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Early View

Original article

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Multicentre observational screening survey for the detection of CTEPH following PE

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe complication of pulmonary embolism (PE). Its incidence following PE is debated. An active screening for CTEPH in patients with acute PE is yet to be recommended.

This prospective, multicentre, observational study (INPUT on PE; ISRCTN61417303) included patients with acute PE from 11 centres in Switzerland from March 2009 to November 2016. Screening for possible CTEPH was performed at 6, 12 and 24 months using a step-wise algorithm that included a dyspnoea phone-based survey, transthoracic echocardiography, right heart catheterisation and radiologic confirmation of CTEPH.

Of 1699 patients with PE, 508 patients were assessed for CTEPH screening over 2 years. The CTEPH incidence following PE was 3.7 per 1000 patient-years, with a two-year cumulative incidence of 0.79%. The Swiss pulmonary hypertension registry consulted in December 2016 did not report additional CTEPH cases in these patients. The survey yielded 100% sensitivity and 81.6% specificity. The second step echocardiography in newly dyspnoeic patients showed a negative predictive value of 100%.

CTEPH is a rare but treatable disease. A simple and sensitive way for CTEPH screening in patients with acute PE is recommended.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is viewed as a long-term complication of acute pulmonary embolism (PE). Although its physiopathology remains poorly understood, the hypothesis relies on fibrotic transformation of thrombi in pulmonary arteries leading to non-homogeneous vascular obstructions. Together with an overflow arteriopathy in the non-obstructed vascular bed, this causes an increase of the pulmonary artery pressure and finally right heart failure [1].

The cardinal symptom is progressive dyspnoea on exertion [2]. When oral anticoagulation was the only available treatment option, the prognosis was poor [3]. Pulmonary endarterectomy is nowadays a well-established therapy that has the potential to improve hemodynamic and survival [4]. Moreover, for the patient ineligible for surgery or with recurrent pulmonary hypertension (PH) after surgery there are new therapeutic options available: balloon pulmonary angioplasty and medical therapy or both together are increasingly used with gain on the hemodynamic and quality of life [5–7]. Therefore, CTEPH can be considered as uncommon but serious and potentially curable complication of the frequently occurring PE [8].

Incidence of CTEPH after acute PE is currently a matter of debate and epidemiological data from large prospective cohorts of patients with acute PE are lacking. As background for our study, in 2008, published reports on the cumulative incidence of CTEPH after PE varied almost five times, from 0.8 to 3.8% [9–11]. Recently a meta-analysis from Ende-Verhaar et al. summed up the actual knowledge of this topic [12]. They stratified previous studies according to their inclusion/exclusion criteria. Lower incidence is observed in unselected population ("all comers") compared to PE survivors or PE survivors without major comorbidity. Therefore, a precise description of the studied population is essential for data analysis and comparison. In Switzerland, incidence of CTEPH can be only estimated from the Swiss Pulmonary Hypertension Registry (SPHR), a registry developed in 1998 to capture and follow-up patients with pulmonary hypertension (PH) [13].

The diagnosis of CTEPH is challenging as symptoms are non-specific. According to the current literature, CTEPH is often diagnosed with a delay of several months after the first symptom [2, 14, 15]. A systematic screening algorithm of patients following a PE event could be helpful for an earlier diagnosis of CTEPH and to identify cases with milder symptoms [16]. However, there is currently a lack of evidence in favour of any routine screening after PE [4, 17].

The study aims were to prospectively assess the CTEPH incidence in patients diagnosed with PE and to test the usefulness of a multi-step screening algorithm based on an initial dyspnoea questionnaire. We also aimed to identify potential risk factors for developing CTEPH.

Methods

Study participants

This prospective, multicentre study was performed between March 2009 and November 2016 in 11 pulmonary hypertension centres in Switzerland. Patients were screened for acute PE and

included in the study if the PE was confirmed by either pulmonary angiography, contrast-enhanced computed tomography (CT) or ventilation/perfusion scan (V/Q scan) within four weeks preceding the enrolment visit. All included patients had to have a signed informed consent. Patients were excluded if they were diagnosed before screening with pulmonary hypertension, pre-existing severe chronic dyspnoea New York Heart Association functional class (NYHA FC) III-IV, cancer or other threatening diseases with a life expectancy inferior to six months. Patients with NYHA FC not assessable due to severe mobility limitation were also excluded. Irrespective of their final enrolment in the study, all patients screened were registered (initials, sex, date of birth).

Outcomes

The primary endpoint was the incidence rate of CTEPH after acute PE. The secondary endpoints were the assessment of the usefulness of a multi-step screening algorithm and the identification of risk factors associated with development of CTEPH. To test the usefulness of the algorithm, we conducted a post-hoc analysis matching the initial 1699 patients with PE with the data of the SPHR. The match was performed in December 2016 using patient's initials, sex and date of birth. We first checked that patients within the study and diagnosed with CTEPH were listed in the SPHR. We then queried the SPHR for incident cases of CTEPH registered during the study period and looked-for individuals among the 1699 screened patients.

Procedures

Baseline health survey was filled at the enrolment visit. This questionnaire focused on demographics, baseline status and potential risk factors for PE or CTEPH. PE therapy, including the choice and duration of anticoagulation was left at the discretion of physicians in charge according to the local practice. We used the term provoked PE and unprovoked PE, respectively defined by the presence or absence of one of the previously defined PE risk factors [18].

A three-step algorithm was created and applied at 6, 12 and 24 months (figure 1). Step one was a phone assessment of dyspnoea, based on a standardised NYHA FC questionnaire translated in German, French and Italian (supplement 1). If the dyspnoea score equalled NYHA FC II or above, the patient advanced to the second step, unless an obvious and/or transient known cause that explained the current dyspnoea was identified. Step two consisted in a hospital visit for clinical examination, unblinded reassessment of the NYHA FC and transthoracic echocardiography (TTE). Based on TTE results, patients were classified as PH unlikely or PH possible. These two groups were adapted over time from the 2004 and 2009 European guidelines [19, 20]. PH was considered possible if the peak tricuspid regurgitation velocity (TRV) was >2.8m/s or if TRV was not measurable or ≤2.8m/s but other signs of PH were present at TTE. If TRV was ≤2.8m/s and there were no other signs of PH, PH was considered unlikely and the patient returned to follow-up. TTE ordered by patient's general practitioner outside the study was also accepted if above variables were assessable. If PH was deemed possible, patients was engaged to step three for assessment by right heart catheterisation (RHC). According to the accepted definition of CTEPH, our diagnosis criteria were: mean pulmonary arterial pressure (mPAP) ≥25mmHg, post capillary wedge pressure <15mmHg, at least three months of effective anticoagulation therapy and radiological confirmation with either V/Q scan, contrast-enhanced CT or pulmonary angiography.

Statistical Analysis

A sample size of 1000 patients was estimated in order to obtain a 2% wide 95% confidence interval (95%CI) for an expected CTEPH incidence after PE of 3%. Incidence rate of CTEPH after PE was expressed as number of events in number of patient-years and cumulative incidence rate in % over two years. Descriptive statistics are presented as mean with standard deviation for continuous data and as absolute numbers with percentages and Wilson 95%CI for categorical data. We calculated the percentage of concordance of the NYHA FC stage between the phone-based survey and the clinical evaluation. Accuracy of the screening algorithm was assessed by comparing it to the data of the SPHR using sensitivity, specificity, negative and positive predictive value at each step of the algorithm. For the risk factors analysis, we used a two-tailed t-test and a Fischer exact test for continuous and categorical values respectively. Significance limit was set at a p-value <0.05 and all tests are conducted two sided.

Primary and secondary endpoints were analysed in patients with complete data. Patients were considered lost-to-follow-up if they withdraw their consent or didn't have at least completed the last follow-up appointment. For the primary endpoint, sensitivity analyses were performed to account for missing data using multiple imputation techniques, described elsewhere [21]. We used R 3.3.3 (R core team, 2016) with the package mice 2.30 and SPSS 24 (IBM, 2016) for statistical analyses [22].

Swiss Ethics Committees approved this study in 2008; all included patients signed an informed consent. The study is registered under WHO: ISRCTN61417303.

Results

Patients

We included patients between March 2009 and November 2013, and the study was closed in November 2016. Overall, 1699 consecutive patients were diagnosed with acute PE and assessed for eligibility. Of those, 542 patients were excluded and 555 could not sign the informed consent (figure 2). For the remaining 602 patients, 94 did not complete the study because they were lost to follow-up (n=51), withdrew their consent (n=7) or died during the study period (n=36). The causes of deaths were neoplasia (n=15; 42%), cardiovascular diseases (n=5; 14%), infection (n=3; 8%), suicide (n=1; 3%), unknown reason (n=9; 25%) and the last 3 (8%) were sudden deaths during the primary hospitalisation that could only be imputed to the acute PE. Thus, 508 patients had a full follow-up during a median time of 2 years. The baseline characteristics of these patients are described in table 1.

Table 1: Baseline characteristics of the INPUT cohort

	Study population (n=508)
Demographic data	**mean ± SD**
Age at baseline	61.2 (16.2)
Sex	
male	271 (53.3%)
female	237 (46.7%)
BMI	28 (5.4)
Smoking status	
current smoker	90 (17.7%)
previous smoker	115 (22.6%)
non-smoker	303 (59.6%)
PE management	
Thrombolysis	25 (4.9%)
Surgery	0 (0%)
Long term anticoagulation	
oral anticoagulation	485 (95.5%)
LWMH	9 (1.8%)
heparin	11 (2.2%)
unknown	3 (0.6%)
Thromboembolic risk factors and history	
Unprovoked PE	227 (44.7%)
Previous history of PE	71 (14.0%)
Concomitant DVT at diagnosis	176 (34.6%)
Previous history of DVT	74 (14.6%)
Family history of DVT or PE	73 (14.4%)
Thrombophilic disorders	25 (4.9%)
antiphopholipid antibodies	4 (0.8%)
Major surgery setting	83 (16.3%)
Trauma (major trauma, fractures)	36 (7.1%)
Immobility (hospital and nonhospital setting)	143 (28.1%)
Hormonal (HRT, pregnancy, oral contraception)	68 (13.4%)
Past medical Record	
History of malignancy	56 (11.0%)
Active malignancy	27 (5.3%)
Rheumatoid arthritis	10 (2.0%)
Inflammatory bowel disease	8 (1.6%)
Splenectomy	3 (0.6%)
Pacemaker / VA shunt	5 (1.0%)
Infection of pacemaker or VA shunt	2 (0.4%)
Congestive heart failure	3 (0.6%)
Cerebrovascular disease	20 (3.9%)

Table 1: Data are n (%) and mean (±SD). BMI=body mass index. SD=standard deviation. LWMH=low weighted molecular heparin. PE = pulmonary embolism. DVT=deep venous thrombosis. HRT=hormone replacement therapy. VA shunt=ventriculoatrial shunt.

Incidence of CTEPH

Over two years of follow-up, four CTEPH cases were diagnosed in the cohort of 508 fully followed PE patients. A description of each CTEPH patient hemodynamic is provided in table 2 (additional clinical parameters are provided in the supplementary material). The cumulative incidence of CTEPH was 0.79% (95%CI 0.31-2.07%) over a median time of 2 years, which yields an incidence rate of 3.7 per 1000 patient-years (95%CI 1.43-9.36). Among patients presenting with a dyspnoea ≥II NYHA FC in the survey (n=97), the cumulative incidence of CTEPH rose to 4.12% (95%CI 1.62-10.13). Matching the 1699 screened patients with the SPHR identified four additional CTEPH cases among the 1097 excluded patients (cause of exclusion: involvement in other studies (n=2), no discernment (n=1), estimated life expectancy under 6 months (n=1)). No other CTEPH who matches the identity of the 508 included patients under study was found in the SPHR. The sensitivity analyses led to similar incidence ranges.

Table 2: Hemodynamic of the CTEPH cases

Patient	1	2	3	4
mPAP (mmHg)	25	25	31	27
PAWP (mmHg)	10	7	10	13
mRAP (mmHg)	10	2	10	12
PVR (dyn· sec· cm^{-5})	317	360	232	151
CO (l/min)	3.79	3.99	7.24	7.50
CI (l/min· m^2)	1.80	2.40	3.89	3.00
BMI (kg/m^2)	28.2	25.2	26.0	52.7

Table 2: CTEPH=chronic thromboembolic pulmonary hypertension. mPAP=mean pulmonary arterial pressure. PAWP=pulmonary arterial wedge pressure. PVR=pulmonary vascular resistance. mRAP=mean right atrial pressure. CO=cardiac output. CI=cardiac index.

Screening algorithm

Screening algorithm profile is described in figure 3. The phone-based dyspnoea survey identified 149 episodes of dyspnoea ≥II NYHA FC in 97 patients (19.1%) over the two-year follow-up. The agreement of the NYHA FC between phone-based survey and clinical evaluation was 86.1% (95%CI 78.1-91.6). The clinical evaluation of NYHA FC class was higher than the phone-based survey in 8.2% (95%CI 4.1-14.8) of these patients and lower in 6.2% (95%CI 2.89-12.4).

TTE identified 15 episodes of possible PH with a mean TRV of 2.96 ±0.05m/s in 14 different patients who were invited for step three. The RHC confirmed PH in four patients with a mean mPAP of 27mmHg. All four cases were CTEPH, confirmed either with V/Q scan (n=3) or contrast-enhanced CT (n=1). In four patients, RHC was not performed because of patient's refusal (n=3) or due to temporary contraindication (n=1). However, for three of them, PH was excluded at the next follow-up visit by TTE. The last one refused to undergo RHC at the final follow-up visit but was then regularly followed without signs of evolution towards a CTEPH during six years.

Accuracy of the screening algorithm compared to SPHR is described in table 3. The survey yielded 100% (95%CI 51-100) sensitivity and 81.6% (95%CI 77.9-88.4) specificity. The second step echocardiography in newly dyspnoeic patients showed a negative predictive value of 100% (95%CI 51-100).

Table 3: Accuracy of the screening algorithm.

	6 months survey (n=508)	**12 months survey (n=506)**	**24 months survey (n=505)**	**overall survey (n=508)**	**overall TTE (n=97)**
Sensitivity	50%	50%	100%	100%	100%
Specificity	88.9%	91.5%	90.9%	81.6%	88.7%
Positive predictive value	3.4%	2.3%	2.1%	4.1%	26.7%
Negative predictive value	99.6%	99.8%	100%	100%	100%

Table 3: Accuracy of the screening algorithm for the survey in detecting CTEPH at six, 12 and 24 months and over the 2 years in all included PE patients and for the TTE in the patients detected with dyspnoea. TTE=transthoracic echocardiography.

Risk factors

The presence of antiphospholipid antibodies was significantly associated with a CTEPH development after PE (p=0.03). No other risk factors were identified in all the other baseline characteristics tested (supplementary material). A multivariate analysis was not applicable due to small number of CTEPH cases.

Discussion

In this prospective observational study, we followed a large population of patients after acute PE. Our main finding is a cumulative incidence of CTEPH of 0.79% over two years. One in five patients will experience a dyspnoea within two years following an acute PE. In these patients, the incidence of CTEPH rises to 4.12%. Furthermore, our results show that our algorithm based on an initial dyspnoea assessment by the NYHA FC is a sensitive way to screen PE patient for CTEPH. They also confirm that the presence of antiphospholipid antibodies is a risk factor for the development of CTEPH after PE.

Compared to the existing literature, our study is the second largest multicentre cohort that have evaluated the incidence of CTEPH prospectively in patients with acute PE [12]. We found an incidence in the lower range of the previously published analogous studies with 0.4% to 9.1% [9–11, 23–26]. The reason for such a wide range between studies may lay in the methodologies applied. The recent meta-analysis of Ende-Verhaar et al. showed the impact of the selection criteria when considering the incidence of CTEPH after PE distinguishing the three subgroups: "all comers", "survivors" and "survivors without PE" [12]. Our study may be classified into the "survivors without major comorbidities" as we have done a complete cases analysis and excluded some patients with severe comorbidity. Thus, we have a lower incidence than described in the meta-analysis for this subgroup (2.8%; 95%CI 1.5-4.1). The published studies included in this subgroup may have overestimated the incidence by the selective inclusion of higher-risk PE (notably the unprovoked PE percentage) while some could have misclassified acute PE for CTEPH [27, 28]. We have addressed this latter issue with a post-hoc control of the CTEPH patient images to ensure that we did not miss any pre-existing pattern suggestive of CTEPH. Therefore, the risk of overestimation has been minimized. To the contrary, we may face a possible underestimation through the negative segregation of high risk patients including the 236 with an estimated life expectancy < six month and the 149 with a NYHA FC ≥ III. However, there was no significant differences in the sex and age distribution between the excluded and the included patient. Furthermore, the post-hoc comparison to the Swiss Pulmonary Hypertension Registry (SPHR) showed a similar incidence range in included and excluded patients. This incidence is in the range of the "all comers" subgroup from the meta-analysis by Ende-Verhaar (0.57%; 95%CI 0.13-0.98). This suggests an unbiased selection of patients. The higher incidence in published studies could also be the consequence of a selection of patients only from tertiary high-volume centres that are probably prone to treat higher-risk PE. As we also included patients from smaller hospitals and ambulatory patients, we probably have included more low-risk PE. Consequently, our results are more prone to be generalised to the entire population than previous reports.

We think that the present study is a valid assessment of the incidence of CTEPH after PE. First, we used recommended criteria to diagnose CTEPH, using strict RHC thresholds for PH and standard radiological examinations [4]. As done previously elsewhere, a senior specialized radiologist assessed the images of CTEPH patients and excluded a pre-existing pattern suggestive of CTEPH at the time of PE [27, 28]. It is now well established that all the studies using TTE as the only diagnostic tool overestimate the incidence of CTEPH [12]. Furthermore, the match with the Swiss Pulmonary Hypertension Registry (SPHR) strengthens our findings. This registry

gathers all recognised PH centres in Switzerland and collects systematically all newly diagnosed CTEPH and PAH cases [13]. It therefore allows us to confirm that we did not segregate a different subpopulation between the excluded and the included patients. It also offers a good tool to eventually detect potential undiagnosed cases within the two-year follow-up. We matched the 1699 screened patients from at least three years and up to seven years after the initial PE event. Given the natural history of the disease, all CTEPH cases, even with a honeymoon period of several months and a diagnosis delay of two years, should be symptomatic, diagnosed and listed in the registry [10, 26, 29]. In the SPHR, there was an average of 20.1 new cases of CTEPH per year between 2000 and 2012 [13]. With an estimated PE incidence rate of 0.6 per 1000 patient-years for a population of 8 million inhabitants, there are approximatively 5000 acute PE per year in Switzerland [8, 30]. If we apply our CTEPH incidence rate to this number of PE, we would expect 17.9 (95% CI 7.2-46.8) new cases per year, which is close to the registry data. However, this calculation did not account for CTEPH cases without clinical PE that could yield a slight lower number.

According to current literature, the diagnosis of CTEPH is often delayed [2, 15]. Most cases are diagnosed when patients reach NYHA FC III or IV [2]. If patients were diagnosed at an earlier stage, such as NYHA FC II, many would benefit from effective therapies [31]. Therefore, a screening strategy may be appealing for earlier diagnosis and treatment [31, 32]. Presently, there is no official recommendation for any systematic screening in patients after PE. The only statement in the latest 2015 (ESC/ERS) guidelines is to consider TTE in all patients with dyspnoea on exertion and history of PE [4]. In that sense, our algorithm represents a step further in favour of an active screening of CTEPH after PE.

With the algorithm applied in our study, we tested the sensitivity of a systematic screening based on a phone-based dyspnoea assessment within two years after acute PE. The group of Held et al. already showed on a smaller population that telephone symptom-based screening is valuable to identify CTEPH cases after PE [16]. Furthermore, our algorithm is easily applicable in the real world as it is simple and conceivable for a general practitioner to follow patients with a practical dyspnoea survey during three visits within two years after acute PE. The first screening step, based on a symptomatic approach is attractive because more than 99% of CTEPH patients will develop dyspnoea [2]. Other algorithms based on risk factors could miss patients that nevertheless develop CTEPH in the absence of such risk factors. “CTEPH rule out criteria” developed and externally validated by Klok et al. addresses the problem by including electrocardiographic features and NT-proBNP value [33]. Whether this strategy could be applied outside an experimental setting remains to be determined. Almost every published screening strategy use TTE as a second step since it is a non-invasive and widely accessible method to evaluate the presence of PH. According to the low incidence of CTEPH, even in patients with dyspnoea, an efficient screening should yield the lowest false positive rate while false negatives should be near zero. Because of the high negative predictive value, present results support the use of TTE to select patients for a RHC. Cardiopulmonary exercise testing is currently assessed in the diagnostic work-up but, up to now, its diagnostic performance is unknown and such test could be difficult to apply widely [34]. Altogether, such a systematic screening may improve the awareness to CTEPH in patients with PE and favour earlier diagnosis.

This study has limitations. First, we did not reach the expected sample size. We decided to end enrolment because the number of positive cases was low and we already had achieved a precision aim of 2% wide 95%CI for the primary endpoint which ensure the internal validity of the study. Secondly, we cannot totally exclude that some CTEPH cases remained undiagnosed. However, it would have been unethical and unrealistic to perform RHC in the 602 patients enrolled in the study. Nevertheless, the two years follow-up together with the back-up control from the SPHR data appears as reasonable way to identify most of symptomatic CTEPH cases. As 94 patients were lost to follow-up for various reasons, it is feasible that CTEPH cases went undetected in this population. To address this problem, we performed several sensitivities analyses that yielded similar results. Among 36 deaths, none had history of chronic right heart failure, although we acknowledge that post mortem examination was not performed. We did not address the situation where a dyspnoeic patient is found with a normal resting hemodynamic at rest but with exercise PH characterised by a steeper pressure-flow slope, as exercise RHC was not performed [35]. According to the current definition, such patients do not have CTEPH and are classified as chronic thromboembolic disease [36]. The prognosis and the indication to treat such cases remains a matter of debate. Third, we acknowledge a high proportion of excluded patients in the initially screened cohort. However, and unlike previous studies, the fate of the excluded patients has been documented though the Swiss PH registry, giving a reasonable estimate of symptomatic CTEPH cases in this population. Finally, we had designed the study a few months before the publication of the 2009 European guidelines [19]. We had therefore to slightly adapt initial TTE criteria initially based on the 2004 guidelines. Post-hoc monitoring ensures that all 101 TTE had been evaluated accordingly to the latest guidelines without change in patients that should have been invited for step three.

In conclusion, CTEPH is a rare but devastating complication of PE. Our proposed algorithm is a simple and sensitive way to assess the development of CTEPH in such patients. We recommend that such systematic CTEPH screening should be done regularly in the two years following PE event for patient with a new dyspnoea. Further research including an external validation and a cost-effectiveness analysis are needed to make this screening algorithm fully suitable for everyday clinical practice.

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Figure 1: Follow-up algorithm

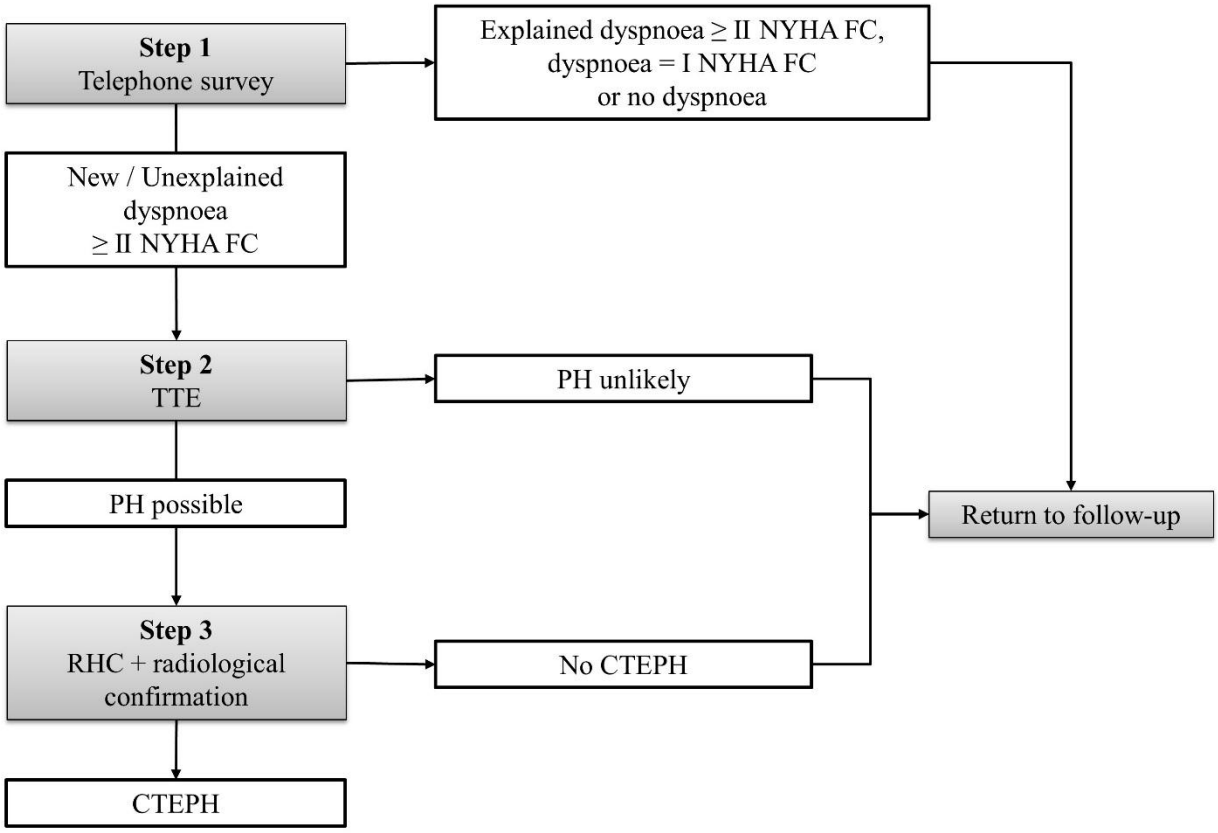


Figure 2: Patients selection profile

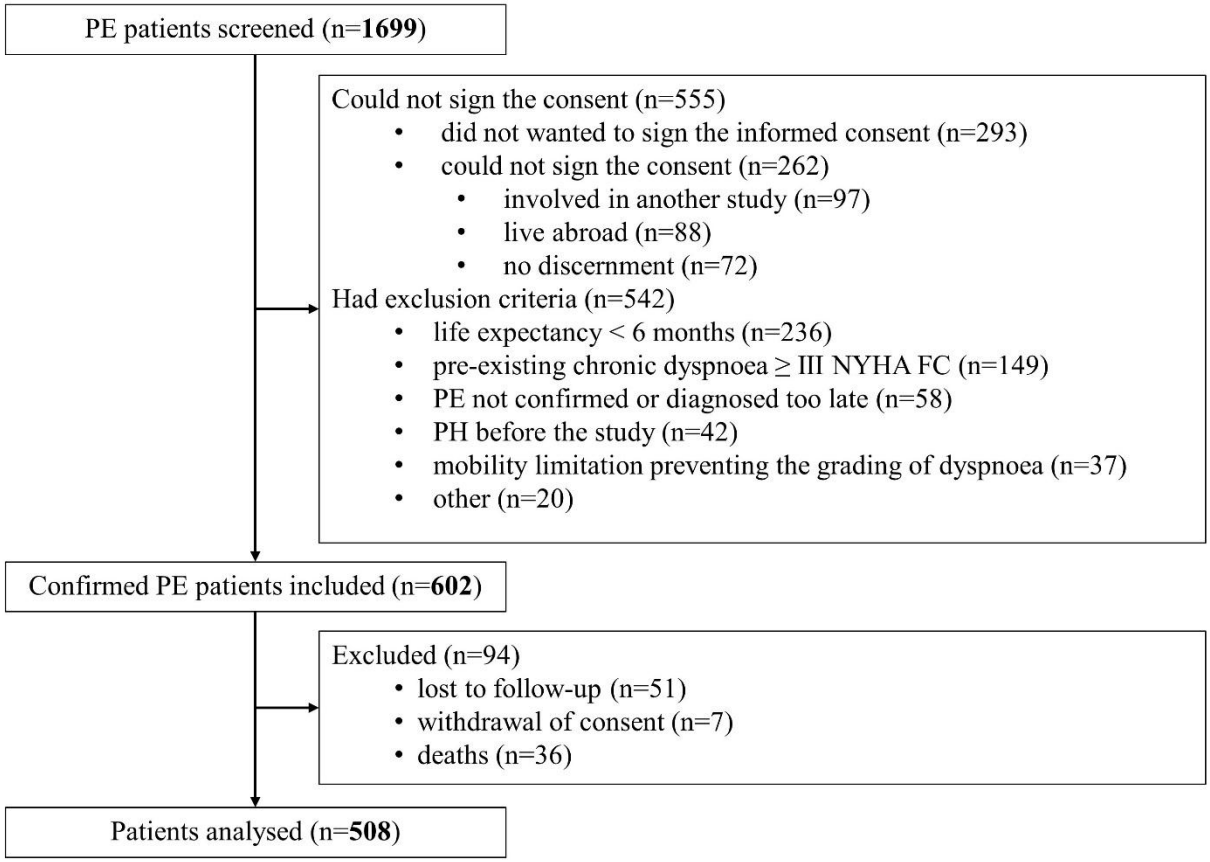
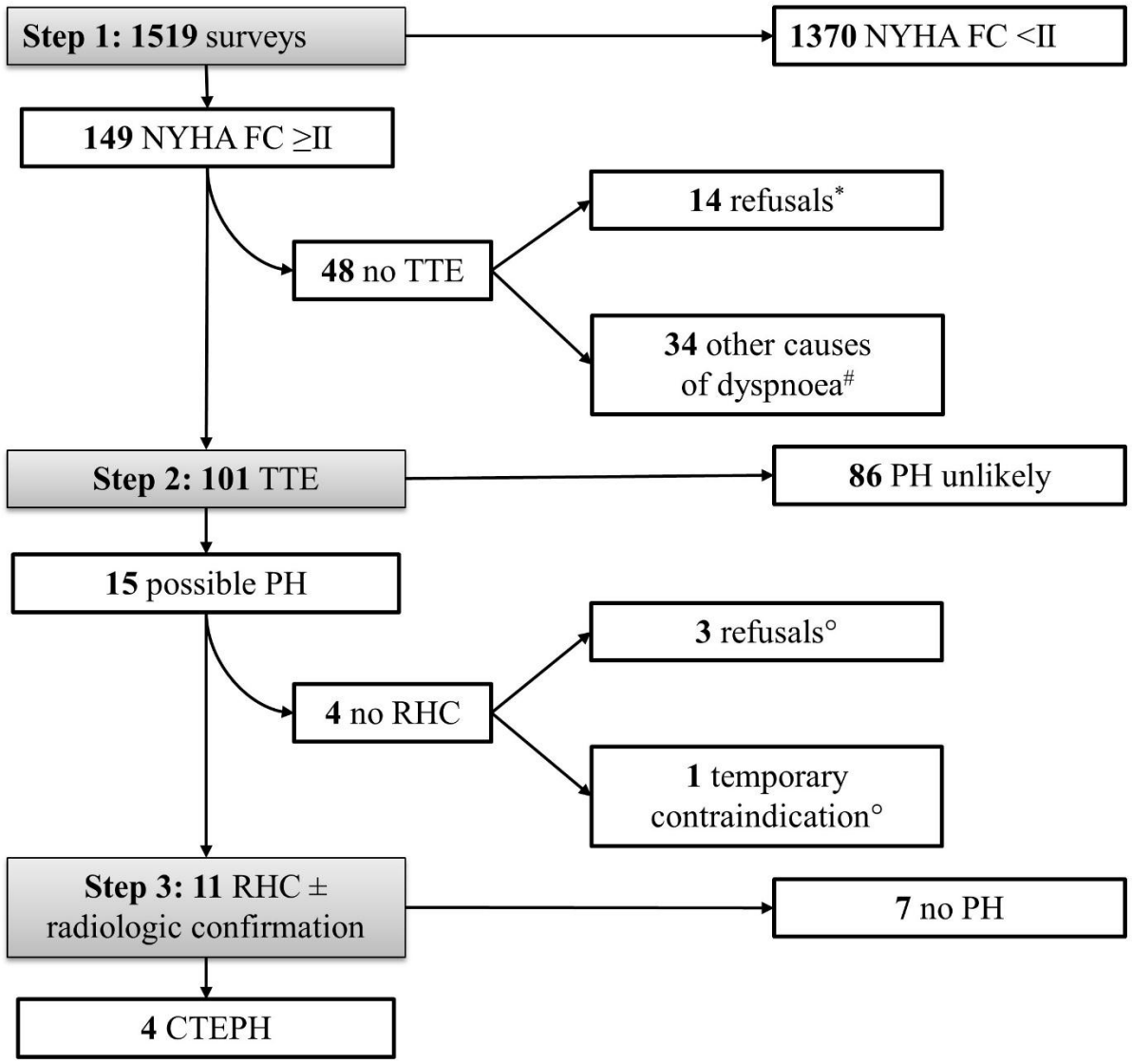


Figure 3: Screening algorithm profile



Supplementary material:

Supplement 1: Protocol.

Schweizerische Gesellschaft für Pulmonale Hypertonie SGPH
Societé Suisse sur l'Hypertension Pulmonaire SSHP
Società Svizzera di Ipertensione Polmonare SSIP
Swiss Society for Pulmonary Hypertension SSPH

INPUT on PE

CTEPH after PE

INPUT on PE

Multicenter, observational screening survey for the detection of chronic thromboembolic pulmonary hypertension (CTEPH) following pulmonary embolism

Author(s)	*Katharina Bruppacher and John-David Aubert*
Document type	Clinical Study Protocol
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Document status	*Final*
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Number of pages	331

SPONSOR CONTACT DETAILS

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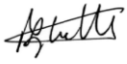
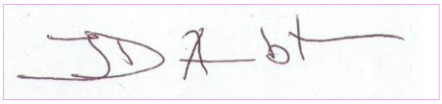
SIGNATURE PAGE FOR SPONSOR

Disease

CTEPH after PE

Acronym

INPUT on PE

President SSPH	Maurice Beghetti, MD	 Signature	28.05.2009 Date
Principal Investigator	John-David Aubert, MD	 Signature	21.12.2008 Date

SIGNATURE PAGE FOR INVESTIGATORS

Disease

CTEPH after PE

Acronym

INPUT on PE

I agree to the terms and conditions relating to this study as defined in this Protocol, Case Report Form (CRF) and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the well being of the patients).

I agree to conduct this study in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and applicable regulations and laws. In particular, I will obtain approval by an Ethics Committee prior to study start and signed informed consent from all patients included in this study. In addition, I will allow direct access to source documents and agree to inspection by auditors from the sponsor and Health Authorities.

Investigator Name/Title	Signature	Date

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LIST OF ABBREVIATIONS

CI	Cardiac Index
CO	Cardiac Output
CRF	Case Report Form
CTEPH	Chronic thrombo-embolic pulmonary hypertension
dPAP	Diastolic pulmonary artery pressure
EC	Ethics Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
LA	Left atrium
RA	Right atrium
mPAP	Mean pulmonary artery pressure
NYHA	New York Heart Association
PCWP	Pulmonary capillary wedge pressure
PE	Pulmonary embolism
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RA	Right atrium
RHC	Right heart catheter
RV	Right ventricle
SAP	Statistical Analysis Plan
sCT	Contrast enhanced spiral CT
sPAP	Systolic pulmonary arterial pressure
SRVP	Systolic right ventricular pressure

TR	Tricuspid regurgitation
V/Q scan	Lung scintigraphy: ventilation/ perfusion scan

PROTOCOL SYNOPSIS

TITLE	Multicenter, observational screening survey for the detection of chronic thromboembolic pulmonary hypertension (CTEPH) following pulmonary embolism (PE).
ACRONYM	INPUT on PE
OBJECTIVES	**Primary Objective** To evaluate the incidence rate of symptomatic CTEPH following PE **Secondary Objectives** To identify and evaluate potential risk factors for developing CTEPH following PE To test the usefulness of a screening algorithm in medical practice for diagnosing CTEPH after PE
DESIGN / PHASE	Prospective, multicenter, observational phase V study.
STUDY PLANNED DURATION	First patient First visit: Q3 2008 — Last patient First visit: Q32010 — Last patient Last visit: Q3 2012
CENTER(S) / COUNTRY(IES)	10-15 centers in Switzerland (planned).
PATIENTS / GROUPS	1000 patients
INCLUSION CRITERIA	Diagnosis of PE confirmed by • pulmonary angiography or • spiral CT or • high probability lung scintigraphy (V/Q scan)
EXCLUSION CRITERIA	• Confirmed diagnosis of pulmonary arterial hypertension (PAH) or CTEPH before inclusion in survey • Pre-existing severe chronic dyspnea (NYHA grade III or IV) due to other reasons than PE, e.g. due to known co-morbidities such as lung disease or congestive heart failure • Cancer or other life-threatening disease with a life expectancy of <6 months

STUDY PERIODS	Patients with PE who are included in the survey will be followed by regular telephone contacts at months 6, 12 and 24 using a specific dyspnea questionnaire. If specific symptoms of dyspnea are reported, patients will be invited to the study center within 4 weeks for confirmation of dyspnea and, if dyspnea confirmed, an echocardiography andfurther diagnostic workup. The study ends, when data of 1000 evaluable patients are collected.
ENDPOINTS	Primary Endpoint Incidence rate of symptomatic CTEPH at 6, 12 and 24 months after confirmed PE Secondary Endpoints Comparison of the baseline parameters of the patients who developed CTEPH with the patients who did not develop CTEPH after PE to identify any risk factors. Comparison of the results of the dyspnea questionnaire answered by telephone with the dyspnea evaluation by the investigator at the clinic.
STATISTICAL METHODOLOGY	Primary Endpoint Incidence rate of CTEPH after PE will be expressed as number of events in number of patient-years. Event rate at months 6, 12 and 24 (with the associated 95% confidence intervals) will also be derived using Kaplan-Meier methodology. Secondary Endpoints Identification of risk factors for the development of CTEPH after PE: baseline parameters of patients developing CTEPH will be compared with those of patients not developing CTEPH. For patients having reported dyspnea (according to the dyspnea questionnaire) during the follow-up, NYHA classification resulting from the dyspnea questionnaire will be compared with the classification performed by the investigator at the hospital visit.
STUDY COMMITTEES	A steering committee (constituted by SSPH members and PE experts) will be responsible for the supervision of the survey, data collection and analysis, as well as publication of results.

Table 1 Visit and Assessment Schedule

VISITS	Number	*1*	*2*	*3*	*4*	*2A, 3A or 4A*
	Name	*Inclusion in survey*	*Telephone follow up*			*Hospital visit*
	Time	*Within 4 weeks after diagnosis of PE*	*Month 6 (±3 weeks)*	*Month 12 (±3 weeks)*	*Month 24 (±3 weeks)*	*Within 4 weeks after TC if specific symptoms detected*
Informed Consent		X				
Medical History		X				
Physical Examination (dyspnea confirmation)						X
Blood sample		X				
Dyspnea questionnaire			X	X	X	
Echocardiography						X
Further diagnostic workup in case of suspicion of PH after echocardiography (RHC, V/Q scan, sCT, angiography)						X

1 BACKGROUND AND RATIONALE

1.1 Medical background and study rationale

Chronic thromboembolic pulmonary hypertension (CTEPH) is considered a relatively rare complication of pulmonary embolism (PE) but is associated with considerable morbidity and mortality [Riedel 1982]. The pathogenesis of CTEPH has been discussed intensively and controversely. Two hypotheses of development of CTEPH exist:

1. There's a more popular hypothesis, which believes that PE (followed by secondary vasculopathy) is the major cause of CTEPH. In the vast majority of patients with acute pulmonary embolism, endogenous fibrinolysis together with therapeutic anticoagulation results in complete or near-complete clot lysis. For unknown reasons, some patients will have insufficient clot lysis and the obstructing material becomes organized in the vessel walls. When pulmonary hypertension develops, it also affects those areas of the pulmonary vascular bed, which originally have not been affected by thromboembolism, resulting in progressive pulmonary vascular remodeling and a steady increase in pulmonary vascular resistance. This vicious cycle eventually causes death from right heart failure.

2. Then, there is the alternative hypothesis which supports the idea that primary arteriopathy (with secondary thrombosis, as described in idiopathic PAH) is the cause of CTEPH [Egermayer 2000]. This is supported by the fact, that CTEPH is nearly impossible to induce in any animal species by means of repeated embolization of thrombotic material. Furthermore many conditions which predispose to venous thromboembolism do not appear to cause CTEPH.

One possible method to verify if PE is a major cause of CTEPH is to follow up a large patient population with well-diagnosed PE in whom other causes of chronic pulmonary hypertension have been excluded. Several smaller, mostly single center studies have followed up different PE populations and found an incidence rate of CTEPH of 1-5% [Pengo 2004, Becattini 2006, Miniati 2006]. Contradictory data were found concerning the form of PE. Some reported CTEPH only after subacute, recurrent or occult emboli, but not after acute PE (Riedel 1982, Egermayer 2000, while others reported CTEPH after acute PE (Becattini 2006, Miniati 2006).

There is also limited documentation concerning predisposing factors that could be addressed in an effort to prevent this feared complication of PE. PE could be one traumatic influence resulting in endothelial damage, but other influences may be more prevalent. Some risk factors for developing CTEPH after PE have been described, such as idiopathic form of PE, multiple PE, and severity of perfusion defect of PE [Pengo 2004], and other clinical conditions such as splenectomy, ventriculo-atrial shunt, chronic inflammatory disorders [Bonderman 2005].

Furthermore, it has been suggested, that CTEPH is still being notoriously underdiagnosed (Hoeper, Circulation 2006) and true prevalence remains unclear. One reason is, the long "honey-moon period" where main symptoms of CTEPH are only exertional dyspnea. Another reason might be, that no guidelines or methods for a follow-up of patients after PE exist. If the previously reported high prevalence shows to be true, an easy and cost-effective tool should be available for a post-PE follow up.

The identification of risk factors and the availability of an appropriate screening tool could allow diagnosis of CTEPH in an early stage. Survival after surgical treatment of CTEPH by TEA is better when performed at an early stage of the disease (Dartevelle 2004). There is also hope, that survival might be better if medical treatment is initiated early, as described for pulmonary arterial hypertension (Galie 2007).

We therefore plan to prospectively follow-up a large population of PE patients to confirm the high incidence rate of CTEPH in that patient population and, if CTEPH is diagnosed, to describe risk factors for developing this disease. We propose to use a screening algorithm based on dyspnea, echocardiography and right heart catheter.

Several centers in Switzerland will participate in the planned survey. After confirmation of the diagnosis of PE, the patients will be followed-up by phone by a dyspnea questionnaire, which is based on the New York Heart Association (NYHA) functional class, as commonly used for the assessment of PAH. Patients will be followed-up for 2 years.

1.2 Patient population

All patients who present with a suspicion of PE should undergo usual diagnostic procedure and be treated according to local guidelines. For an accurate study result, a confirmation of PE by pulmonary angiography or spiral CT or high probability lung scintigraphy is needed before inclusion in the survey

1.3 Study design

To best describe the incidence rate of symptomatic CTEPH after PE a prospective, multicenter, observational design was considered optimal.

1.4 Primary endpoint

A certain amount of patients with confirmed PE are expected to develop CTEPH within the following 2 years. Incidence rate of CTEPH 2 years after PE is expected to be negligible (Pengo 2004).

1.5 Sample size

A sample size of 1000 patients with confirmed PE was chosen to confirm previously reported incidence rates of CTEPH. This would be the largest prospective survey. A CTEPH incidence rate of approximately 3% is assumed, i.e. 30 CTEPH patients will be identified. If this survey confirms the high prevalence rates, the identification of any subgroups or potential risk factors would ease the future identification of patients at risk.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the incidence rate of symptomatic CTEPH following PE

2.2 Secondary Objectives

- To identify and evaluate potential risk factors for developing CTEPH following PE
- To test the usefulness of a screening algorithm based on dyspnea in medical practice for diagnosing CTEPH after confirmed PE

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a prospective, multicenter, observational phase V study designed to assess the incidence rate of CTEPH following PE. 1000 patients will be enrolled. The study will be conducted in 10-15 centers in Switzerland.

The screening period to confirm diagnosis of PE and obtain informed consent will last 4 weeks.

Patients will be followed-up for 2 years or until CTEPH is diagnosed.

The study will be finished when data of 1000 evaluable patients are collected. Evaluable patients are patients who performed at least the 1-year follow-up or have been diagnosed with CTEPH during the follow-up period.

Every participating center will nominate a survey coordinator (e.g. study nurse) who will collaborate with the department of radiodiagnostics (where patients are usually centrally diagnosed) to identify eligible patients. The study coordinator will invite patients to participate in the survey, get patient informed consent, and, if not outsourced,perform the regular telephone follow ups (6, 12 and 24 months after inclusion) by using a standardized dyspnea questionnaire. Blood samples of patients will be taken at time of inclusion and frozen at a central lab to allow retrospective analysis of risk factors.

If the questionnaire discovers previously unreported symptoms of dyspnea, patients are invited to the center for confirmation of dyspnea and, if confirmed, an echocardiography will be performed.

In the diagnostic work up of CTEPH right heart catheterization is necessary, plus additionally lung scintigraphy or an imaging technique of the pulmonary arteries (i.e. contrast enhanced spiral CT or pulmonary angiography):

In case of a suspicion of PH at echocardiography, right heart catheterisation with the measurement of mPAP and PCWP is performed for the confirmation of PH. Further diagnostic work up is then performed for the confirmation of CTEPH.

CTEPH is confirmed if mPAP ≥25 mmHg, PCWP < 15 mmHg and PVR ≥ 300 dyn*sec/cm5 (3.75 Wood units), and additionally if V/Q scan shows a mismatch or imaging of the lung vessels show a pulmonary vessel obstruction. Any other causes of dyspnea or elevated PH have to be excluded.

The Steering Committee is involved in the design of the study and will be consulted for any protocol amendments.

3.2 Study Population

3.2.1 Patient population

Patients participating in the study are men or women diagnosed with PE at the participating center. Patients with suspected PE have to undergo pulmonary angiography or spiral CT or lung scintigraphy. When characteristic angiographic, tomographic or scintigraphic findings of PE are detected and typical PE symptoms have occurred, the patient is defined as having PE.

3.2.2 Inclusion criteria

Eligible patients must meet all of the following inclusion criteria:

- Men and women with pulmonary embolism, demonstrated by
    - Pulmonary angiography or
    - Contrast enhanced spiral computed tomography or
    - High probability lung scintigraphy (perfusion and ventilation imaging)

  Within the preceding 4 weeks
- Signed informed consent prior to any study-mandated procedure.

3.2.3 Exclusion criteria

Eligible patients must meet none of the following exclusion criteria:

- Confirmed diagnosis of pulmonary arterial hypertension (PAH) or CTEPH before inclusion in survey

- Pre-existing severe chronic dyspnea (NYHA grade III or IV) due to other reasons than PE, e.g. due to known co-morbidities such as lung disease or congestive heart failure
- Cancer or other life-threatening disease with a life expectancy <6 months

3.2.4 Medications

Any medication is allowed according to the investigators discretion.

3.2.5 Study withdrawal

A patient will be considered as withdrawn from the study if he/she is lost to follow-up after exhausting all means of contact or if the patient withdraws consent or if the cause of dyspnea is discovered after the enrollment of the patient to be due to a co-morbidity such as lung disease or congestive heart failure.

3.2.6 Replacement policy

The goal is to follow-up at least 1000 patients over 2 years or until CTEPH is diagnosed within 2 years. In practice only patients withdrawn from the study for consent withdrawal prior to telephone visit 1 or loss to follow-up prior to telephone visit 1 will be replaced.

3.2.7 Screening List

To get an appropriate incidence rate and to exclude any center bias of inclusion/exclusion decisions of the individual PE patients a screening list will be maintained by the survey coordinator (study nurse) at the center where all diagnosed PE patients will be recorded irrespective of their enrollment in the study. Patients diagnosed with PE based only on high clinical probability, positive D-dimers and venous ultrasound will also be entered in the screening list but will not participate in the study.

Basic data will be collected and the reason for non-inclusion will be documented in line with data protection regulations in the absence of informed consents (initials, year of birth, gender, reason for non-inclusion).

3.3 Study Endpoints

3.3.1 Primary endpoint

- Amount of patients who develop symptomatic CTEPH at 6, 12 and 24 months after PE.

A maximum of 200 patients are estimated to report dyspnea during follow-up by the dyspnea questionnaire. Dyspnea is defined as a NYHA class II of higher. Dyspnea patients will be invited to the center for a confirmation of dyspnea and if confirmed an echocardiographic assessment will be performed. It is estimated to identify around 30 patients with CTEPH by echocardiography and confirmed by right heart catheter, V/Q scan and sCT or lung angiography.

3.3.2 Secondary endpoints

- Comparison of collected baseline data of the patients who developed CTEPH with the baseline data of the patients who did not develop CTEPH within the 2 year period after diagnosis of PE to identify any potential risk factors.
- Comparison of the results of the dyspnea questionnaire answered by telephone with the dyspnea evaluation by the investigator at the clinic to test the usefulness of the telephone screening algorithm in medical practice for diagnosing CTEPH after PE.

3.3.3 Exploratory endpoints

If appropriate, exploratory endpoints, derived from the clinical database, will be analyzed based on data-driven considerations.

3.4 Study Assessments

Table 1 provides an overview of the chronological sequence of the assessments.

3.4.1 Baseline parameters

3.4.1.1 Demographics

Baseline demographics, including date of birth, gender, weight, and height are recorded in the enrollment visit CRF page.

3.4.1.2 Baseline status

The following parameters will be recorded in the relevant enrollment visit CRF page:

- Date of onset of PE symptoms
- Severity and treatment of recent PE
- Existence of any other potential causes of PH besides PE

Special investigations/examination methods may be conducted at the discretion of the investigator to exclude any possible pathological findings.

3.4.1.3 Potential risk factors for PE and / or CTEPH

Any known risk factors for VTE and potential risk factors for CTEPH are listed on the CRF page of the enrollment visit and each has to be rejected or confirmed.

3.4.1.4 Blood samples

~~Extra serum samples are frozen and stored until needed for a retrospective evaluation of different parameters (to be defined) in the identified CTEPH patients.~~

Replaced by Amendment #1 21.12.2008 cf p 31

3.4.2 Telephone Follow ups 1, 2 and 3

Follow up of the patients is done by telephone 6, 12 and 24 months after enrollment. The dyspnea questionnaire has to be completed together with the patient via telephone. The results of the telephone visit, e.g. drop out of patient, any hospital readmission and the results of the dyspnea questionnaire have to be recorded in the relevant CRF page. If the patient reports new or worsening of dyspnea, and dyspnea is classified as NYHA II or more, he has to be invited to the hospital for clarification of dyspnea, and if confirmed for an echocardiography.

3.4.3 Hospital Visit

The hospital visit should be performed within 4 weeks after telephone visit.

3.4.3.1 Confirmation of dyspnea

Presence of dyspnea and its severity has to be confirmed by the investigator in the center during the hospital visit.

3.4.3.2 Echocardiography

If dyspnea is confirmed by the investigator at grade NYHA II or higher an echocardiographic examination will be performed to look for signs of a right heart overload. Left heart disease as a possible reason for pulmonary hypertension has to be ruled out. Systolic pulmonary artery pressure, more precisely right ventricular pressure, will be estimated by measurement of the tricuspid regurgitation jet velocity. The results will be documented in the relevant CRF page.

If TR jet velocity shows to be > 2.8 m/s (estimated sRVP >35 mmHg) PH is considered to be highly possible and a right heart catheterisation is necessary for confirmation of PH.

If TR jet velocity is ≤ 2.8 m/s (estimated sRVP is ≤ 35 mmHg) PH is considered less possible but can not definitely be excluded. Therefore these patients will again be asked for dyspnea with the telephone dyspnea questionnaire at the next scheduled telephone visit (month 12 or 24). If dyspnea worsened the patient will be re-invited to the hospital.

If TR jet velocity is not measurable, and dyspnea can not be explained by any other possible causes, right heart catheterization is necessary for identification of PH.

3.4.3.3 Right heart catheter

The results of a performed RHC (sPAP, dPAP, mPAP, PCWP, CO, CI, PVR) will be documented in the relevant CRF page.

If mPAP ≥25 mmHg, PCWP < 15 mmHg and PVR ≥ 300 dyn*sec/cm^5 (3.75 Wood units) at right heart catheterization PH is confirmed.

3.4.3.4 Lung scintigraphy

For lung scintigraphy a ventilation/perfusion mismatch has to be recorded in the relevant CRF page.

3.4.3.5 Contrast enhanced spiral CT

CT features of CTEPH are complete occlusion of pulmonary arteries, eccentric filling defects consistent with thrombi, recanalization, and stenosis or webs. The presence of such features has to be recorded in the relevant CRF page.

3.4.3.6 Pulmonary angiography

Pulmonary angiography is indicated in cases of inconclusive spiral CT in patients with clinical and lung scintigraphy suspicion of CTEPH. CTEPH is then confirmed if narrowing and/or occlusion of a pulmonary artery can be shown at pulmonary angiography. The presence of these features has to be recorded in the relevant CRF page.

Pulmonary angiography may be more accurate in the identification of distal obstructions.

3.4.3.7 CTEPH diagnosis

CTEPH is confirmed if the echocardiographic, right heart catheterization, scintigraphic and tomographic findings show of the following results:

- TR jet velocity > 2.8 m/s at echocardiography and
- mPAP ≥25 mmHg, PCWP < 15 mmHg and PVR ≥ 300 dyn*sec/cm5 (3.75 Wood units) at right heart catheterization and
- evidence of occlusion and/ or filling defects of pulmonary arteries at spiral CT and/orevidence of ventilation/perfusion mismatch diagnostic for CTEPH at lung scintigraphy

If spiral CT and scintigraphy show inconclusive results pulmonary angiography may be performed and CTEPH is then confirmed if narrowing and/or occlusion of a pulmonary artery is shown.

Any other causes of elevated PH have to be excluded.

The confirmation of the diagnosis has to be recorded in the relevant CRF page.

Special cases:

If mPAP and PVR requirements are met, but PCWP is slightly elevated (15-20 mmHg), and left heart failure is questioned to be the cause of dyspnea by judgement of the investigator, the case will be forwarded to the Steering Committee for evaluation. The Steering Committee will then decide if the transpulmonary gradient is sufficiently elevated to diagnose CTEPH in a patient with concomitant left heart failure.

A mean pulmonary artery pressure of 20-24 mmHg is considered to be a borderline PH. All available data of the CTEPH confirmatory tests of these patients will be collected in the hospital visit CRF page. If no other cause of dyspnea can be found, the patients will again be asked for dyspnea with the telephone dyspnea questionnaire at the next scheduled telephone visit (month 12 or 24). If dyspnea worsened the patient will be re-invited to the hospital.

4 STATISTICAL METHODOLOGY AND ANALYSES

4.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be written and finalized before the study closure, i.e., database closure. The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivations.

The SAP will include the definition of major and minor protocol deviations and the link of major protocol deviations to the analysis sets.

4.2 Primary Endpoint

Incidence rate of CTEPH after PE.

4.2.1 Primary endpoint analysis

Incidence rate of CTEPH after PE (with the associated 95% confidence interval) will be expressed as number of events in number of patient-years.

Event rate at months 6, 12 and 24 (with the associated 95% confidence intervals) will also be derived using Kaplan-Meier methodology.

4.2.2 Sample size

A CTEPH incidence rate of approximately 3% is assumed. The sample size needed to estimate such a proportion with a precision of 33% (i.e. to get a 95% confidence interval of +/- 1%) would

be 1118 patients. Conversely with a sample size of 1000 patients an observed proportion of 3% (i.e. 30 patients identified within 1000 patients sampled) would lead to a 95% exact binomial confidence interval of [2.0%, 4.3%].

Therefore a sample size of 1000 patients with confirmed PE was chosen to confirm previously reported incidence rates of CTEPH. This would be the largest prospective survey. If this survey confirms the high prevalence rates, the identification of any subgroups or potential risk factors would ease the future identification of patients at risk.

4.3 Secondary Endpoints

Identification of risk factors for the development of CTEPH after PE.

Comparison of the dyspnea classification resulting from questionnaire answered by telephone with the dyspnea classification by the investigator at the clinic.

4.3.1 Secondary endpoints analysis

Baseline parameters will be summarized using mean, standard deviation, median, quartiles, minimum and maximum for continuous variables, using counts and percentages for categorical variables. Distributions of these parameters will be compared between patients developing CTEPH and patients not developing CTEPH, using t-test or Wilcoxon test for continuous variables and chi-square test (or Fisher's exact test) for categorical variables. These tests will be used for screening potential risk factors. Further exploratory analyses will be conducted.

For patients having reported dyspnea (according to the dyspnea questionnaire) during the follow-up, agreement between the NYHA classification resulting from the dyspnea questionnaire and the NYHA classification performed by the investigator at the hospital visit will be assessed. The comparison will be performed on the original data (4 levels: I, II, III, IV) and also on collapsed data (2 levels: I, II/III/IV).

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6 STUDY MANAGEMENT

6.1 Ethical approval and subject consent

The institution and investigator commit to obtaining approval for the study including the patient informed consent form from their respective EC, prior to commencement of the study. Moreover, the institution and investigator will obtain written informed consent from each patient prior to enrolment.

6.2 Subject confidentiality

By signing the protocol. The institution and/ or the investigator commit to complying with all related applicable local privacy legislation.

6.3 Safety reporting

No investigational medicinal products will be used in this observational study. Therefore, no expedited safety reporting is required and no adverse events will be recorded in the CRF.

Neither are there any invasive study-mandated procedures planned in this survey. A study-mandated procedure is defined as a procedure that is required by the study protocol but is not part of the usual practice of the investigator.

6.4 Monitoring

A study nurse of the SSPH will contact and visit the investigators regularly and will be allowed, on request, to have access to all source documents needed to verify the entries on the CRF and other protocol-related documents; provided that patient confidentiality is maintained. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, and the recording of the main endpoints. Additional checks of the consistency of the source data with the CRFs are also performed.

The investigator must ensure that patients' anonymity will be maintained. On CRFs or other documents patients should not be identified by their names, but by the patient initials and birth date. Documents identifying the patients (e.g., patients' signed informed consent forms) must be kept by the investigator in strict confidence.

The investigator and co-investigators agree to cooperate with the SSPH study nurse to ensure that any issue detected in the course of these monitoring visits are resolved.

6.5 Data management

For each patient enrolled, a CRF must be completed. This also applies to those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis.

The entered data is systematically checked for completeness and correctness by the center's survey coordinator/ study nurse.

6.6 Premature termination or suspension of the study

Both the sponsor and the investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators and the ECs, and provide the reason(s) for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the investigator should promptly inform the enrolled patients and ensure their appropriate treatment and follow-up.

Any premature termination or suspension of the study must be discussed with the Steering Committee.

6.7 Publication and reporting of study results

The main investigator(s) and the Steering Committee will have the opportunity to review the analysis of the data and to discuss with the sponsor the interpretation of the study results prior to publication.

Any study-related article or abstract written independently by investigators should be submitted to the sponsor for review prior to submission for publication or presentation.

The list of authors of any formal publication or presentation of study results will be determined by mutual agreement. First author will be the writer of the manuscript and last author the principal investigator.

Appendix 1 Dyspnea questionnaire (German)

Fragebogen ATEMNOT (Gemäss der funktionellen Klassifikation der NYHA in 4 Stadien)

NYHA IV (Bei Antwort „JA" für eine der folgenden Verrichtungen)

1. Atemnot in Ruhe	ja o	nein o	n/a o
2. Atemnot beim Aufstehen oder beim Anziehen*	ja o	nein o	n/a o
3. Atemnot bei der Morgentoilette oder beim Duschen*	ja o	nein o	n/a o
4. Atemnot beim Herumgehen in der Wohnung*	ja o	nein o	n/a o
5. Atemnot beim Gehen auf ebener Strecke (< 50m) in langsamem Tempo*	ja o	nein o	n/a o

* zum Abbruch zwingend

NYHA III (Bei Antwort „JA" für eine der folgenden Verrichtungen und „NEIN" für die Verrichtungen 1 bis 5)

6. Atemnot bei langsamem Treppensteigen oder bei Gehen auf ebener Strecke (< 100m) in normalem Tempo*
ja o nein o n/a o

7. Atemnot bei Haushaltsarbeit (Betten machen, Aufwischen, Wäsche aufhängen, Boden putzen) oder bei Freizeitaktivitäten (Boccia, Golf, Rasenmähen) (oder Ähnlichem)* ja o nein o n/a o

* zum Abbruch zwingend

NYHA II (Bei Antwort „JA" für eine der folgenden Verrichtungen und „NEIN" für die Verrichtungen 1 bis 7)

8. Atemnot beim Treppensteigen über 2 Stockwerke in normalem Tempo oder beim Aufwärtsgehen*
ja o nein o n/a o

9. Atemnot bei Aktivitäten wie langsames Tanzen, im Garten arbeiten, Rechen, Unkraut rupfen (oder Ähnlichem)*
ja o nein o n/a o

* zum Abbruch zwingend

NYHA I (Bei Antwort „JA" für die folgende Verrichtung und „NEIN" für die Verrichtungen 1 bis 9)

10. Atemnot bei grösserer Anstrengung (1/2 Stunde Joggen, Alpin-Skilaufen, Radfahren…)
ja o nein o n/a o

Begleitsymptome:	Kraftlosigkeit o	Herzklopfen o
	Übelkeit / Ohnmacht o	Brustschmerzen o

Appendix 2 Dyspnea questionnaire (French)

Questionnaire ESSOUFLEMENT (correspondance classification fonctionnelle NYHA en 4 stades)

NYHA IV (si réponse OUI à un des items suivants)			
1. Essoufflement au repos	oui o	non o	n/a o
2. Essoufflement lors du lever ou de l'habillage*	oui o	non o	n/a o
3. Essoufflement lors de la toilette du matin ou de la douche*	oui o	non o	n/a o
4. Essoufflement lors de la marche au domicile*	oui o	non o	n/a o
5. Essoufflement lors de la marche à plat (< 50m) à faible allure*	oui o	non o	n/a o

* l'obligeant à l'interrompre

NYHA III (si réponse <u>OUI</u> à un des items suivants et <u>NON</u> aux items 1 à 5)			
6. Essoufflement lors de la montée d'un étage d'escaliers à faible allure ou de la marche à plat (< 100m) à allure normale*	oui o	non o	n/a o
7. Essoufflement lors du ménage (faire son lit, passer la serpillière, étendre le linge, laver les carreaux) ou des activités de loisirs (jouer aux boules, au golf, pousser la tondeuse à gazon) (ou équivalents)*	oui o	non o	n/a o

* l'obligeant à l'interrompre

NYHA II (si réponse <u>OUI</u> à un des items suivants et <u>NON</u> aux items 1 à 7)			
8. Essoufflement lors de la montée de 2 étages d'escaliers à allure normale ou lors de la marche en pente*	oui o	non o	n/a o
9. Essoufflement lors d'activités telles danser le slow, jardiner, ratisser, désherber (ou équivalents)*	oui o	non o	n/a o

* l'obligeant à l'interrompre

NYHA I (si réponse <u>OUI</u> à l' item suivant et <u>NON</u> aux items 1 à 9)			
10. Essoufflement lors d'efforts importants (jogging 1/2h, ski alpin, vélo…)	oui o	non o	n/a o

Symptômes associés	Asthénie o	Palpitations o
	Lipothymies / syncopes o	Douleurs thoraciques o

Appendix 3 Dyspnea questionnaire (Italian)

Questionario RESPIRO AFFANNOSO (in accordo con la classificazione funzionale NYHA a 4 stadi)

NYHA IV (in caso di risposta positiva ad una delle seguenti domande)			
1. Respiro affannoso a riposo	sì o	no o	n/a o
2. Respiro affannoso al risveglio o mentre si veste*	sì o	no o	n/a o
3. Respiro affannoso durante la toeletta mattutina o la doccia*	sì o	no o	n/a o
4. Respiro affannoso mentre cammina a domicilio*	sì o	no o	n/a o
5. Respiro affannoso mentre cammina in pianura (< 50 m) ad andatura ridotta*	sì o	no o	n/a o

* che obbliga all'interruzione

NYHA III (in caso di risposta <u>SÌ</u> ad una delle seguenti domande e <u>NO</u> alle domande da 1 a 5)			
6. Respiro affannoso quando sale un piano di scale ad andatura ridotta o quando cammina in pianura (< 100 m) ad andatura normale *	sì o	no o	n/a o
7. Respiro affannoso mentre si fanno le pulizie (rifare il letto, passare lo strofinaccio per pavimenti, appendere i panni, pulire le finestre) o durante attività del tempo libero (giocare alle bocce, al golf, spingere il tosaerba) (o equivalenti)*	sì o	no o	n/a o

* che obbliga all'interruzione

NYHA II (in caso di risposta <u>SÌ</u> ad una delle seguenti domande e <u>NO</u> alle domande da 1 a 7)			
8. Respiro affannoso quando sale due piani di scale ad andatura normale o quando cammina in salita*	sì o	no o	n/a o
9. Respiro affannoso durante attività quali danzare un lento, dedicarsi al giardinaggio, rastrellare, diserbare (o equivalenti)*	sì o	no o	n/a o

* che obbliga all'interruzione

NYHA I (in caso di risposta <u>SÌ</u> ad una delle seguenti domande e <u>NO</u> alle domande da 1 a 9)			
10. Respiro affannoso in caso di sforzi intensi (jogging 1/2h, sci alpino, bicicletta…)	sì o	no o	n/a o

Sintomi associati	Astenia o	Palpitazioni o	
	Lipotimie / sincopi o		Dolori al torace o

Appendix 4 Calculation of hemodynamic parameters

Cardiac index (CI) will be calculated according to the formula:

CI (L/min/m^2) = Cardiac output ÷ body surface area where

Body surface area (m^2) = 0.007184*(weight$^{0.425}$)*(height$^{0.725}$) with

weight expressed in kg and height in cm

Pulmonary vascular resistance (PVR) will be calculated according to the formula:

PVR (dyn.sec/cm^5) = 80*(mPAP - PCWP) ÷ cardiac output.

Appendix 5 Mastora CTA severity score of PE

The Mastora CTA severity scoring system is applied to 5 mediastinal, 6 lobar, and 20 segmental arteries.

The 5 mediastinal arteries comprise the pulmonary artery trunk, the right and left main pulmonary arteries, and the right and left interlobar arteries.

The 6 lobar arteries include the right truncus anterior, the left upper lobe pulmonary artery (upper arterial branch, i.e., the culminal branch), the right middle lobe pulmonary artery, the left upper lobe pulmonary artery (lower arterial branch, i.e. the lingular arery), and the right and left lower lobe pulmonary arteries.

The 20 segmental pulmonary arteries consist of the 3 right and left upper lobe (upper division) segmental arteries, the 2 right middle lobe and left upper lobe (lower division) segmental arteries, and the 5 right and left lower lobe segmental arteries.

The CTA severity score is based on the percentage of obstructed surface of each central and peripheral pulmonary arterial section using a 5-point scale:

1: <25%, **2**: 25-49%, **3**: 50-74%, **4**: 75-99%, **5**: 100% obstruction.

Each individual score is established after visual analysis of the artery of interest on the CT section enabling the most accurate delineation of the arterial branch.

The sum of the detailed scores attributed to the 5 mediastinal arteries (range 0-25), 6 lobar arteries (range 0-30), and 20 segmental arteries (range: 0-100) per patient lead to the determination of central, peripheral and global CT severity scores.

The percentage of the pulmonary artery circulation obstructed by endoluminal clots is calculated by dividing the observed CT severity score at a given anatomical level by the maximal CT score of obstruction for this anatomical level. This procedure leads to he determination of the percentage of obstruction of the central pulmonary arterial bed (corresponding to the obstruction of both mediastinal and lobar pulmonary arteries), the peripheral pulmonary arterial bed (namely, the segmental pulmonary arteries), and the entire pulmonary arterial bed (including central and peripheral pulmonary arteries).

Mastora I, Remy-Jardin M, Masson P, et al. Severity of acute pulmonary embolism: evaluation of a new spiral CT angiographic score in correlation with echocardiographic data. Eur Radiol. 2003 Jan;13(1):29-35.

Study Amendment #1

The item 3.4.1.4 (p.18) is replaced by the following text

"At inclusion in the study blood sample (20 mL) will be taken by venous puncture for the measurement of D-dimers, NT-proBNP , PAI-1, FactorVIII, antiphospholipid antibodies, lipoprotein A in plasma or serum respectively. The first four parameters will be measured immediately by standard and routine procedures, whereas for antiphospholipid antibodies and Lipoprotein A the material will be kept frozen until the simultaneous measurement at the end of the inclusion period. All remaining plasma or serum samples will be eliminated at the end of the inclusion period".

approved by the steering committe– 21.12.2008

Supplement 2: Study monitoring

For each patient enrolled, an electronic case report form (ECRF) was completed, collected on a centralised database and systematically checked for completeness by the local study nurse and/or the local investigator. During the study, the protocol observance was assessed by a study coordinator associated with the Swiss Society for Pulmonary Hypertension (SSPH). This monitoring consisted in a full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and the recording of the endpoints. These checks were done comparing source data to the ECRF.

Supplement 3: Incidence of CTEPH in the INPUT cohort and sensitivity analysis.

	%	95% CI	unit
Cumulative incidence of complete cases	0.79	[0.31 ; 2.07]	% over 2 year
Incidence rate of complete cases	3.65	[1.43 ; 9.36]	1000 persons / year
Cumulative incidence in dyspneic patients ≥ II NYHA	4.12	[1.62 ; 10.13]	% over 2 year
Imputation model 1	1.15	[0.30 ; 2.62]	% over 2 year
Imputation model 2	0.86	[0.27 ; 2.08]	% over 2 year
Imputation model 3	0.91	[0.33 ; 2.11]	% over 2 year

Supplement 3: Each missing variable was imputed 15 times (10.6% of data) and then regrouped after a previously described method. This process was repeated 10 times for each method. Model used (1) most correlated characteristics with centre: antiphospholipid antibody, age at baseline, BMI, current smoker, centre (2) most correlated characteristics without centre: antiphospholipid antiphospholipid antibody, age at baseline, BMI, current smoker (3) recognised risk factors in the literature: antiphospholipid antibody, splenectomy, recurrent PE, inflammatory bowel disease, thyroid replacement therapy, active cancer, ventriculoatrial shunt and pacemaker with or without infection, unprovoked PE.

Supplement 4: Baseline variable correlated to CTEPH.

	CTEPH	no CTEPH	Pearson	Fischer	t-test
antiphopholipid antibody	1 (25%)	3 (0.6%)	0.22	0.03	
thrombophilic disorder	1 (25%)	24 (4.8%)	-0.16	0.18	
body mass index	33 (13.2)	28.0 (5.3)	0.08		0.49
age at baseline	47 (25.8)	61.3 (16.0)	0.08		0.34
current smoker	2 (50%)	88 (17.5%)	-0.08	0.15	
current weight in kilograms	92 (33.9)	81.7 (17.2)	0.07	0.34	
male	1 (25%)	270 (53.6%)	0.05	0.58	
previous smoker	0	115 (22.8%)	-0.05	1	
previously documented deep venous thrombosis	0	74 (14.6%)	-0.05	1	
history of malignancy	0	56 (11.1%)	-0.04	1	
protracted travel more than 4 hours	0	51 (10.1%)	-0.03		0.51
height in centimetre	167.3 (8.7)	170.6 (9.6)	-0.03	0.44	
history of confirmed pulmonary embolism	1 (25%)	70 (14.0%)	0.03	1	
prolonged immobilidy non hospital setting more than 7 days	0	47 (9.3%)	-0.03	1	
hormonal contraception	0	49 (9.7%)	-0.03	1	
prolonged hospitalization more than 7 days	0	45 (8.9%)	-0.03	0.46	
family history of deep venous thrombosis or pulmonary embolism	1 (25%)	72 (14.3%)	0.03	1	
massive pulmonary embolism (with shock)	0	38 (7.5%)	-0.03	1	
are any other potential causes of PH present besides PE	0	39 (7.7%)	-0.02	1	
chronic venous insufficiency	0	35 (7.0%)	-0.02	1	
active cancer	0	27 (5.4%)	-0.02	1	
noninsulindependent diabete	0	29 (5.8%)	-0.02	1	
oral anticoagulation	4 (100%)	481 (95.4%)	0.02	1	
coronary disease and or myocardial infarction	0	27 (5.4%)	-0.02	1	
major surgery more than 2 and a half hour	1 (25%)	82 (16.3%)	0.02	0.52	
thrombolytics	0	25 (5.0%)	-0.02	1	
cerebrovascular disease	0	20 (4.0%)	-0.02	1	
recent fracture	0	22 (4.4%)	-0.02	1	
has vena cava filter	0	21 (4.2%)	-0.02	1	
chemotherapy used	0	13 (2.6%)	-0.02	1	
concomitant symptomatology of deep venous thromobosis	0	175 (34.7%)	-0.02	1	
thyroid replacement therapy	0	18 (3.6%)	-0.02	1	
major trauma (spinal, low extermities, pelvis, head or thorax	0	14 (2.7%)	-0.02	1	
nephrotic syndrome	0	9 (1.8%)	-0.01	1	
hormone replacement therapy	0	13 (2.6%)	-0.01	1	
low molecular weighted heparin	0	9 (1.79%)	-0.01	1	
metastatic cancer	0	4 (0.8%)	-0.01	1	
unfractionned heparin	0	11 (2.18%)	-0.01	1	
rheumatoid arthritis	0	10 (2.0%)	-0.01	1	
provoked pulmonary embolism	0	279 (55.4%)	-0.01	1	
inflammatory bowel disease	0	8 (1.5%)	-0.01	1	
insulindependant diabete	0	9 (1.2%)	-0.01	1	
unknown anticoagulation therapy	0	3 (0.6%)	-0.01	1	
congestive heart failure	0	3 (0.6%)	-0.01	1	
pregnancy	0	6 (1.2%)	-0.01	1	
splenectomy	0	3 (0.6%)	-0.01	1	
pacemaker	0	5 (1.0%)	-0.01	1	
obesity with body mass index more than 30	1 (25%)	147 (29.2%)	-0.01	1	
thrombectomy device angiojet	0	3 (0.6%)	-0.01	1	
liver cirrhosis	0	3 (0.6%)	-0.01	1	
dialysisdependent replacement therapy	0	2 (0.4%)	-0.01	1	
infection of ventriculoatrial shunt	0	0	-0.01	1	

Supplement 4: Data are n (%) and mean (±SD). CTEPH=chronic thromboembolic pulmonary hypertension.

Supplement 5: Detail of the sensitivity/specificity.

6 months	M+	M-	Total	Sensitivity	50% (15-85)
T+	2	56	58	Specificity	88.9% (85.6-91.3)
T-	2	448	450	PPV	3.5% (1.0-11.7)
Total	4	504	508	NPV	99.7% (98.4-99.9)
12 months	M+	M-	Total	Sensitivity	50% (9.5-90.5)
T+	1	43	44	Specificity	91.5% (88.7-93.6)
T-	1	461	462	PPV	2.3% (0.4-11.8)
Total	2	504	506	NPV	99.8% (97.8-100)
24 months	M+	M-	Total	Sensitivity	100% (20.7-100)
T+	1	46	47	Specificity	91.0%
T-	0	458	458	PPV	2.1%
Total	1	504	505	NPV	100% (99.2-100)
overall survey	M+	M-	Total	Sensitivity	100% (51.0-100)
T+	4	93	97	Specificity	81.6% (77.9-84.7)
T-	0	411	411	PPV	4.1% (1.6-10.1)
Total	4	504	508	NPV	100% (99.1-100)
overall TTE	M+	M-	Total	Sensitivity	100% (51.0-100)
T+	4	11	15	Specificity	88.2% (80.8-93.5)
T-	0	82	82	PPV	26.7% (10.9-52.0)
Total	4	93	97	NPV	100% (95.5-100)
overall RHC	M+	M-	Total	Sensitivity	100% (51.0-100)
T+	4	0	4	Specificity	100% (74.1-100)
T-	0	10	10	PPV	100% (51.0-100)
Total	4	10	14	NPV	100% (74.1-100)
overall algorithm	M+	M-	Total	Sensitivity	100% (51.0-100)
T+	4	145	149	Specificity	90.4% (88.9-91.8)
T-	0	1370	1370	PPV	2.7% (1.1-6.7)
Total	4	1515	1519	NPV	100% (99.7-100)

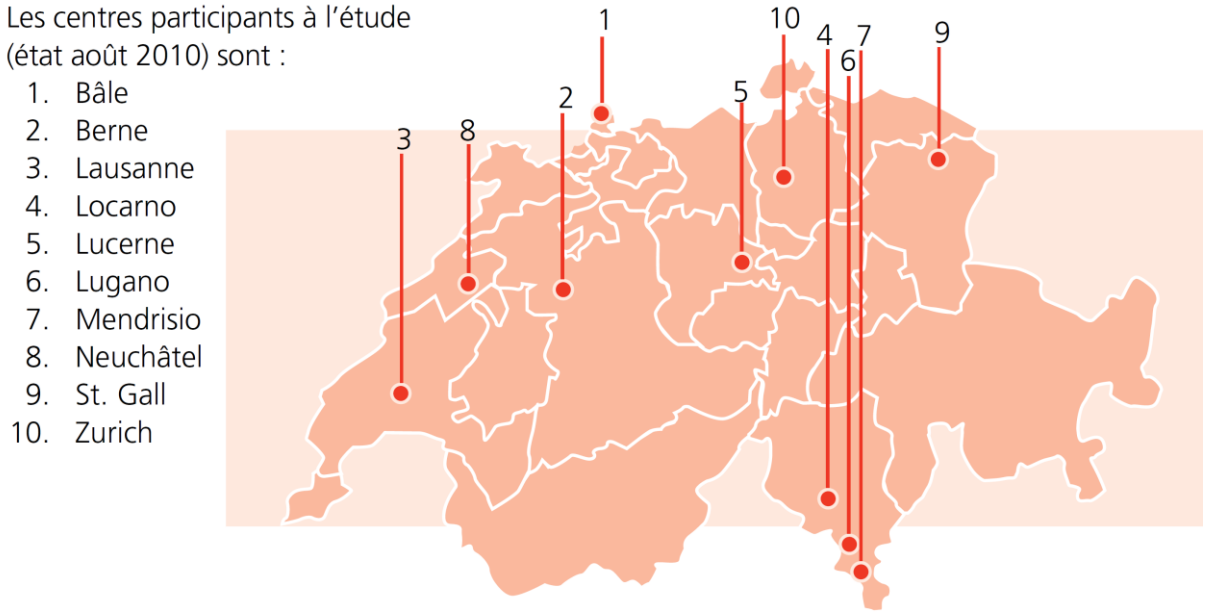
Supplement 5: M+=CTEPH confirmed. M-=no CTEPH. T+=test positive. T-=test negative. PPV=positive predictive value. NPV=negative predictive value. RHC=right heart catheterization.

Supplement 6: Characteristics of the CTEPH cases

Baseline characteristics	**1**	**2**	**3**	**4**
Sex	Male	Female	Female	Female
Age at baseline	44	81	18	45
BMI	28·2	25·2	26·0	52·7
Qanadli index of obstruction in %		37·5	20	77·5
Amputation of perfusion on V/Q scan in %	40			
Thrombolysis	no	no	no	no
Long term anticoagulation	OA	OA	OA	OA
History of PE (n)	no	no	yes (1)	no
Recurrent PE during follow-up (n)	no	no	yes (1)	yes (1)
Concomitant DVT	no	no	yes	no
Family history of PE or DVT	no	yes	no	no
Other risk factors for PE	no	no	antiphospholipid antibody	previous major surgery
Time to the CTEPH diagnosis in months	6	6	25	17
Treatment of CTEPH at 24 months	PEA + OA	OA	OA	OA
Follow up 1 (6 months)	**1**	**2**	**3**	**4**
NYHA Class	II	II	I	III
TTE (TRV in ms)	PH possible (3·0)	PH possible (3·0)		PH unlikely (not measurable)
RHC (mPAP in mmHg)	PH confirmed (25)	PH confirmed (25)		
Radiologic confirmation (modality)	CTEPH confirmed (S.)	CTEPH confirmed (CT)		
Follow up 2 (12 months)	**1**	**2**	**3**	**4**
NYHA Class	#	#	I	III
TTE (TRV in ms)	#	#		PH possible (not measurable)
RHC (mPAP in mmHg)	#	#		PH confirmed (27)
Radiologic confirmation (modality)	#	#		CTEPH confirmed (S.)
Follow up 3 (24 months)	**1**	**2**	**3**	**4**
NYHA Class	#	#	III	#
TTE (TRV in ms)	#	#	PH possible (3·2)	#
RHC (mPAP in mmHg)	#	#	PH confirmed (31)	#
Radiologic confirmation (modality)	#	#	CTEPH confirmed (S.)	#

Supplement 6: CTEPH=chronic thromboembolic pulmonary hypertension. OA=oral anticoagulation. PEA=pulmonary endarterectomy. PH=pulmonary hypertension NYHA FC=New York Heart Association functional class. I-II-III-IV=dyspnoea NYHA FC. mmHg=millimetre of mercure. TTE=transthoracic echocardiography. TRV=tricuspid regurgitation jet velocity. m/s=meter per second. mPAP=mean pulmonary artery pressure. VQ=ventilation-perfusion scan. CT=contrast-enhanced chest computed tomography. #=diagnosed.

Supplement 7: Study centres



The 11 study centres are: Basel (Bâle), Bern (Berne), Lausanne, Locrano, Luzern (Lucerne), Lugano, Mendrisio, Neuchâtel, Sankt Gallen (St. Gall), Zürich (Zurich)