# Early non-invasive detection of CTEPH after pulmonary embolism

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Heart failures |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON46977

**Source**
ToetsingOnline

**Brief title**
The InShape-2 study

### Condition

- Heart failures
- Pulmonary vascular disorders
- Embolism and thrombosis

**Synonym**
CTEPH, high blood pressure in pulmonary hypertension due to chronic thrombi

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum
**Source(s) of monetary or material Support:** Afdelingsbudget

## Intervention

**Keyword:** CTEPH, Prediction, Pulmonary embolism, Screening

## Outcome measures

### Primary outcome

The primary endpoint is the accuracy of the screening algorithm to detect CTEPH, as reflected by the 2-year incidence of confirmed CTEPH in patients in whom CTEPH was initially ruled out without performing echocardiography.

### Secondary outcome

1) Incidence of CTEPH

2) Feasibility of the screening algorithm, i.e. number of necessary echocardiograms at baseline and the number of relevant echocardiographic findings at baseline, i.e. a finding that warrants therapeutic intervention;

3) Cost-effectiveness of the screening algorithm;

4) Additional diagnostic accuracy of electrocardiographically derived ECG-vector cardiogram (VCG) analysis on top of the manual ECG assessment;

5) Determination of the inter-observer variability in the measurement of the RV/LV ratio on computed tomography pulmonary angiography (CTPA).

6) Prevalence of the six radiological predictors of CTEPH (according to the InShape III study) and correlate this with the InShape II screening program.

# Study description

### Background summary

The ultimate consequence of hemodynamic compromise and persistent pulmonary perfusion defects after acute pulmonary embolism (PE) is chronic thromboembolic

pulmonary hypertension (CTEPH), which is a lethal condition unless a timely diagnosis is followed by adequate treatment. The exact incidence of CTEPH after PE is estimated to be 0.5% to 4.0% within the first 2 years after diagnosis. Notably, there are no specific signs or symptoms of CTEPH and patients may remain asymptomatic for months to years although clinically significant pulmonary hypertension (PH) is already present. Also, subjecting all patients who survived acute PE to transthoracic echocardiography, which is the recommended screening tool for suspected PH, has been shown to have a low diagnostic yield. Due to these uncertainties, international guidelines do not provide a clear recommendation on the frequency and duration of medical follow-up after acute PE or on specific screening programs for CTEPH. Early diagnosis of CTEPH is nonetheless essential, since when detected in an early stage, CTEPH may be cured by pulmonary endarterectomy while delay in diagnosis may be associated with worse prognosis, higher perioperative mortality and inoperable disease stages. It has been estimated that the majority of CTEPH diagnoses nowadays still have a diagnostic delay well over 1 year.
We have developed a CTEPH screening program based on a combination of a very recently derived risk stratification score11 and a validated non-invasive set of rule-out criteria. This screening program is aimed at 1) early diagnosis of CTEPH and 2) ruling out CTEPH with high certainty using standardized non-invasive test in patients with persistent dyspnea after acute PE. The former is likely associated with improved CTEPH prognosis, the latter with more cost-efficient long-term care for PE patients.

## Study objective

The primary objective of the study is to evaluate the diagnostic accuracy of a CTEPH screening program based on the stratification score and the *rule out criteria*.

To prospectively assess the feasibility and cost-effectiveness of the CTEPH screening algorithm as well as the incidence of CTEPH in the studied population.

To assess the prevalence of radiological signs of CTEPH in the studied population.

## Study design

This is a prospective, international, multicenter outcome cohort study. This study starts at the moment patients visit the outpatient clinic 3 to 6 months after a diagnosis of acute PE as part of routine medical care. If patients consent to study participation, the CTEPH clinical prediction score will be calculated. CTEPH is considered to be ruled out in patients with a low probability (*6 points) and no symptoms suggestive of CTEPH, i.e. dyspnea on exertion, edema, newly developed palpitations, syncope or chest pains. The remaining patients with either high probability (>6 points) or who report

symptoms that may be associated with CTEPH will be subjected to the *rule-out criteria*. CTEPH will be assumed ruled out in patients with an age- and gender dependent normal NT-proBNP level (as defined by the assay*s manufacturer), in the absence of any of the 3 ECG criteria. Patients who have an abnormal result from the *rule-out criteria* will be referred for transthoracic echocardiography. All echocardiograms will be performed according to a predefined standardized protocol, and judged by the following echocardiographic criteria for suspected PH according to the ESC guidelines. The presence of CTEPH will be considered ruled out in the absence of all of these criteria.

In case PH is suspected by echocardiography, patients will be referred for further diagnostic work-up of suspected CTEPH starting with perfusion lung scan or VQ-scan and right heart catheterization, of which the results will be discussed by an independent interdisciplinary working group of PH specialists, to ensure optimal diagnostic management. This latter diagnostic work-up of an abnormal echocardiograph lies within the setting of standard medical care.

All patients who were not diagnosed with pulmonary hypertension of any origin, or with NYHA class III or IV heart failure due to left ventricular systolic dysfunction, left ventricular diastolic dysfunction or significant valvular lesions, will be followed for a total of 2 years from the index PE diagnosis. During that period, the study protocol will not interfere with standard patient care, allowing diagnostic tests as deemed indicated by the treating physician including echocardiography in case of new respiratory symptoms. At the end of the follow-up period, all patients will be subjected to a second echocardiography that will be handled according to the above stated procedures to evaluate the presence of CTEPH.

### Study burden and risks

n.a.

## 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) All patients with an objectivated first or recurrent diagnosis of symptomatic acute PE, who have been treated for at least three months with therapeutically dosed anticoagulant therapy according to current guidelines;
2) Signed and dated informed consent of the subject available before the start of any specific study procedures;
3) Age *18 years;

## Exclusion criteria

1) Known CTEPH or PH;
2) 2) Known (i.e. echocardiographic confirmed) NYHA class III or IV chronic heart failure due to left ventricular systolic dysfunction with an EF <50%, left ventricular diastolic dysfunction of at least grade 2 or significant valvular lesions;
3) Severe renal failure (eGFR <15 ml/min) or renal replacement therapy;
4) Medical or psychological condition that would not permit completion of the study or signing of informed consent, including life expectancy less than six months, or unwillingness to sign informed consent;
5) Non-compliance or inability to adhere to treatment or to the follow-up visits.

# Study design

## Design

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 15-02-2016 |
| Enrollment: | 240 |
| Type: | Actual |

# Ethics review

Approved WMO

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|---|---|
| Date: | 07-01-2016 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

Approved WMO

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|---|---|
| Date: | 23-03-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

Approved WMO

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|---|---|
| Date: | 28-06-2016 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 29-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>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 |
|---|---|
| ClinicalTrials.gov | NCT02555137 |
| CCMO | NL54450.058.15 |

# Study results

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| Date completed: | 22-01-2020 |
| Actual enrolment: | 239 |

**Summary results**
Trial is onging in other countries