-month course with direct oral anticoagulants). Projections from 6 European countries with 300 million inhabitants demonstrate that about 300,000 episodes of PE occur every year.70 Assuming a prevalence of isolated SSPE of 15% (45,000 cases), a major bleeding rate of 2% within the first 3 months of treatment,17 a ratio of major to clinically relevant non-major bleeding of 8,19,21 and that anticoagulation could be withheld in about 50% of patients with isolated SSPE, about 500 major bleedings and about 4000 clinically relevant non-major bleedings could be avoided per year. Given the high case-fatality (11%) and prevalence of intracranial hemorrhage (10%) in patients with major bleeding17 and the costs per major ($4300-13,000) and non-major bleeding ($200-2800) episode,71-73 a substantial reduction in mortality, morbidity, and cost could be achieved. In Switzerland, an estimated 8000 cases of PE were diagnosed in 2016,74 of which

up to 1200 cases are isolated SSPE.
Because no study has compared the level of resource utilization and productivity between patients with isolated SSPE who are managed by clinical surveillance alone or anticoagulation, our trial will also assess common measures of resource utilization and productivity, such as the initial length of hospital stay (LOS), subsequent hospitalizations, emergency department (ED) and outpatient physician visits, and the time to return to work or usual activities. To date, no studies have examined health-related quality of life in patients with SSPE. Because patients managed with clinical surveillance alone are less likely to develop bleeding events, we expect clinical surveillance to be associated with a higher quality of life and will assess this outcome as part of this trial.
Successful completion of this study will provide a strong scientific basis for withholding anticoagulation in low-risk patients with isolated SSPE and may therefore to improve quality and efficiency of care by reducing bleeding episodes and resource utilization and increasing health-related quality of life. Our project will have value to physicians who are committed to optimizing patient safety and providing high-quality, cost-effective care and fits well with the Choosing Wisely initiative and other efforts to reduce unnecessary care and patient harm.75,76
For the individual participating patient, we cannot guarantee any benefits arising from study participation. It may be possible that potential complications such as recurrent VTE or bleeding events can be recognized more quickly given that regular follow-up phone calls or visits are performed.

Potential risks
Potentially, withholding anticoagulation in patients with VTE (including SSPE) may be associated with an increased risk of recurrent VTE. However, we expect that clinical surveillance without anticoagulation does not pose additional risks in terms of VTE-recurrence or mortality for study participants compared to anticoagulation, because (1) only clinically stable patients at low risk of VTE recurrence will be enrolled (see eligibility criteria in section 7.1), and (2) prior comparative studies do not suggest a risk difference in VTE recurrence or mortality between patients with isolated SSPE who receive anticoagulant treatment or not.54 We expect to find a lower risk of significant bleeding in patients in whom anticoagulants are withheld.49,50 Anticoagulation treatment is associated with an increased risk of bleeding.

Measures to mitigate the risks
Patients with a high risk of bleeding or conditions that can increase rivaroxaban-associated bleeding risk (e.g. severe renal failure, use of strong CYP3A4 inhibitors) will be excluded from the study (see section 7.1) in order to decrease the risk of anticoagulation-related bleeding. Patients with a high risk of recurrent VTE, namely patients with concomitant DVT, active cancer, previous episodes of unprovoked VTE, or clinical instability (see section 7.1)

will be excluded from the study, in order to decrease the risk of recurrent VTE.
At the baseline visit, patients will be informed about symptoms and signs suggestive for recurrent VTE and bleeding orally and in writing (in the patient information and in the information booklet distributed to the participants), and will be instructed to immediately present to the study site*s ED for evaluation in case of suspected recurrent VTE or bleeding. Study personnel will contact patients 10, 30, and 90 days after randomization to assess outcomes and ask for signs and symptoms compatible with recurrent VTE or significant bleeding and if present, patients will be instructed to immediately present to the study site*s ED for evaluation. The higher frequency of contacts during the first month following enrolment will decrease the likelihood that that symptoms or signs of recurrent VTE will be missed during the period of highest risk for recurrence.65
The investigator*s contact information and an emergency telephone number (with 24h availability) will be provided in the information booklet if signs and symptoms of VTE or bleeding occur, or if participants have questions/concerns relating to study drugs/procedures. In addition, a credit-card sized information card will be provided to the patients containing basic information about the patient*s participation in the study and the investigator*s contact information and the emergency phone number.
In pre-defined clinical situations (need for anticoagulation reversal, recurrent VTE, or new pregnancy) emergency unblinding is possible (see section 6.3).
Finally, the trial will be under the surveillance of an independent Data Safety and Monitoring Board (DSMB) that will evaluate unblinded VTE outcomes on a regular basis and make recommendations to the Steering Committee to amend or terminate the trial should any safety concerns arise (see section 11.3).

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) Informed Consent as documented by signature
2) Age >=18 years
3) Objective diagnosis of symptomatic or asymptomatic isolated SSPE

Exclusion criteria

1) Presence of leg deep vein thrombosis (DVT) or upper extremity DVT (subclavian vein or above)
2) Active cancer, defined as cancer treated with surgery, chemotherapy, radiotherapy, or palliative care during the last 6 months
3) >=1 prior episode of unprovoked VTE (absence of a transient or permanent risk factor)
4) Clinical instability (systolic blood pressure <100 mm Hg or arterial oxygen saturation <92% at ambient air) at the time of presentation
5) Active bleeding or at high risk of bleeding
6) Severe renal failure (creatinine clearance <30ml/min)
7) Severe liver insufficiency (Child-Pugh B or C)
8) Concomitant use of strong CYP3A4 inhibitors or strong CYP3A4 inducers
9) Known hypersensitivity to rivaroxaban
10) Need for therapeutic anticoagulation for another reason
11) Therapeutic anticoagulation for >72 hours for any reason at the time of screening
12) Hospitalized for >72 hours prior to the diagnosis of isolated SSPE (hospital-acquired VTE)
13) Known pregnancy or breast feeding (pregnancy test to be performed for women of childbearing potential)
14) Lack of safe contraception in women of childbearing potential

15) Refusal or inability to provide informed consent
16) Prior enrolment in this trial

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-09-2021
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xarelto
Generic name:	Rivaroxaban
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	29-04-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	20-09-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-03-2022
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
EU-CTR	CTIS2023-506943-40-00
EU-CTR	CTIS2023-507801-32-00
EudraCT	EUCTR2020-000353-26-NL
ClinicalTrials.gov	NCT04263038
CCMO	NL72741.058.20