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Prediction of long-term complications of venous thromboembolism

Yvonne M. Ende-Verhaar

The studies described in this thesis were performed at the Department of Thrombosis and Hemostasis of the Leiden University Medical Center, Leiden, the Netherlands

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Prediction of long-term complications of venous thromboembolism

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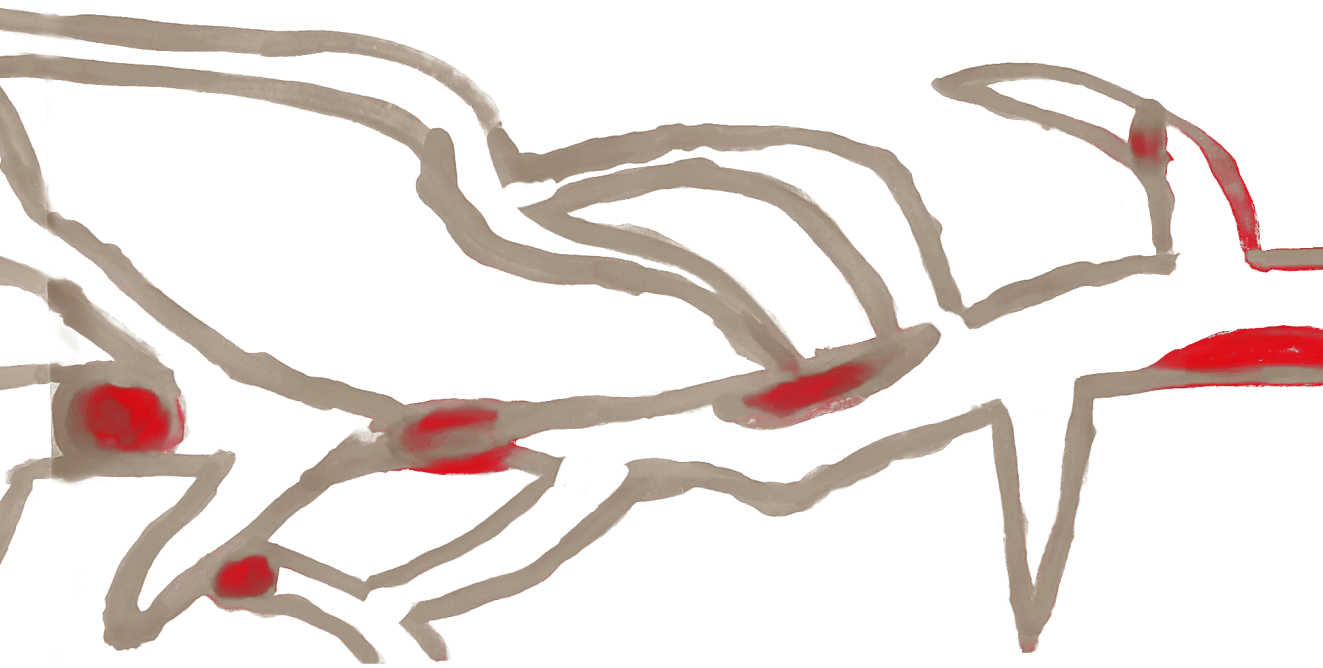
CONTENTS

Chapter 1

Introduction



Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and acute pulmonary embolism (PE). A DVT is caused by thrombi formed in the deep venous system of the extremities, most commonly in the legs. A PE develops when DVT dislodges and travels through the heart into the pulmonary arteries [1].

Common clinical symptoms of DVT are acute pain, swelling and redness of the leg. Most PE patients present with sudden onset of dyspnea without an apparent cause, pleuritic chest pain that worsens with breathing, or other less common symptoms such as syncope or hemoptysis. Patients with a VTE diagnosis are primarily treated with anticoagulants to prevent formation of new thrombi. Their short-term prognosis is highly variable and dependent on initial presentation: especially patients with PE diagnosis who present with signs of right ventricular heart failure (such as persistent arterial hypotension or cardiogenic shock) have a high risk of death [2].

On the long term, both DVT and PE can cause chronic complications due to persistent thrombotic obstruction. The most feared long-term complication of DVT is the post-thrombotic syndrome (PTS). PTS is caused by persistent venous outflow obstruction and reflux by valvular incompetence which causes chronic venous hypertension [3]. Patients with PTS present with a heterogenous spectrum of symptoms such as pain, feeling of heaviness, oedema, skin pigmentation and in more severe cases venous ulcers in the affected limb. The first-line treatment of PTS is venous compression therapy by wearing elastic compression stockings. In parallel with PTS, patients with a history of PE are at risk of developing the post-PE syndrome, which is best characterised by long-lasting functional limitations despite adequate anticoagulant therapy after the acute episode. While heterogeneous explanations for post-PE syndrome have been described, the most frequent cause is functional deconditioning [4]. The most severe -but relatively rare- presentation of the post-PE syndrome is chronic thromboembolic pulmonary hypertension (CTEPH). This distinct form of pulmonary hypertension (PH) is characterised by persistent obstruction of the pulmonary arteries due to thrombus occlusion and progressive vascular remodelling in the non-occluded arteries caused by redistribution of the blood flow and at the end the development of progressive right heart failure [5, 6]. If CTEPH is left untreated, it is associated with a poor prognosis and higher mortality [5, 7, 8]. A surgical procedure called pulmonary endarterectomy (PEA) is a potential curative treatment option for patients with CTEPH [6, 7, 9]. During this surgical procedure all thrombotic material is removed from the pulmonary arteries resulting in normalisation or at least in an improvement of the pulmonary hemodynamics. For inoperable patients or those with persistent or recurrent PH after PEA, balloon pulmonary angioplasty (BPA) might be an option. BPA is a catheter-based invasive procedure to open stenotic or obstructed lesions in the pulmonary artery. Riociguat is currently the only therapeutic agent approved for pharmacological treatment of CTEPH [5].

In most patients the natural course of CTEPH involves more distal involvement of the pulmonary artery tree which makes surgical treatment more challenging, early CTEPH diagnosis is crucial for optimal treatment outcome. Notably, according to the International CTEPH registry, this is still a major clinical challenge with a current unacceptable median diagnostic delay of over one year in western Europe [10]. The most likely explanations for this are diagnostic misclassifications of CTEPH as acute PE or other conditions, the nonspecific and often insidious clinical presentation of CTEPH, and the cumbersome diagnostic process of CTEPH, which involves multiple healthcare providers from different clinical specialties. Since international guidelines for treatment of PE do not provide clear recommendations on the frequency and duration of medical follow-up after the acute event, specific screening programs for CTEPH are unavailable and awareness for CTEPH is generally low [5]. The overall aim of this thesis was to provide more accurate estimations of the incidences of post-VTE syndromes and to evaluate ways to improve the outcomes of these patients by identifying relevant risk factors, proposing risk stratification models and improving health care utilisation.

The first chapters of this thesis focus on the question whether we should screen for CTEPH in all patients after an episode of acute PE or not. The purpose of screening for a certain disease is to identify patients in a preclinical or early stage of the disease, and ultimately to improve patient's outcome after early treatment. The 10 principles for screening proposed by Wilson and Jungner in 1968 provide guidance for the selection of diseases suitable for screening [11]. In **chapter 2** we discuss the arguments pro and contra CTEPH screening in patients after an acute PE event by using these principles. An important question according to these principles is whether the evaluated condition is an important and/or prevalent health problem. For instance, a CTEPH incidence of more than 10% of PE patients would certainly warrant a standardised screening strategy while an incidence of less than 0.1% would certainly not. In **chapter 3** of this thesis, we describe a systematic review and meta-analysis aimed at establishing this incidence. To gain the most accurate view of the literature we aimed to evaluate the incidence of CTEPH in three predefined cohort subtypes 1) the *all comers* i.e. all consecutive patients with symptomatic PE, no exclusion criteria, 2) the *survivors* i.e. all consecutive patients who survived the initial follow-up period of 3 to 6 months, and 3) the *survivors without major comorbidities* i.e. all consecutive survivors without any major cardiopulmonary, oncologic or rheumatologic comorbidities. The CTEPH incidence in all-comers would provide the best estimate on its occurrence on population level, where the last two categories are more relevant to patient management in daily clinical practice.

The next chapters of this thesis focus on possible screening strategies to establish an early CTEPH diagnosis after acute PE. Recently a clinical prediction score aiming to identify patients with a high risk on CTEPH development within 6 months after the initial acute PE diagnosis was constructed [12]. A combination of this clinical predic-

tion score with a set of rule out criteria including electrocardiography reading and N-terminal pro-brain natriuretic peptide measurement [13, 14] is currently being evaluated in an international multicentre prospective management study (InShape II study, ClinicalTrials.gov identifier NCT02555137). The low incidence of CTEPH in the general PE population makes it difficult to evaluate the sensitivity of this screening algorithm. Therefore, in **chapter 4** we investigate the sensitivity of the combination of this clinical prediction score and set of rule out criteria in early CTEPH detection in selected patients with a previous PE event who were later on diagnosed with CTEPH in order to evaluate whether by using this screening algorithm no patients with CTEPH were missed. One of the items scored in the clinical prediction score is the right-to-left ventricle (RV/LV) diameter ratio on computed tomography pulmonary angiography (CTPA) [12]. The aim of **chapter 5** was to determine the accuracy of calculating the RV/LV diameter ratio on CTPA in patients with an acute PE diagnosis by three residents internal medicine without specific training in CTPA reading compared with an expert thoracic radiologist. A finding of good reproducibility would support the wide application of the proposed screening algorithm in clinical practice.

An alternative strategy for achieving early CTEPH diagnosis is based on the suggestion that that signs of CTEPH may already be present on the initial CTPA scan made for the PE diagnosis [15]. In **chapter 6** we investigate the presence and predictive value of specific signs of CTEPH on the CTPA scans performed routinely in patients with suspected PE.

As mentioned earlier, the median diagnostic delay of CTEPH is well over 1 year [10]. In addition to screening strategies, an important step in improvement of this long diagnostic process is to understand the health care utilisation of these patients. In the study described in **chapter 7**, we reconstructed the clinical pathways from the moment of symptom onset to the moment of CTEPH diagnosis in 40 Dutch patients.

The last chapter of this thesis focuses on the development of PTS in patients diagnosed with a DVT in the leg. Where available studies have focussed on the occurrence of and risk factors for PTS in the first 2 years after a DVT diagnosis, little is known of the PTS incidence beyond this time period. In **chapter 8** we describe the 0-1 and 1-8- year cumulative incidence of PTS, the evolvement of symptoms and signs over time and relevant risk factors for PTS development in patients diagnosed with a first DVT event in the lower extremity included in the Multiple Environmental and Genetic Assessment (MEGA) study [16].

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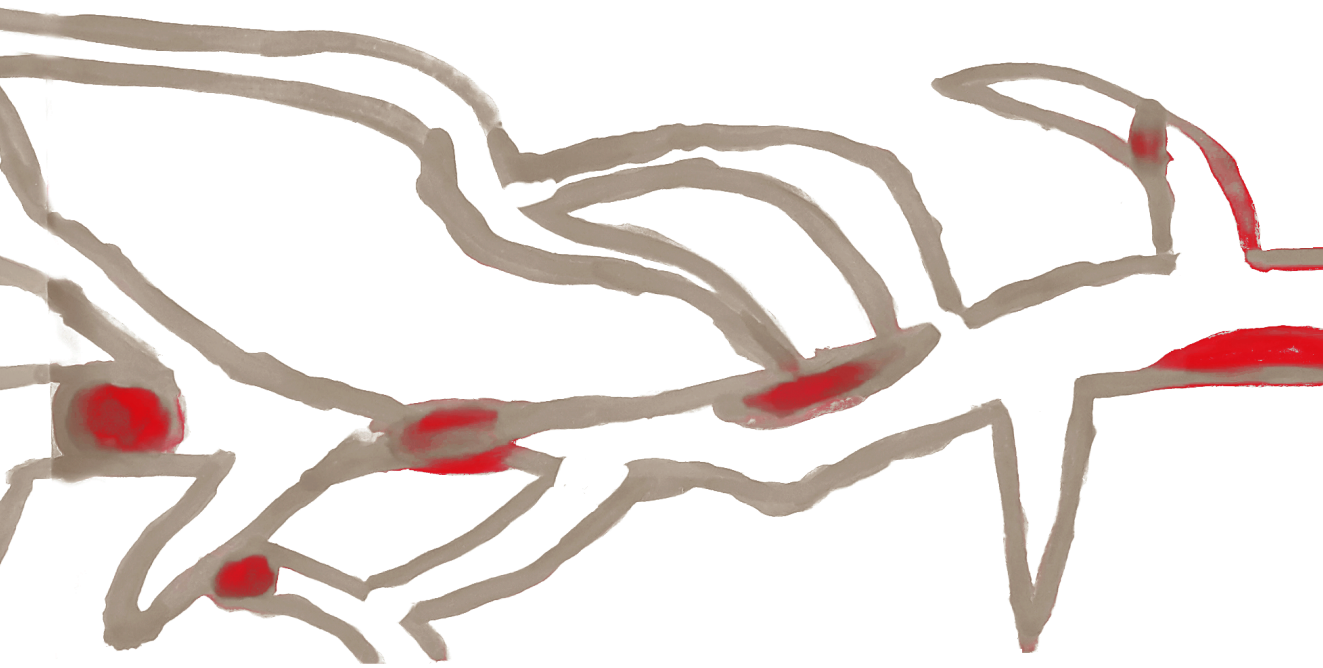
Chapter 2

To screen or not to screen for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

Yvonne M. Ende-Verhaar, Menno V. Huisman, Frederikus A. Klok

Thrombosis Research 2017; 151:1-7



ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is the most severe long term complication of acute pulmonary embolism (PE). Untreated, CTEPH is associated with a very poor prognosis and high risk of mortality, although curation can be achieved by surgical removal of the obstructive endothelialised thromboemboli from the pulmonary arteries. Early CTEPH diagnosis may improve surgical possibilities and patients outcome. Currently, early diagnosis of CTEPH is a major challenge as demonstrated by an unacceptable median diagnostic delay of over a year and as a result, surgery is impossible in 40% of patients. Most important reasons for this delay are the non-specific clinical presentation of CTEPH and lack of guideline recommendations with regard to the optimal follow-up of patients with acute PE. Despite compelling reasons to diagnose CTEPH earlier, acute PE is not classified among the conditions that warrant screening for pulmonary hypertension. Meaningful screening programs improve the patients' prognosis, and screening tools should be simple, widely available, non-invasive and acceptable to patients. In this review, we discuss current knowledge of available screening instruments for CTEPH, provide recommendations for clinical practice and expand on future developments of this particular subject.

INTRODUCTION

The purpose of screening for a certain disease is to identify patients with preclinical or early stages of disease in order to prevent or delay progression of disease through early management. Medical screening has been increasingly implemented over the past half century and is widely recognized to be one of the 'success stories' of modern medicine. Pulmonary hypertension (PH) is a serious disease spectrum associated with a poor prognosis [1, 2]. Screening programs play an important part in the detection of PH in certain at-risk populations to enable early identification and treatment. Specifically, screening for PH is recommended for patients with systemic sclerosis, scleroderma spectrum disorders, BMPR2-mutation carriers, first-degree relatives of patients with familial pulmonary artery hypertension (PAH), portal hypertension and for patients with sickle-cell disease [2-7]. This screening has been shown to result in earlier diagnosis [5, 8, 9] and earlier treatment initiation, which was demonstrated to lead to improved long-term survival [9, 10].

Chronic thromboembolic pulmonary hypertension (CTEPH), a specific subclass of PH, is a life-threatening complication of acute pulmonary embolism (PE). CTEPH is caused by persistent obstruction of the pulmonary arteries and progressive vascular remodelling giving rise to PH and right ventricular failure. CTEPH may be cured by pulmonary endarterectomy (PEA) [2, 11]. When surgery is not feasible or fails in significantly reducing the pulmonary artery pressure, the patient's prognosis is poor [1, 2, 12]. Operability of a patient depends among others on the presence of more advanced distal pulmonary artery remodelling, a feature that is less expected if CTEPH is diagnosed early. The duration between last PE and PEA was indeed found to be a risk factor for mortality in the European CTEPH registry [13]. Hence, early diagnosis may be crucial for an optimal treatment and outcome [14-16].

Early diagnosis of CTEPH has however been shown to be a major clinical challenge as demonstrated by a median diagnostic delay of 14 months in the European CTEPH registry [17]. Also, 81% of patients diagnosed with CTEPH presented in NYHA functional class III or IV, indicating an advanced stage of disease. Notably, 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 [18]. Even more, the ESC guideline recommends against routine echocardiography in all patients who are treated for acute PE (Class 3, level C) [2, 18, 19].

In this review, we aimed to discuss arguments pro and contra CTEPH screening. To do so, we used the principles for screening proposed by Wilson and Jungner. These principles give guidance in the selection of conditions that would be suitable for screening, based on the diagnostic capacity to detect the condition at an early state and the availability of an acceptable treatment [20] (**Table 1**).

Table 1. Wilson and Jungner principles of early disease detection.

1	The condition sought should be an important health problem.
2	There should be an accepted treatment for patients with recognized disease.
3	Facilities for diagnosis and treatment should be available.
4	There should be a recognizable latent or early symptomatic stage.
5	There should be a suitable test or examination.
6	The test should be acceptable to the population.
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8	There should be an agreed policy on whom to treat as patients.
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10	Case-finding should be a continuing process and not a "once and for all" project.

THE CONDITION SOUGHT SHOULD BE AN IMPORTANT HEALTH PROBLEM

A health problem is considered important if a certain disease has serious consequences for the patient and his or her family, or serious consequences for the community if not discovered and treated [20]. In a recent meta-analysis, CTEPH has been estimated to occur in 0.13-0.98% of all patients who are diagnosed with acute PE on a population level [21]. This incidence is mainly based on two cohort studies of patients with acute PE with very few exclusion criteria who were followed for the occurrence of CTEPH, reporting incidences of 0.57% and 1.3% respectively [19, 22]. The estimated incidence of a first venous thromboembolic event in the general population is 1-2 per 1000 person-years [23-25]. Assuming 743 million inhabitants of Europe, each year an estimated 4000 to 8000 patients with a history of PE will develop CTEPH. Of note, the reported weighted pooled incidence of CTEPH in patients who survive the PE event and visit the outpatient clinic after an initial anticoagulant treatment period of 3 to 6 months is ~3%. This incidence reported in the so called survivors is higher than the reported incidence on population level [21].

Before the introduction of PEA the prognosis of these patients was very poor. In older series in patients who only were prescribed vitamin K antagonists, the 3-year survival was as low as 30% [26, 27]. In addition to a shorter life expectancy compared to the general population, patients with CTEPH have a substantially reduced quality of life in terms of physical capability, psychological wellbeing and social relationships [28]. Considering the above, CTEPH should be considered an important health problem.

THE NATURAL HISTORY OF THE CONDITION, INCLUDING DEVELOPMENT FROM LATENT TO DECLARED DISEASE, SHOULD BE ADEQUATELY UNDERSTOOD. THERE SHOULD BE A RECOGNIZABLE LATENT OR EARLY SYMPTOMATIC STAGE

CTEPH, a distinct form of PH, is believed to arise from one or multiple endothelialized pulmonary thrombi that do not resolve but lead to chronic obstruction of the pulmonary artery tree, small-vessel arteriopathy, high pulmonary vascular resistance, PH and progressive right heart failure. The pathophysiological mechanisms that prevent complete resolution of the embolic material after acute PE are not fully elucidated yet but involve among others inflammation, abnormal fibrinogen variants and aberrations in angiogenesis [29].

The most common presenting symptom in patients with CTEPH is dyspnoea [17]. The acute embolic event in patients with CTEPH can typically be followed by a so-called 'honeymoon' period during which the patients gradually recover [30]. This period can last for several months and sometimes even years. Later on, patients develop progressive dyspnoea on exercise as initial symptom of CTEPH [30]. Signs of right heart failure only become evident in more advanced disease [17]. Importantly, CTEPH can be diagnosed accurately in symptomatic as well as non-symptomatic patients if the correct diagnostic tests are applied (see below).

Several circumstances complicate easy clinical recognition of patients with CTEPH in the clinical course of PE, contributing to the substantial diagnostic delay of CTEPH. First, 36-56% of patients who survive an episode of acute PE report exertional dyspnoea [31, 32]. Only a small number of these patients actually develop CTEPH [32]. CTEPH seems to be the extreme manifestation of a much more common phenomenon of permanent changes in pulmonary artery flow, pulmonary gas exchange and/or cardiac function caused by acute PE in combination with deterioration of the clinical symptoms, functional status or quality of life. This is in analogy to post-thrombotic syndrome after deep vein thrombosis referred to as the post-PE syndrome. Taking the above described frequently occurring honeymoon period of no or very limited symptoms into account as well, it is a challenge to easily identify patients with CTEPH at early stage based on their clinical presentation [33].

Second, CTEPH should be distinguished from chronic thromboembolic disease (CTED). CTED is defined as persistent pulmonary vascular obstruction and exercise intolerance without PH at rest [34]. CTED is one of the manifestations of the post-PE syndrome, as is CTEPH. It has however been suggested that some of these patients may have exercise induced PH [35]. PH on exercise may be an intermediate pathophysiological stage of PH although limited data exist on the natural history of PH on exercise and it is currently not recognized as disease entity in current guidelines. The prognosis of patients with

CTED is favourable without treatment, although PEA has been suggested to result in significant improvement in symptoms and quality of life in this patient category too [36]. Finally, growing evidence supports the hypothesis that CTEPH is often misclassified as acute PE [2, 37-39]. The clinical course of symptom relief after initiation of anticoagulant treatment in such patients is likely different from patients with true acute PE. Of note, early screening programs for CTEPH after acute PE would be suitable to identify this specific patient category as well.

FACILITIES FOR DIAGNOSIS AND TREATMENT SHOULD BE AVAILABLE

According to the current guidelines, patients with a history of venous thromboembolism who present with signs or symptoms suggestive for right sided heart failure should be subjected to a diagnostic evaluation for CTEPH. A CTEPH diagnosis is based on findings obtained after at least three months of effective anticoagulation in order to discriminate CTEPH from acute PE. The recommended diagnostic work-up starts with transthoracic echocardiography, during which an estimate of pulmonary artery pressure can be made by Doppler evaluation. A tricuspid regurgitation velocity of >2.8m/s indicates an intermediate to high probability of PH. Other signs suggesting PH are right ventricle/left ventricle basal diameter ratio >1.0, flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole), right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching, early diastolic pulmonary regurgitation velocity >2.2 m/sec, inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration), right atrial area (end-systole) >18 cm^2 and lastly PA diameter >25 mm [2].

When echocardiographic findings are indicative for PH, the next diagnostic step is ventilation/perfusion (V/Q) lung scintigraphy carrying a 96%-100% sensitivity and 86%-95% specificity for CTEPH [2, 40-42]. The gold standard test to diagnose CTEPH is right heart catheterisation (RHC) with digital subtraction pulmonary artery angiography, the latter being crucial for the assessment of surgical treatment as well. A pulmonary arterial pressure ≥25mmHg and pulmonary artery wedge pressure ≤15mmHg, in combination with multiple chronically organized occlusive thrombi in the pulmonary arteries is diagnostic for CTEPH [2, 18, 43]. Initial steps of this recommended diagnostic algorithm, i.e. echocardiography and V/Q lung scintigraphy, are widely available, while the final diagnosis should be confirmed in a PH/CTEPH expert centre.

THERE SHOULD BE AN ACCEPTED TREATMENT FOR PATIENTS WITH RECOGNIZED DISEASE AND AN AGREED POLICY ON WHOM TO TREAT AS PATIENTS

PEA is the only curative treatment option for patients with CTEPH and treatment of choice according to the guidelines [2]. This surgery is performed through a median sternotomy incision, followed by a cardiopulmonary bypass enabling hypothermia to 20°C and intermittent deep hypothermic circulatory arrest. During the circulatory arrest, all obstructive thromboembolic material of the affected parts of the lung will be removed with dissection of the intima and part of the media [44]. Most patients experience immediate improvement in symptoms and near normalization of pulmonary hemodynamics [13, 17, 45], even in patients with limited segmental-level disease [46]. Recent large cohort studies show in-hospital mortality rates between 2.2% and 6.5% [13, 17, 45, 46], 1-year survival rates of 91-93% [1, 13, 45] and 3-5 year survival rates of 82-90% [1, 46, 47].

At time of diagnosis, up to 40% of patients are not suitable for surgery in some centers for reasons including surgical inaccessibility of the thrombotic lesions, the degree of impairment of pulmonary hemodynamics or the presence of severe comorbidities [1, 13]. Notably, the threshold for surgery is shifting throughout recent years to more and more peripheral disease. For patients who are deemed inoperable, pharmacological therapy may be considered. Long term clinical outcome studies have however shown that patients who underwent PEA had lower 3-year mortality rate compared with non-operated, medically treated patients (11-13% compared to 30-35%) [1, 48]. The five-year survival rate was 86.3% compared to 64.9% respectively [12]. PEA is thus the only curable treatment option and should be considered in every patient with CTEPH. Since the natural course of disease includes progressive involvement of distal pulmonary arteries, implicating that diagnostic delay may possibly be associated with a lower chance of operability, it can by hypothesised that early diagnosis is essential for the patients' prognosis [11]. Importantly it has never been indisputably shown that earlier diagnosis is associated with better operability and improved prognosis.

To date, only two large randomized controlled trials have assessed the efficacy and safety of pharmacological treatment in inoperable CTEPH patients. Riociguat, a soluble guanylate cyclase stimulator stimulates and increases the sensitivity of the guanylate cyclase receptor to the vasodilatator nitric oxide, is the only therapeutic agent approved for pharmacological treatment of CTEPH [49, 50]. Compared with placebo, riociguat was associated with an increased 6-min walking distance and reduced pulmonary vascular resistance in inoperable CTEPH patients after 16 weeks of treatment [50]. With continued treatment (CHEST-2 study), these improvements maintained for up to 2 years with an estimated survival rate at 1 year of 93% [51]. Bosentan, a dual endothelin receptor antagonist, reduces the endothelin levels and the endothelin receptor expression, a

process involved in the vascular remodelling in CTEPH [52]. It was shown to significantly reduce pulmonary vascular resistance after 16 weeks of treatment, but without improvement of the 6-minute walking distance compared to placebo [52]. New pharmacological treatment options being studied are macitentan, a dual endothelin receptor antagonist (phase 2 MERIT-2 trial; NCT02060721) and ambrisentan, a selective endothelin receptor antagonist trial (phase3 AMBER II; NCT01894022).

Balloon pulmonary angioplasty (BPA) is a novel treatment for patients with inoperable, persistent or recurrent pulmonary hypertension after PEA. BPA is a catheter-based invasive procedure to open stenotic or obstructed lesions in the pulmonary artery with a balloon catheter. Several studies have shown that BPA can lead to haemodynamic improvements that are compatible to those typically seen following PEA, although further evaluation of BPA as first or second line treatment of CTEPH is needed [53-57].

THERE SHOULD BE A SUITABLE SCREENING TEST OR EXAMINATION AND THIS TEST SHOULD BE ACCEPTABLE TO THE POPULATION

Candidate screening instruments for CTEPH in the clinical course of acute PE include echocardiography, V/Q lung scintigraphy, CT pulmonary angiography (CTPA), electrocardiography (ECG), measurement of biomarkers and clinical pre-test probability assessment. For obvious reasons RHC, while being the diagnostic standard, is not a suitable first line screening test.

Echocardiography

Echocardiography is widely accepted by the medical community as the first-line non-invasive diagnostic tool for PH and CTEPH specifically. Transthoracic echocardiography is a non-invasive, simple test and can be used to image structural and functional effects of PH on the heart as well as to estimate the pulmonary artery pressure from continuous Doppler measurements. However and especially in patients with mild disease, both false positive and false negative estimates may occur due to the lack of precision in estimating the pulmonary artery pressure (reported range -19 mmHg to 18 mmHg) [58]. Six cohort studies including 1045 patients after an episode of acute PE reported the incidence of CTEPH using echocardiography as the first diagnostic test. For every correct diagnosis of CTEPH, echocardiography appeared to be false positive in three patients, who were consequently incorrectly referred for further invasive diagnostic tests (**Table 2**) [19, 37, 59-62]. Also, performing echocardiography in all patients with a history of acute PE has been shown to be cost-ineffective due to the low diagnostic yield of less than 1% [19]. Lastly, in patients with severe tricuspid regurgitation, transthoracic echocardiography cannot be used to exclude CTEPH [2]. For all above reasons, the ESC

Table 2. Post PE patients screened for CTEPH with echocardiography.

Article	Number of patients screened with echocardiography	Number of patients with an abnormal echocardiography result	Number of patients diagnosed with CTEPH (n, %)
Giuliani *et al* 2014[59]	111	15	5 (33)
Guerin *et al* 2014[37]	146	8	7 (88)
Kayaalp *et al* 2014[61]	85	31	5 (6)
Klok *et al* 2015[60]	134	25	4 (16)
Klok *et al* 2010[19]	459	44	6 (14)
Marti *et al* 2010[62]	110	23	10 (44)
Total	1045	146	37 (25)

Note: PE: pulmonary embolism. CTEPH: chronic thromboembolic pulmonary hypertension.

guideline recommend against routine application of all patients who are treated for acute PE to transthoracic echocardiography during follow-up [2].

V/Q lung scintigraphy

Multiple wedge-shaped perfusion defects with normal ventilation scan is typical for CTEPH while a normal scan results virtually rules out CTEPH. Previous studies have reported that in patients suspected of having PH, V/Q lung scintigraphy has a sensitivity of 96%-100% and a specificity of 86%-95% for detection of CTEPH using RHC as diagnostic standard [40-42]. However it has been estimated that 10-30% of PE patients have persistent perfusion defects despite adequate anticoagulant treatment, contributing to an average specificity of V/Q scintigraphy for CTEPH in unselected PE survivors [22, 63]. Taking the costs and associated radiation exposure [64] into account, this imaging modality cannot be recommended as a first-line routine screening tool for CTEPH in all PE survivors.

CT pulmonary angiography

CTPA is considered suggestive of CTEPH if it shows intravascular webs, recanalized thrombi, perfusion abnormalities or vascular strictures. In general, CTPA detects less residual PE than V/Q lung scintigraphy [65] and CTPA is more widely available and less costly. Even so, the sensitivity of CTPA is lower than that of V/Q lung scintigraphy, i.e. 51-92% using RHC as diagnostic standard [40, 41]. Consequently, a normal CTPA cannot rule out CTEPH. Also, the subtle characteristics of CTEPH are quite different from those of acute PE and may be misinterpreted by physicians lacking experience in the imaging of CTEPH. Moreover, the radiation exposure of CTPA exceeds that of V/Q lung scintigraphy. In conclusion, CTPA is not the optimal screening instrument for CTEPH after acute PE and guidelines recommend against routine CTPA in the clinical course of acute PE [66].

ECG

Several ECG abnormalities suggestive of the presence of PH include right axis derivation, right ventricular hypertrophy, right ventricular strain, right bundle branch block and QTc prolongation [2]. Conventional ECG assessment however lacks sufficient sensitivity and is not recommended as a screening tool for the detection of PH or CTEPH according to current guidelines [2, 67]. Interestingly, both the combination of several ECG variables as well as three-dimensional electrocardiography, i.e. electrocardiogram-derived ventricular gradient, have been suggested to be sensitive to early changes in right ventricular afterload as well as to clinically overt PH (sensitivity 89% and 97% respectively) [67, 68]. Confirmation of this high sensitivity for PH of both in large studies is however lacking.

Biomarkers

A wide variety of biomarkers have been explored for their potential to diagnose or screen for PH and CTEPH [2, 69]. No valid biomarker for CTEPH or vascular remodelling has however been identified. N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) is the only biomarker that is being widely used in diagnostic and therapeutic work-up of suspected PH, although it has been shown that it lacks sensitivity as well as specificity to function as stand-alone test for PH or CTEPH screening [2].

Combination of ECG and biomarkers

The combination of ECG and biomarker assessment as diagnostic test for PH has been evaluated in several settings. In one study, none of the 251 patients referred for suspicion of pre-capillary PH was diagnosed with PH in the absence of both a right ventricular strain pattern on ECG and elevated NT-proBNP [70]. In another study, it was shown that ECG assessment (right axis) and NT-proBNP measurement (threshold 100 pg/ml) are major components of a non-invasive algorithm that accurately excludes precapillary PH in patients with systemic sclerosis [5].

The combination of ECG and biomarker assessment has also been studied for its ability to rule out CTEPH. In a case control study, several combinations of ECG characteristics and biomarkers were evaluated to distinguish patients with the post-PE syndrome without CTEPH from patients with confirmed CTEPH [69]. The so called 'CTEPH rule out criteria' consisting of a normal NT-proBNP test result in combination with the absence of three specific electrocardiographic characteristics of right ventricular overload (rSR' or RSr' pattern in lead V1; R:S >1in lead V1 with R >0.5mV and QRS axis >90°; **Figure 1**) were found to be the optimal combination for this purpose, with a sensitivity of 94% (95% confidence interval (CI) 86-98%) and a specificity of 65% (95%CI 56-72%). The area under the receiver-operator-characteristic curve was 0.80 (95%CI 0.74-0.85%) for the diagnosis of CTEPH. Even with high CTEPH prevalences of up to 10%, the negative predictive value of the 'CTEPH rule out criteria' were very high (99%, 95%CI 97-100%).

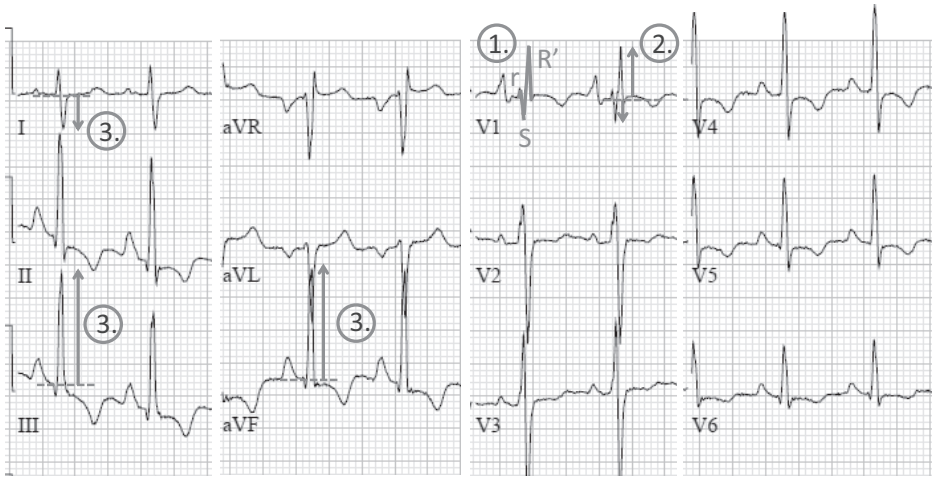


Figure 1. ECG demonstrating the three specific electrocardiographic characteristics of right ventricular overload, the 'CTEPH rule out criteria' .1) Right bundle branch block: rSR' or RSr' pattern in lead V1 with a QRS duration ≥ 120ms; 2) R:S >1 in lead V1 with R>0.5mV and 3) Right QRS axis deviation QRS axis >90°.
Note: CTEPH: chronic thromboembolic pulmonary hypertension. ECG: electrocardiography.

The diagnostic accuracy as well as the reproducibility of the 'CTEPH rule out criteria' were recently subjected to external validation in a real-world cohort of PE patients: inter-observer agreement for the adjudication of the ECG characteristics was found to be excellent (kappa-statistic 0.97) and the sensitivity for CTEPH was 100% [60]. A total of 47% of all patients with a recent PE scored none of the 'CTEPH-rule out criteria' positive, of whom none were diagnosed with CTEPH. The high sensitivity of the 'rule-out criteria' comes however at cost of an average specificity and thus false positive results in up to 40% if all patients with one or more 'CTEPH-rule out criteria' criteria present are referred for echocardiography.

Clinical prediction score

In a recent patient-level meta-analysis including 772 PE-survivors without major cardiopulmonary comorbidities, a clinical prediction score for diagnosis of CTEPH after PE was developed, the so called 'CTEPH prediction score' [71]. Factors associated with the development of CTEPH were unprovoked PE, known hypothyroidism, symptom onset >2 weeks before PE diagnosis, right ventricular dysfunction on CT or echocardiography, known diabetes mellitus and thrombolytic therapy or embolectomy (**Table 3**), all scored at the moment of PE diagnosis. The CTEPH prediction score has a 2-level outcome, with 6 points or less indicating low-risk (73% of patients, 0.38% CTEPH incidence) and more than 6 points indicating high risk (27% of patients, 10% CTEPH incidence). The area under the receiver operating characteristic curve of this score was 0.89. The score still awaits external validation [71].

Table 3. CTEPH prediction score.

Unprovoked PE	+6 points
Known hypothyroidism	+3 points
Symptom onset > 2 weeks before PE diagnosis	+3 points
Right ventricular dysfunction on computed tomography or echocardiography	+2 points
Known diabetes mellitus	-3 points
Thrombolytic therapy or embolectomy for the acute PE event	-3 points

Note: Cut-off points: low risk (-6 to 6 points), high risk (>6 points).
CTEPH: chronic thromboembolic pulmonary hypertension. PE: pulmonary embolism.

Combining the 'CTEPH prediction score' with the 'rule-out criteria' might constitute a feasible and cost-effective strategy for standardized follow-up after acute PE. At present, this screening algorithm is being evaluated in an international multicentre prospective management study (Clinical Trials.gov identifier NCT02555137). This study will likely answer the question whether the implementation of screening will lead to an earlier CTEPH diagnosis.

THE COSTS OF CASE-FINDING SHOULD BE ECONOMICALLY BALANCED IN RELATION TO POSSIBLE EXPENDITURE ON MEDICAL CARE AS A WHOLE AND CASE-FINDING SHOULD BE A CONTINUING PROCESS AND NOT A "ONCE AND FOR ALL" PROJECT.

As outlined above, studies focussing on the cost-effectiveness of any screening strategy are currently unavailable. Even so, especially screening algorithms that apply inexpensive non-invasive tests such as clinical probability assessment, ECG and/or NT-proBNP measurement, and if indeed associated with an earlier CTEPH diagnosis and increased likelihood of operability, may very well be associated with an overall reduction in costs and a beneficial incremental cost-effectiveness ratio. Considering the high incidence of acute PE, it will not be appropriate to actively recall every single patient with a history of PE to be screened for CTEPH in a single effort, but -if a screening strategy is proven accurate and cost-effective- it should become incorporated in routine care for all future PE patients.

CONCLUSION

Despite several compelling reasons for early identification of CTEPH and the current undesirable long diagnostic delay, firm conclusions to answer the question whether 'we

should screen for CTEPH after acute PE or not' cannot be drawn yet due to lack of conclusive evidence. Even so, bearing in mind the principles of Wilson and Jungner, screening for CTEPH fulfils the basic criteria with regard to magnitude and frequency of the health problem, the ability to recognize early and advanced disease stages, and the availability of diagnostic tests as well as effective treatment. The main questions that still need to be answered are 1) whether the implementation of one of the candidate screening tests indeed leads to an earlier CTEPH diagnosis, 2) whether earlier CTEPH diagnosis by screening is associated with better operability and improved prognosis and 3) whether CTEPH screening algorithms prove to be cost-effective. For now, we recommend not to screen unselected PE patients for CTEPH with echocardiography, CTPA or VQ lung scintigraphy in accordance with current European guidelines [2]. Clinicians should nonetheless maintain a low threshold of suspicion for CTEPH after acute PE and pursue targeted diagnostic tests in patients who report new or persistent dyspnoea after three months of anticoagulant treatment or symptoms of right heart failure. We speculate that in a few years from now, routine assessment of the presence of CTEPH with subsequent application of non-invasive tests in all patients with a recent PE diagnosis will become the standard of care.

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Chapter 3

Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism, a contemporary view on the published literature

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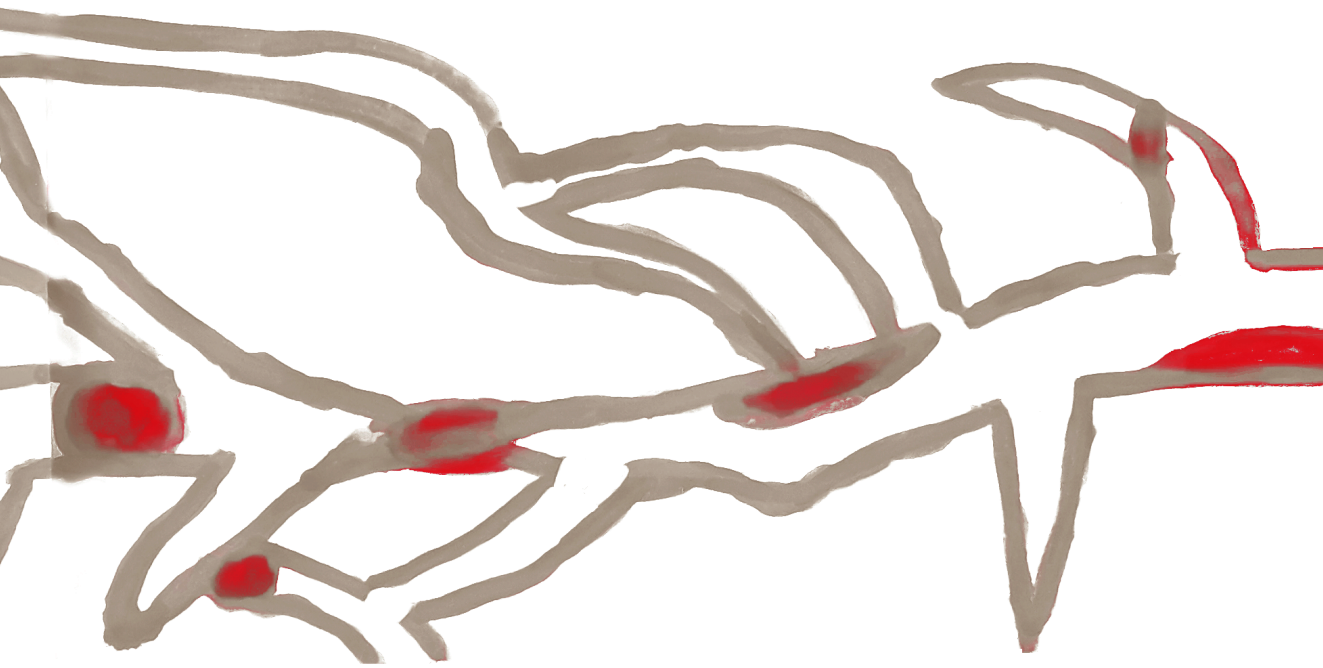

ABSTRACT

Introduction: The incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary embolism (PE) is relevant for management decisions but is currently unknown.

Methods: We performed a meta-analysis of studies including consecutive PE patients followed for CTEPH. Study cohorts were predefined as '*all comers*', '*survivors*' or '*survivors without major comorbidities*'. CTEPH incidences were calculated using random effects models.

Results: We selected 16 studies totalling 4047 PE patients who were mostly followed up for >2-year. In 1186 '*all comers*' (2 studies), the pooled CTEPH incidence was 0.56% (95%CI 0.1-1.0). In 999 '*survivors*' (4 studies), CTEPH incidence was 3.2% (95%CI 2.0-4.4). In 1775 '*survivors without major comorbidities*' (9 studies), CTEPH incidence was 2.8% (95%CI 1.5-4.1). Both recurrent venous thromboembolism and unprovoked PE were significantly associated with a higher risk of CTEPH, with Odds Ratios of 3.2 (95%CI 1.7-5.9) and 4.1 (95%CI 2.1-8.2) respectively. Pooled CTEPH incidence in 12 studies that did not use right heart catheterisation as diagnostic standard was 6.3% (95%CI 4.1-8.4).

Conclusion: The 0.56% incidence in the all-comer group probably provides the best reflection of the incidence of CTEPH after PE on population level. The ~3% incidences in the survivor categories may be more relevant for daily clinical practice. Studies that assessed CTEPH diagnosis by tests other than right heart catheterisation provide overestimated CTEPH incidences.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct form of pulmonary hypertension (PH). CTEPH is believed to arise from one or multiple endothelialized pulmonary thrombi that do not resolve but lead to chronic obstruction of the pulmonary artery tree, small-vessel arteriopathy, high pulmonary vascular resistance, PH and progressive right heart failure [1]. Patient prognosis is very poor when CTEPH is left untreated [2]. The only curative treatment option is surgical removal of these chronic thrombi with pulmonary endarterectomy (PEA) [1, 3]. If PEA is not feasible or fails to significantly reduce the pulmonary artery pressure, the patient's prognosis is poor. Operability of a patient depends among others factors on the presence of more advanced distal pulmonary artery remodelling, a feature that is less expected if CTEPH is diagnosed early. Also, the duration between last pulmonary embolism (PE) and PEA was found to be a risk factor for in-hospital mortality [4]. Hence, early diagnosis is crucial for optimal treatment and a favourable outcome.

Early CTEPH diagnosis, however, has proven to be a major clinical challenge. This is demonstrated by a staggering median diagnostic delay of 14 months demonstrated in the European CTEPH registry [5]. One explanation for this delay could be that symptoms of CTEPH are largely non-specific. Patients can even remain asymptomatic or do not mention their symptoms for months despite the presence of relevant PH [1, 5]. Also, validated cost-effective CTEPH screening tools remain unavailable to date. The incidence of CTEPH after symptomatic acute PE is not exactly known and is reported to range from 0.1% to 11.8% [6-9]. More precise knowledge of the incidence of CTEPH after acute PE is clearly relevant for defining the appropriate long-term management of acute PE. An incidence of 10% or higher would certainly warrant a standardized screening protocol for CTEPH, whereas an incidence of 0.1% or lower would not.

The notable wide range in reported incidences could be caused by major differences in the selection of the studied patient populations. For instance, most studies focussed on smaller subgroups of PE patients selected by the presence or absence of thrombotic risk factors, previous venous thromboembolism (VTE) and/or absence of cardiopulmonary comorbidities. In addition and importantly, in several reports the CTEPH diagnosis was not based on the diagnostic gold standard, i.e. right heart catheterisation (RHC) [3].

We aimed to gain an accurate overview in the variety of reported incidences of CTEPH after acute PE in different patient subgroups. To do so, we conducted a systematic review and meta-analysis of the literature focussing on those studies that applied validated diagnostic criteria of CTEPH according to current guideline recommendations [3].

METHODS

Data sources and literature search

We conducted a search for all relevant publications in PubMed, MEDLINE, Embase, Web of Science, Cochrane, CINAHL, Academic Search Premier and Science Direct. We performed our search in August 2015 with a search string focusing on 'chronic thromboembolic pulmonary hypertension,' 'pulmonary embolism,' 'thromboembolism,' 'incidence' and 'risk' (**Supplementary material**). These key words were database-specifically translated. We additionally performed a manual search of references of the identified relevant original and review articles.

Study selection, data extraction and quality assessment

Search results were combined and duplicates were removed. Studies were screened for relevance by two independent reviewers (Y. E-V and F.K), on the basis of title and abstract. Discrepancies were resolved by consensus or by contacting a third reviewer (S.C). Full-text articles or conference abstracts in the English or Dutch language identified by either reviewer as potentially relevant were retrieved for further evaluation. We did not apply any time limitations. Final selection of studies for the meta-analysis was restricted to cohort studies of patients with an objectified index diagnosis of the first or recurrent acute PE episode, who were followed for the development of CTEPH for a period of six months or longer and that explicitly reported the incidence of CTEPH.

The PRISMA statement [10] was used as a basis for reporting our systematic review. Data extraction was performed by two reviewers (Y. E-V and F.K). For each included study, we extracted the first author's name and year of publication, study design (prospective or retrospective), setting of the study (single- or multicentre), number of patients in the index cohort, number of patients who were followed for the occurrence of CTEPH, number of patients with a recurrent venous thromboembolic event, number of patients with unprovoked PE, the method of selection of patients for assessment of CTEPH (all patients or only those with specific signs and symptoms), the primary test for assessment of CTEPH, the applied gold standard for CTEPH diagnosis, the total duration of follow up, and finally the incidence of CTEPH as reported by the authors.

For included studies, the risk of bias was evaluated in accordance with the Cochrane Collaboration's tool for assessing risk of bias and the PRISMA statement [10, 11]. We focussed on the following criteria: 1) pre-specified study protocol, 2) clear description of inclusion and exclusion criteria, 3) inclusion of consecutive patients, 4) objectified diagnosis of PE and CTEPH based on the results of a RHC according to current guidelines [3, 12], 5) adequate anticoagulant treatment according to international standards, 6) loss to follow up, and 7) assessment of the primary endpoint in all patients. Only studies with a low risk of bias were included in the meta-analysis.

Study outcomes and definitions

Our primary aim was to determine the incidence of CTEPH after acute PE in three predefined cohort subtypes: 1) *'all comers'* (i.e. all consecutive patients with symptomatic PE, no exclusion criteria), 2) *'survivors'* (i.e. all consecutive patients with symptomatic PE who were alive after an initial treatment period of 6 months), and 3) *'survivors without major comorbidity'* (i.e. all consecutive patients with symptomatic PE who were alive after an initial treatment period of 6 months and did not have predefined significant cardiopulmonary, oncologic or rheumatologic comorbidities).

Our secondary aim was to determine the association of unprovoked PE and recurrent VTE with the incidence of CTEPH. Unprovoked PE was defined as VTE occurring without any of the following risk factors: major surgery or immobilization for at least 3 days within 4 weeks preceding the PE diagnosis, active malignancy (a diagnosis of cancer within 6 months prior to enrolment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer), a recent long flight (more than 6 hours) in the past 3 weeks, being pregnant or in the peripartum period, and use of oral contraceptives or hormone replacement therapy. Recurrent VTE was defined when a documented prior episode of objectified deep vein thrombosis or PE was available [12]. We additionally aimed to evaluate the method of CTEPH screening (application of a CTEPH specific diagnostic test in all patients or only in those who displayed or reported signs and symptoms suggestive of CTEPH) on the incidence of CTEPH. To compare the reported incidences in studies that diagnosed CTEPH based on the results of a RHC we aimed to establish the reported incidence of CTEPH after acute PE in studies in which the diagnosis of CTEPH was based on other diagnostic criteria.

Statistical analysis

The incidence was calculated by dividing the number of confirmed cases of CTEPH during follow-up by the number of patients in the cohort initially selected for screening. For the calculation of the pooled incidences of CTEPH in the three cohort subtypes, we applied a random effects model according to DerSimonian and Laird [13]. To assess the association for unprovoked PE and recurrent VTE with CTEPH, we calculated the pooled odds ratios (OR) and 95% confidence intervals (95%CI) for both settings, applying the same random effects model to all studies that reported the study outcomes for these subgroups separately, irrespective of the cohort subtype. We assessed heterogeneity across the various cohort studies by calculating the I^2 statistic. Heterogeneity was defined as low in when I^2 <25%, as intermediate when I^2 =25-75% and as high when I^2 >75% [14]. The presence of publication bias was evaluated using funnel plot analysis. All analyses were performed in Stata 14.0 (Stata Corp., college Station, TX USA).

RESULTS

Study selection

The initial search identified 477 records in PubMed, 381 records in Medline, 555 records in EMBASE, 302 records in Web of Science, 19 records in the Cochrane Library, 36 records in CINAHL, 85 records in Academic Search Premier and 108 records in Science Direct, resulting in a total of 1062 unique references, including 170 meeting abstracts. After the first screening of title and abstract, 991 records were excluded leaving 71 for more detailed evaluation. An additional 31 studies were excluded after full review: 18 concerned a cohort that (partly) overlapped with other cohorts identified in our search strategy, 7 studies did not provide the study endpoint, 3 were review articles, 2 studies included fewer than 20 patients, and in one study the CTEPH diagnosis was based on International Classification of Diseases insurance codes. We identified one additional relevant study by reviewing the references of the included studies. Therefore, 41 studies were fully assessed for study quality (**Figure 1**) [7, 9, 15-53]. Of those, 13 had intermediate to high risk of bias and were thus not included in the meta-analysis. The evaluation of quality of bias is shown in **Table 1**.

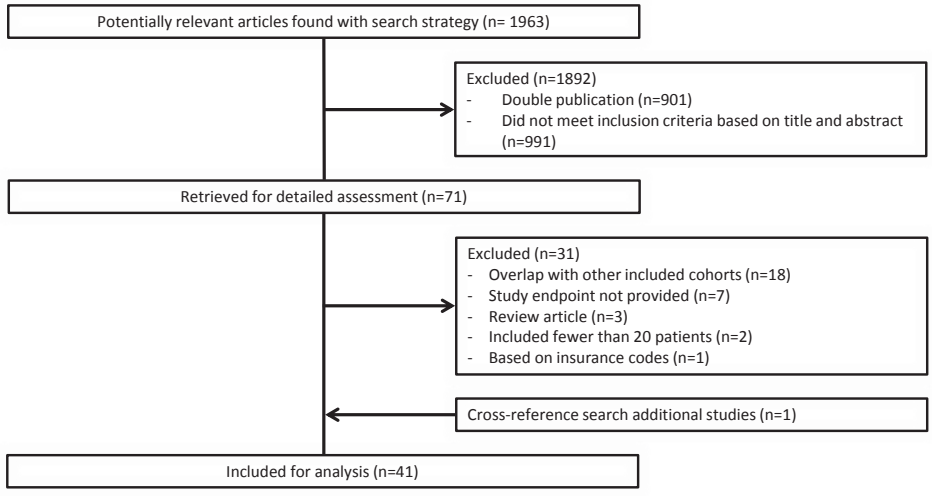

Figure 1. Flow diagram of study selection.

Included studies

All studies were cohort studies including consecutive patients with an episode of acute PE. Sixteen studies confirmed the presence of CTEPH with RHC [7, 17, 18, 22, 27, 28, 30, 31, 33-35, 38, 40, 44, 46, 50] and 12 applied other tests as diagnostic standard (**Table 1**) [9, 15, 19, 21, 23, 26, 37, 41, 43, 45, 48, 49].

The 16 articles using RHC were published between 2004 [7] and 2015 [35], and included 4047 patients selected for screening (range 87-866 per study) [18, 34]. The follow-up duration varied between ≥3 months [22] to 8 years [31], with most studies reporting a follow-up period of 2 years (**Table 2**). The diagnostic process of selecting patients for RHC differed among the selected studies. In nine studies all included patients were screened by echocardiography [18, 27, 28, 33-35, 38, 44, 50] and in one study all patients underwent a lung scintigraphy investigation as initial step [40]. In five other studies, echocardiography was only performed if dyspnoea was reported by the individual patients [7, 17, 30, 31, 46]. One study applied the need for further investigation based on a not further defined clinical assessment prior to RHC [22]. Three studies targeted patients with a first PE (595 patients in total) [17, 44, 50] and one study included 87 patients with recurrent VTE only [18]. The other studies focussed on a combination of first and recurrent PE. The general characteristics of the studies are shown in **Table 2**.

Primary analysis: meta-analysis of incidence of CTEPH

The overall weighted pooled incidence of CTEPH across all 16 studies was 2.3% (95%CI 1.5-3.1; I^2= 70.3; **Figures 2 and 3**). Two studies reported the CTEPH incidences in 1186 *'all comers'* who had been followed for 2-3 years [34, 40]. The weighted pooled incidence of CTEPH in the *'all comers'* was 0.56% (95%CI 0.13-0.98; I^2=98.3%). Four studies focussed on unselected consecutive patients who were alive after an initial treatment period of at least 3 months [22, 30, 31, 35]. The weighted pooled incidence of CTEPH in these 999 *'survivors'* followed for a period varying from 3 months to 8 years was 3.2% (95%CI 2.0-4.4; I^2= 7.0%). One additional study in *'survivors'* included 87 patients with recurrent PE only, of whom 5.7% (95%CI 2.5-12.8) were diagnosed with CTEPH after a 22-month follow-up period [18]. Lastly, nine studies focussed on *'survivors without major comorbidity'* [7, 17, 27, 28, 33, 38, 44, 46, 50]. In these studies, 1775 patients were followed for 24 months or longer. Their weighted pooled incidence of CTEPH was 2.8% (95%CI 1.5-4.1; I^2=74.0%) (**Figures 2 and 3**). Overall, there was no difference in the incidence of CTEPH between the studies that screened all included patients versus studies that only screened patients who developed symptoms during the follow-up period. Also, a sensitivity analysis confined to studies with ~2 years of follow-up did not yield different incidences. Funnel plot analysis illustrated asymmetry which based on the distribution of the studies, is most likely due to between-study heterogeneity (**Figure 4**).

Secondary analysis: effect of unprovoked and recurrent PE

In six of the 16 included articles, the incidences of CTEPH were provided for patients with unprovoked and provoked PE separately [7, 17, 34, 35, 38, 44]. In all these studies, the incidence of CTEPH was higher after unprovoked PE versus provoked PE, for a pooled weighted OR of 4.1 (95%CI 2.1-8.2; I^2=0.0%). A total of seven articles allowed for the

Table 1. Evaluation of presence of bias for all 41 identified relevant studies.

	Assessment of relevance				Assessment of bias						Study included	Study included
					Incomplete outcome data		Selective outcome reporting	Representative study sample	Quality of CTEPH diagnosis	Overall judgement		
Article	Cohort of consecutive patients	Confirmed PE	Follow-up for CTEPH	CTEPH incidence reported	Described follow-up of all patients	Missing outcome data <5%	Reporting study protocol and all pre-specified outcomes	Described inclusion and exclusion criteria	CTEPH diagnosed according to current guidelines	Bias in a certain direction?	CTEPH diagnosed according to current guidelines	CTEPH not diagnosed according to current guidelines
Abul *et al* 2014 [15]	○	○	○	○	○	○	○	○	●	●	●	○‡
Barros *et al* 2013 [16]	○	○	○	○	○	●	○	●	●	●	●	●
Becattini *et al* 2006 [17]	○	○	○	○	○	●	○	○	○	○	○	●
Berghaus *et al* 2011 [18]	○	○	○	○	○	●	○	○	○	○	○	●
Beyer-Westendorf *et al* 2013 [19]	○	○	○	○	○	●	○	○	●	●	●	○
Casazza *et al* 2014 [20]	○	○	○	○	●	●	●	○	○	○	●	●
Choi *et al* 2014 [21] *	○	○	○	○	○	○	○	○	●	●	●	○‡
De Foneska *et al* 2014 [22] *	○	◍†	○	○	○	○	○	○	○	○	○	●
Dentali *et al* 2009 [23]	○	○	○	○	○	○	○	○	●	●	●	○‡
Dutt *et al* 2013 [24]	○	○	○	○	○	●	●	●	●	●	●	●
Fagerbrink *et al* 2011 [25]*	○	◍†	○	○	●	●	○	●	○	●	●	●
Gary *et al* 2012 [26]	◍	○	○	○	○	○	○	○	●	●	●	○
Giuliani *et al* 2014 [27]	○	○	○	○	○	○	○	○	○	○	○	●
Golpe *et al* 2010 [9]	○	○	○	○	○	○	○	○	●	●	●	○
Guerin *et al* 2014 [28]	○	○	○	○	○	●	○	○	○	○	○	●
Hall *et al* 1977 [29]	○	○	○	○	○	●	●	●	○	●	●	●
Held *et al* 2014[30]£	○	○	○	○	○	◍	○	○	○	○	○	●
Hogele *et al* 2014 [31]*	○	◍†	○	○	○	○	○	●	○	○	○	●
Jie *et al* 2011 [32]*	◍	○	○	○	○	●	●	●	●	●	●	●
Kayaalp *et al* 2014 [33]	○	◍†	○	○	●	●	○	○	○	○	○	●
Klok *et al* 2010 [34]	○	○	○	○	○	○	○	○	○	○	○	●
Klok *et al* 2015 [35]	○	○	○	○	○	●	○	○	○	○	○	●
KolatKirkpantur *et al* 2004 [36]	◍	◍†	○	○	○	◍	●	●	●	●	●	●

Table 1. Evaluation of presence of bias for all 41 identified relevant studies. (continued)

	Assessment of relevance				Assessment of bias						Study included	Study included
					Incomplete outcome data		Selective outcome reporting	Representative study sample	Quality of CTEPH diagnosis	Overall judgement		
Article	Cohort of consecutive patients	Confirmed PE	Follow-up for CTEPH	CTEPH incidence reported	Described follow-up of all patients	Missing outcome data <5%	Reporting study protocol and all pre-specified outcomes	Described inclusion and exclusion criteria	CTEPH diagnosed according to current guidelines	Bias in a certain direction?	CTEPH diagnosed according to current guidelines	CTEPH not diagnosed according to current guidelines
Korkmaz *et al* 2012 [37]	○	○	○	○	○	○	○	○	●	●	●	○‡
Marti *et al* 2010 [38]	○	○	○	○	○	●	○	○	○	○	○	●
Mi *et al* 2012 [39]*¥	◍	○	○	○	●	●	○	●	◍	●	●	●
Miniati *et al* 2006 [40]	○	○	○	○	●	○	○	○	○	○	○	●
Otero *et al* 2011 [41]	○	○	○	○	○	●	○	○	●	●	●	○
Palwatwinchai *et al* 2000 [42] *	◍	◍†	○	○	◍	◍	○	●	◍	●	●	●
Pengo *et al* 2004 [7]	○	○	○	○	○	○	○	○	○	○	○	●
Pesavento *et al* 2015 [43] *	○	○	○	○	●	●	○	○	●	●	●	○‡
Poli *et al* 2010 [44]	○	○	○	○	○	●	○	○	○	○	○	●
Ribeiro *et al* 1999 [45]	◍	○	○	○	○	●	○	○	●	●	●	○
Surie *et al* 2010 [46]	○	○	○	○	○	●	○	○	○	○	○	●
Thomas *et al* 2012 [47]*	○	◍†	○	○	●	◍	●	●	●	●	●	●
Tosun *et al* 2014 [48]*	◍	○	○	○	○	○	○	○	●	●	●	○
Vanni *et al* 2010 [49]*	○	◍†	○	○	○	○	○	○	●	●	●	○
Vavera *et al* 2014 [50]	○	○	○	○	○	●	○	○	○	○	○	●
Wilczynska *et al* 2011 [51]*	◍	◍†	○	○	●	●	●	●	○	●	●	●
Xi *et al* 2014 [52]	○	○	○	○	●	◍	●	○	○	●	●	●
Yang *et al* 2014 [53]*	○	◍†	○	○	●	◍	●	●	○	●	●	●

Note**:** Data are presented as the risk of bias. white: low risk of bias; black: risk of bias; grey: uncertain risk of bias.

PE: pulmonary embolism; CTEPH: chronic thromboembolic pulmonary hypertension. * Only the abstract was available; £ Study is still recruiting patients, data collection not finalized yet; ¥ Article in Chinese; † diagnostic criteria for PE not specified; ‡ Number of patients with abnormal echocardiography not reported.

comparison of first PE versus recurrent VTE [7, 28, 34, 35, 38, 40, 46]. As with unprovoked PE, recurrent VTE was associated with a higher CTEPH incidence than after a first PE for a weighted pooled OR of 3.2 (95%CI 1.7-5.9; I^2=0.0%; **Figure 3**).

Reported incidence of CTEPH not based on RHC

Twelve additional studies that reported the incidence of CTEPH after PE, but failed to confirm this diagnosis by RHC, were selected (**Table 1**). The overall pooled CTEPH incidence in these studies was 6.3% (95%CI 4.1-8.4; I^2=91.0%). In six of these 12 studies CTEPH was diagnosed by echocardiography only, for a pooled CTEPH incidence of 9.1% (95%CI 4.1-14.0; I^2=94.4%) (**Supplementary figure S1**) [9, 19, 26, 41, 45, 48].

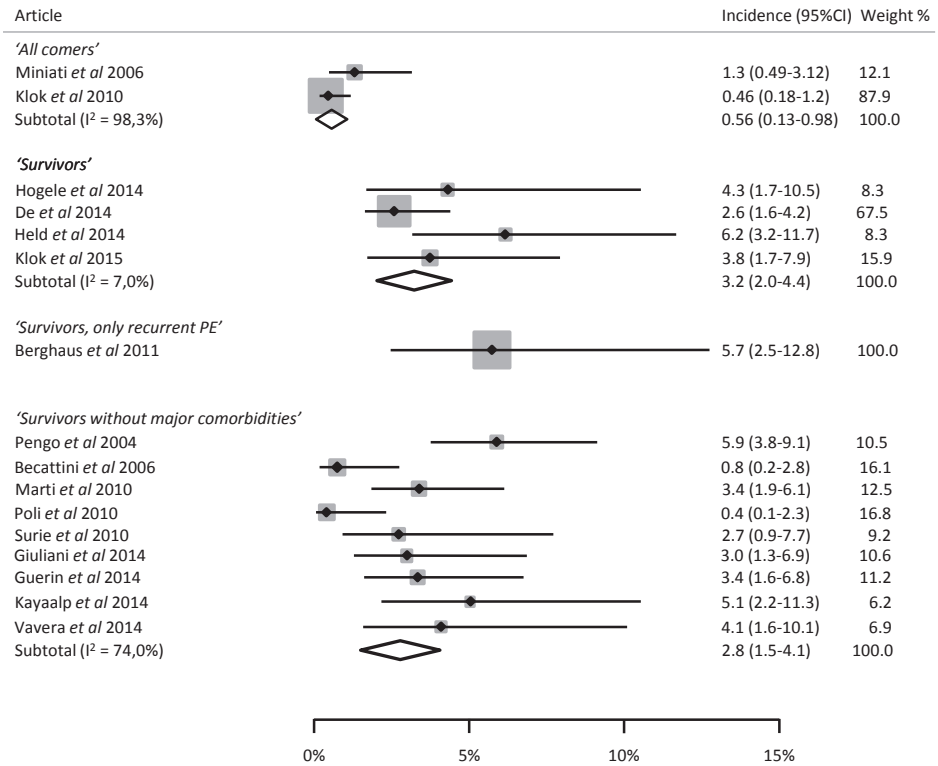

Figure 2. Meta-analysis of the incidences of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism diagnosed with right heart catheterisation.

DISCUSSION

This systematic review and meta-analysis summarizes the existing literature on the incidence of CTEPH after acute PE. Our main findings are incidences of 0.56%, 3.2% and

Table 2. Characteristics of the included articles for the meta-analysis of the primary endpoint.

	Analysis in pro- / retrospective	Single / multicentre	Number of patients selected for screening	Follow up duration months	Study design	Echo criteria	Number of patients with CTEPH
'All comers'							
Miniati *et al* 2006 [40]	prospective	single	320	0-4.8	A	*not specified*	4
Klok *et al* 2010 [34]	prospective	multi	866	34 †	A	C	4
'Survivors'							
Hogele *et al* 2014 [31]	*not specified*	single	93	96	B	D	4
De Foneska *et al* 2014 [22]	retrospective	single	616	3 £	B	*not specified*	16
Held *et al* 2014 [30]	prospective	single	130	3-6	B	E	8
Klok *et al* 2015 [35]	prospective	single	160	7	A	F	6
'Survivors, only recurrent PE'							
Berghaus *et al* 2011 [18]	retrospective	single	87	22.5 ¥	A	G	5
'Survivors without major comorbidities'							
Pengo *et al* 2004 [7]	prospective	single	314	94 ¥	B	*not specified*	18
Becattini *et al* 2006 [17]	prospective	multi	259	46 †	B	H	2
Marti *et al* 2010 [38]	prospective	single	294	24	A	I	10
Poli *et al* 2010 [44]	prospective	single	239	36 ¥	A	J	1
Surie *et al* 2010 [46]	retrospective	single	110	24-48	B	D	3
Giuliani *et al* 2014 [27]	retrospective	single	164	24 †	A	I	5
Guerin *et al* 2014 [28]	prospective	multi	208	26 ¥	B	K	7
Kayaalp *et al* 2014 [33]	prospective	single	99	12-24	A	*not specified*	5
Vavera *et al* 2014 [50]	prospective	single	97	24	A	*not specified*	2

Note**:** CTEPH: chronic thromboembolic pulmonary hypertension; PE: pulmonary embolism; SPAP: systolic pulmonary artery pressure; MPAP: mean pulmonary artery pressure; RVSP: right ventricular systolic pressure; ePASP: estimated pulmonary arterial systolic pressure PAP: pulmonary artery pressure; rV-rA: right ventricle – right atrial; VTR: velocity of the tricuspid regurgitation; VPR: velocity of pulmonary regurgitation. * range in years; † Average; £ Approximately; ¥ Median; A: all consecutive patients with PE were screened for CTEPH; B: Only patients with symptoms were screened for CTEPH; C: SPAP ≥ 35 or MPAP ≥ 25 or 4 other criteria, needed was 1; D SPAP >40; E: RVSP ≥ 35; F: SPAP >36 or 2 other criteria; G: ePASP >50 mmHg; H: PASP >40mmHg, PAP >30; I: PASP ≥ 40mmHg; J: rV-rA gradient >35; K: VTR ≥ 2,8m/sec or proto-diastolic VPR ≥ 2,0 /s and end-diastolic VPR ≥1,2m/s.

2.8% in the three predefined subpopulations that we focussed on: '*all comers*', '*survivors*' and '*survivors without major comorbidities*'. In accordance with current knowledge [54], we identified unprovoked PE and recurrent VTE as strong risk factors for the development of CTEPH. Lastly, we showed that studies assessing the CTEPH diagnosis with other tests than RHC provide an overestimation of CTEPH incidence (pooled incidence 6.3%), especially those using echocardiographic assessment only (pooled incidence 9.1%).

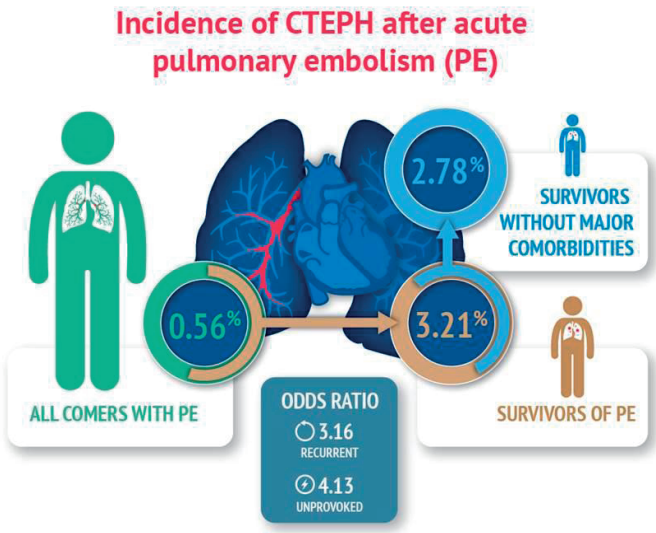

Figure 3. Infographic of primary and secondary study outcomes.
Note**:** PE: pulmonary embolism.

The pooled incidence of the '*all comers*' after a follow up period of 2-3 years was found to be 0.56%. This number represents the development of CTEPH in unselected patients after a PE diagnosis within this period and best reflects the incidence of CTEPH on population level, mostly because no selection criteria were applied in the relevant studies. Nonetheless, several factors could have influenced this number. The incidence of 0.56% could be an underestimation caused by patients that died or were lost to follow-up without being subjected to objective tests for CTEPH. On the other hand, this number could be an overestimation caused by the possibility that patients diagnosed with an acute PE had been misdiagnosed and already had CTEPH at baseline. This may be even more relevant to studies applying ventilation perfusion (VQ)-scintigraphy as primary diagnostic test for PE, because computed tomography (CT) can show signs of PH that will remain hidden on VQ-scintigraphy. Increasing evidence supports the hypothesis that CTEPH is often misclassified as acute PE [3, 28, 55, 56]. One of the included survivor studies addressed this issue with an echocardiography shortly after the PE diagnosis and a retrospective evaluation of the initial CT for signs of CTEPH at the time of the index PE. It appeared that 5 out of 7 patients diagnosed with CTEPH already had signs of the disease at the initial presentation [28].

Epidemiological studies in CTEPH patients further support the validity of the incidence of CTEPH in the '*all comers*' we describe. Reported annual incidence rates of confirmed CTEPH are 0.9, 4.0 and 5 per million adults in the western world [57-59]. Approximately 25% of these CTEPH patients lack a history of acute PE [5]. Considering the latter and a 1-per-1000 annual rate of PE, the estimated incidence of confirmed CTEPH after acute

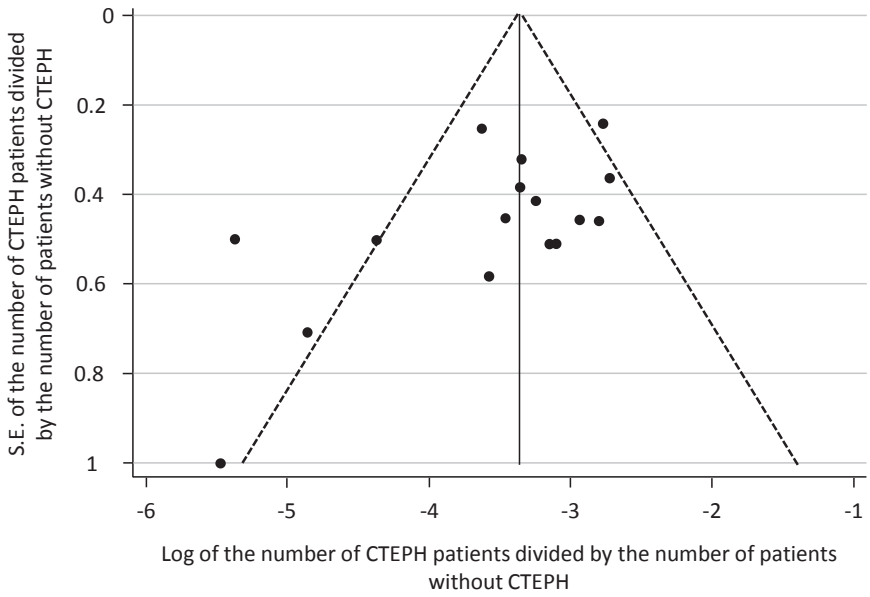

Figure 4. Funnel plot analysis with the log of the number of patients with CTEPH divided by the number of patients without CTEPH.
Note**:** CTEPH: chronic thromboembolic pulmonary hypertension; SE: Standard Error.

PE ranges between 0.1 and 0.4%. Of note, it is generally accepted that CTEPH is underdiagnosed in current clinical practice [60]. Taking the latter into account, the upper limit of this range is likely more accurate.

The incidence of 3.2% in the '*survivor*' cohort and 2.8% in the '*survivor without major comorbidities'* cohort may be more relevant for clinical practice because these are the patients who visit the outpatient clinic of our daily practices. With a 0.56% incidence in '*all comers*' and considering the number of patients who died or were lost to follow-up without being subjected to objective tests for CTEPH, we expected to find an incidence of CTEPH between 1.2 and 1.8%. However, we observed a five-fold higher incidence in the survivor cohorts instead. The main reason for an overestimation of the CTEPH incidence in the *'survivor'* cohorts is that patients with unprovoked PE were overrepresented in the *'survivor'* cohort (48% versus 36% in the '*all comer'* cohort), indicating patient selection towards a higher CTEPH risk profile. Other, less clear patient selection differences between all-comer patient cohorts and survivor patient cohorts could have further contributed to an overestimation of the CTEPH incidence in the latter, such as the exclusion of patients with high risk PE who were not excluded from the '*all-comer*' study cohorts but were mostly excluded from the studies evaluating the '*survivors*'. Also, misclassification of acute PE at baseline as described above may be more relevant for the *'survivor'* cohorts since VQ-scintigraphy was not applied as diagnostic test for PE in

the '*all comer*' cohorts, in contrast to the '*survivor cohorts*'. Of note, the differentiation of acute PE, CTEPH or subacute PE in pre-existing CTEPH is very difficult to make in clinical practice because PH is a common finding in acute PE and information on the preceding pulmonary hemodynamic status is lacking for most patients. Although no systematic search has ever been performed, perhaps extensive evaluation of the CT scans including actively looking for webs, bands, vascular strictures, recanalised thrombi and right ventricular hypertrophy, which are all findings of CTEPH and not acute PE, as well as monitoring of the hemodynamic recovery by sequential echocardiography in the weeks after treatment initiation may help the clinician to make the distinction. This would have to be the topic of further study.

We expected to find a higher incidence of CTEPH in the '*survivors without major comorbidities*' compared to the '*survivors*' because the presence of cardiopulmonary diseases may impede optimal diagnosis of CTEPH. Nevertheless, we did not find a difference in the pooled incidence of CTEPH between survivors with or without major comorbidities (3.2% versus 2.8%). In a recent study of the European CTEPH registry including 679 patients diagnosed with CTEPH, many indeed had a concomitant diagnosis of cancer (12.7%), of coronary disease and/or myocardial infarction (11.8%) and chronic obstructive pulmonary disease (9.5%) [5]. From this we conclude that CTEPH should be considered in all patients with CTEPH-associated symptoms despite any known other cardiopulmonary disease.

Interestingly, the reported incidences of CTEPH after acute PE in the studies that applied screening tests to all patients were not higher than in those that only screened patients who reported CTEPH-associated signs or symptoms throughout the study period. This could indicate that, although CTEPH can remain asymptomatic for months, all or almost all patients will become symptomatic at some point in the course of the disease. Notably, the studies that screened all patients and described whether the patients diagnosed with CTEPH had symptoms or not, reported that all CTEPH patients had mild to severe symptoms at the moment of diagnosis, and all were diagnosed within a period of 2 years from the PE diagnosis [18, 34, 38, 44]. Based on this observation one might argue that specific diagnostic tests for CTEPH need only be initiated when symptoms occur, as recommended by the European Society of Cardiology guideline [3]. On the other hand, the mean time to diagnosis may have been considerably shorter in the studies that screened all patients. This would support a strategy of screening patients independent of symptoms. Unfortunately, these relevant data could not be extracted from the included studies. Based on current analysis, no firm conclusions can be made on if, in whom, when and how screening for CTEPH should optimally be performed. An algorithm that was specifically designed for this purpose consisting of sequential application of a recently published clinical decision rule and the simple 'CTEPH rule-out' criteria, is being evaluated in an international multicentre prospective outcome study

(Clinical Trials.gov identifier NCT02555137) [35, 61, 62]. The results of this study will allow for more accurate recommendations with regard to optimal follow-up of patients with PE on the development of CTEPH.

Strengths of our analysis include the strict selection criteria applied, allowing for the pooling of high quality studies with adequate diagnosis of CTEPH. We also harmonized the calculation of the CTEPH incidences using identical criteria for each study. Further, we predefined three relevant subcategories and compared studies that did or did not use RHC to diagnose CTEPH. Lastly, our finding that unprovoked PE and recurrent VTE are risk factors for CTEPH are in accordance with the literature which underlines the validity of our work [54].

This meta-analysis has limitations as well. First as mentioned before CTEPH can be misclassified as acute PE [3, 28, 55, 56] although unfortunately we are not able to make this distinction in the information that was available from the studies. Of note, because CTEPH could have been present at baseline in some patients, the incidences found in our meta-analyses could actually reflect a combination of the incidence and prevalence of CTEPH. Second the duration of follow-up varied between the included studies. Because we did not have access to patient level data and the reporting of the follow-up time differed (means versus medians versus ranges), it was technically impossible to take individual follow-up time into account. Nonetheless, 12 of the 16 studies reported on a follow-up duration ≥2 years. As argued above, this period is likely to capture all cases of CTEPH. Third, the echocardiographic criteria for referral for RHC were slightly different across the studies, which could have induced misclassification and further patient selection. Fourth, we were not able to select the number of patients adequately treated with anticoagulants, because this was not reported in any of the studies. Inadequate anticoagulation may contribute to the development of CTEPH [63]. Fifth, despite categorizing the included studies in 3 subgroups, we only achieved relevant inter-study homogeneity for the cohort that included '*survivors*' (I^2 =7.0) [14]. The main reason this was not achieved in the *'all-comer'* cohort was the low number of two studies in this category. For the '*survivors without major comorbidities*', this lack of homogeneity was probably caused by important differences in the definition of major comorbidities among the studies. finally, by design, we were unable studying interesting patient groups such as those with cancer or systemic inflammatory disease [64].

In conclusion, the overall pooled incidence of CTEPH in the included studies was 2.3%. The incidence of CTEPH in '*all comer*' cohort was low (0.56%). This number provides the best estimation of the incidence of CTEPH on population level while the ~3% incidences in the survivor categories may be more relevant for daily clinical practice. Studies that assessed the CTEPH diagnosis by tests other than RHC provide overestimated CTEPH incidences.

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APPENDIX A: SEARCH STRATEGY

PubMed

('CTEPH'[tw] OR 'chronic thromboembolic pulmonary hypertension'[tw] OR chronic thromboembolic pulmonary hypertens*[tw] OR 'chronic thromboembolic pulmonary arterial hypertension'[tw] OR 'chronic thrombo-embolic pulmonary hypertension'[tw] OR chronic thrombo-embolic pulmonary hypertens*[tw] OR chronic major vessel thromboembolic pulmonary hypertens*[tw] OR 'chronic thromboembolic PH'[tw] OR 'chronic thrombo-embolic PH'[tw] OR 'chronic thromboembolic hypertension'[tw] OR 'chronic thrombo-embolic hypertension'[tw] OR ('chronic'[tw] AND (thromboembolic pulmonary hypertens*[tw] OR thrombo-embolic pulmonary hypertens*[tw])) OR (('chronic'[ti] AND (thromboembol*[ti] OR thrombo-embol*[ti]) AND pulmonary hypertens*[ti])) OR (('Chronic Disease'[mesh] AND 'Hypertension, Pulmonary'[mesh] AND 'Pulmonary Embolism'[mesh])) OR (('chronic'[tw] AND (thromboembol*[tw] OR thrombo-embol*[tw]) AND pulmonary hypertens*[tw])) OR ('Hypertension, Pulmonary'[mesh] AND 'Pulmonary Embolism'[mesh] AND 'Thromboembolism'[mesh]) OR (('Hypertension, Pulmonary'[majr] AND 'Pulmonary Embolism'[mesh]) OR ('Hypertension, Pulmonary'[mesh] AND 'Pulmonary Embolism'[majr]))) AND ('Incidence'[Mesh] OR 'incidence'[tw] OR incidence*[tw] OR 'Epidemiology'[Mesh] OR 'epidemiology'[Subheading] OR 'Risk Factors'[Mesh] OR 'Risk'[mesh] OR 'clinical profile'[tw] OR 'clinical profiles'[tw])

MEDLINE

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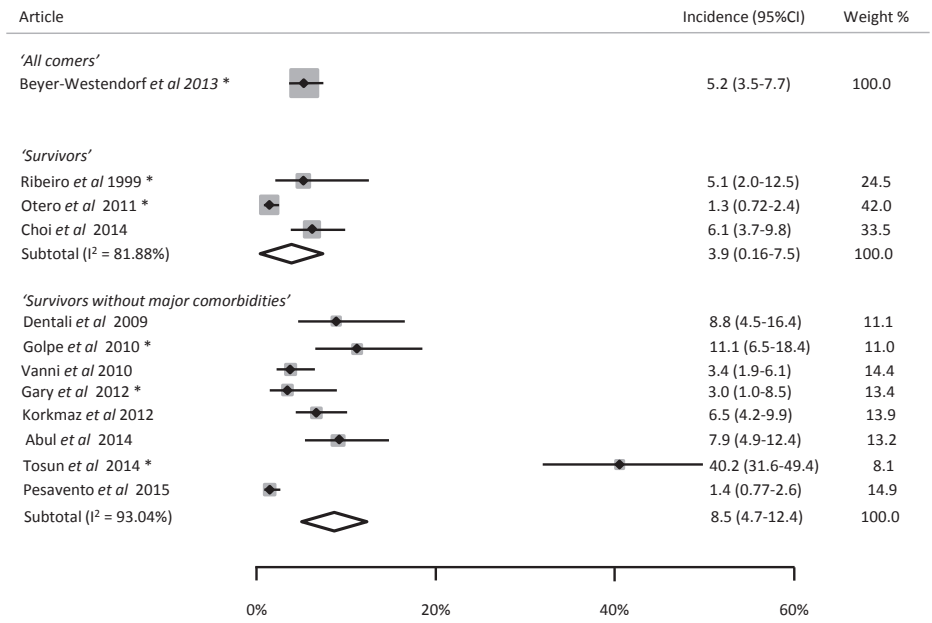

Appendix B. Meta-analysis of the incidences of CTEPH diagnosed with other diagnostic tests than RHC. Note**:** * CTEPH diagnosed by echocardiogram only; CTEPH: chronic thromboembolic pulmonary hypertension; RHC: right heart catheterization.

Chapter 4

Sensitivity of a simple non-invasive screening algorithm for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

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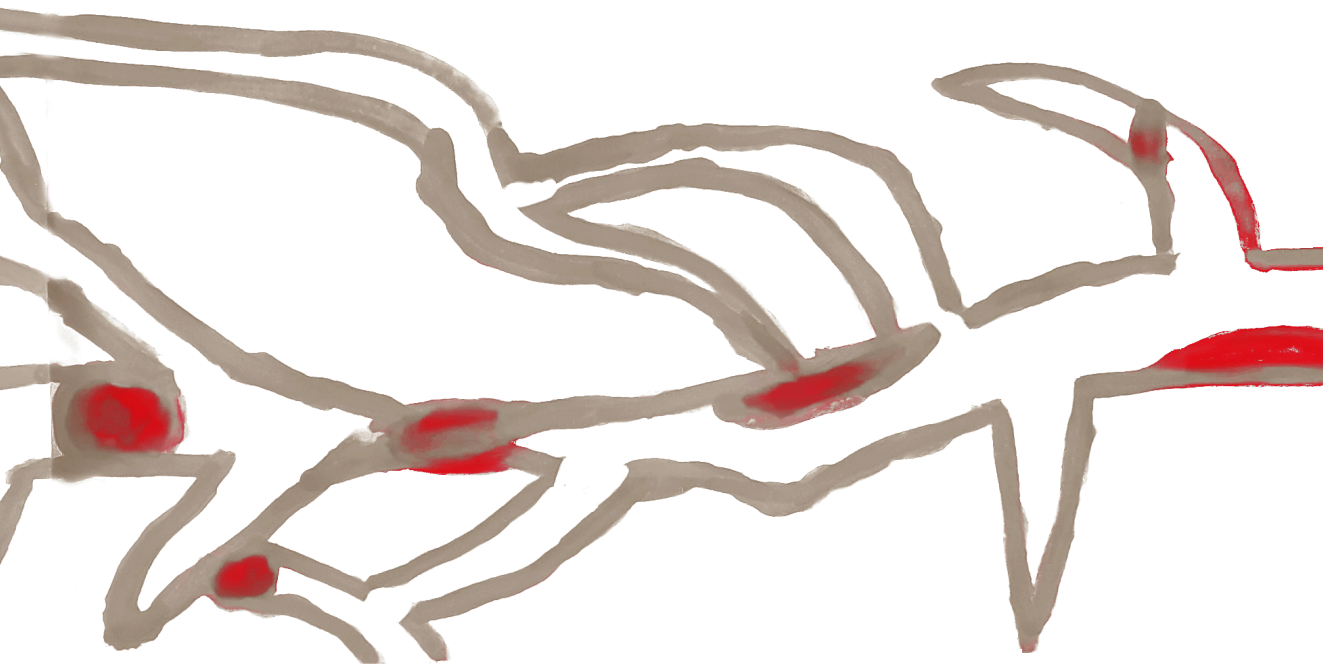

ABSTRACT

Background: Recently, we constructed a non-invasive screening algorithm aiming at earlier chronic thromboembolic pulmonary hypertension (CTEPH) detection after acute pulmonary embolism (PE), consisting of a prediction score and combined electrocardiogram (ECG)/ N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) assessment. The aim of this study was to confirm the algorithm's sensitivity for CTEPH detection and to evaluate the reproducibility of its individual items.

Methods: Two independent researchers calculated the prediction score in 54 consecutive patients with a history of acute PE and proven CTEPH based on clinical characteristics at PE diagnosis, and evaluated the ECG and NT-proBNP level assessed at the moment of CTEPH diagnosis. Interobserver agreement for assessment of the prediction score, right-to-left ventricle (RV/LV) diameter ratio measurement on computed tomography pulmonary angiography as well as ECG reading was evaluated by calculating Cohen's kappa statistics.

Results: Median time between PE diagnosis and presentation with CTEPH was 9 months (interquartile range 5-15). The sensitivity of the algorithm was found to be 91% (95%CI 79-97%), indicating that 27 of 30 cases of CTEPH would have been detected when applying the screening algorithm to 1000 random PE survivors with a 3% CTEPH incidence (projected negative predictive value 99.7%; 95%CI 99.1-99.9%). The interobserver agreement for calculating the prediction score, RV/LV diameter ratio measurement and ECG reading was excellent with a kappa of 0.96, 0.95 and 0.89, respectively.

Conclusion: The algorithm had a high sensitivity of 91% and was highly reproducible. Prospective validation of the algorithm in consecutive PE patients is required before it can be used in clinical practice.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious long-term complication of acute pulmonary embolism (PE) [1]. In CTEPH, persistent obstruction of the pulmonary arteries causes vascular remodelling, pulmonary hypertension (PH) and right heart ventricular failure. The natural course of CTEPH includes progressive involvement of distal pulmonary arteries due to thrombotic occlusion as well as secondary vasculopathy in the not-occluded arteries caused by redistribution of the blood flow via multiple anastomoses between the systemic and pulmonary circulation. CTEPH may be cured by pulmonary endarterectomy (PEA) [1, 2], whereas patients who are deemed inoperable, due to extensive involvement of distal pulmonary arteries, have a lower survival in the first 3 years following CTEPH diagnosis (70% versus 89%) [3]. Hence, early CTEPH diagnosis is of relevance for optimal treatment and patient outcome [2, 4, 5]. Notably, as recently demonstrated in the European CTEPH registry, diagnosing CTEPH at an earlier time is still a major clinical challenge with a reported median diagnostic delay of 14 months [6]. Until now international guidelines recommend to perform an echocardiography in patients with signs and symptoms suggestive of CTEPH after a PE event and do not provide clear recommendations for strategies to reduce this delay in the follow-up of patients with acute PE [1].

Recently, a non-invasive screening algorithm for patients with a recent PE was constructed aiming at earlier CTEPH detection. This screening algorithm, consisting of sequential application of a clinical prediction score [7] and a set of rule out criteria [8, 9] within 6 months following a PE diagnosis (**Figure 1**), is currently being evaluated in an international multicenter prospective management study (InShape II study, Clinical Trials.gov identifier NCT02555137). The decision rule identifies the majority of patients with a low risk of CTEPH (i.e. six points or less) who do not need further diagnostic tests [7]. The rule out criteria consist of electrocardiogram (ECG) reading and N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement with a sex- and age-dependent threshold [8, 9]. These latter two tests will be applied in patients with a high pre-test probability (more than six points) or clear symptoms suggestive of CTEPH (e.g. persistence of physical impairment or dyspnoea). In the absence of three specific ECG characteristics suggestive of right ventricular overload (**Figure 2**) and a normal age- and gender-adjusted NT-proBNP level, CTEPH is considered excluded with a sensitivity of over 90% [8, 9]. Hence, only patients with abnormal rule-out criteria need to be referred for echocardiography [1]. By this design, CTEPH diagnostic resources can be focussed not only on patients with clear symptoms of CTEPH but also on those with a high pre-test probability of CTEPH, with a limited number of required echocardiographs.

Due to the relatively rare occurrence of CTEPH after acute PE, i.e. ~3% of PE survivors [10], the sensitivity of the algorithm can only be rigorously tested in selected patients

with a much higher CTEPH prevalence. In the current study we assessed the sensitivity of the screening algorithm in selected patients with confirmed CTEPH after acute PE to evaluate whether these patients would not have been missed by the algorithm. In addition, we assessed the reproducibility of the individual items of the algorithm.

METHODS

Study population

This is a retrospective analysis of consecutive patients diagnosed with CTEPH between 2014 and 2016 in the VU University Medical Center Amsterdam (VUMC), the Dutch referral center for CTEPH. The CTEPH diagnosis was based on the results of right heart catheterisation (RHC) and pulmonary angiography in all patients according to current guidelines [1]. For the present analysis, only patients with a documented previous episode of acute PE for whom the original medical charts were available were eligible for inclusion. The institutional review board (IRB) of the VUMC approved the study protocol and waived the need for informed consent due to the observational nature of the study.

Assessment of the CTEPH screening algorithm

All components of the CTEPH screening algorithm (**Figure 1**) were assessed from the original patient charts by two reviewers (Y.E-V and D.R), who were blinded for each other's findings. Using this info, the clinical prediction score [7] was calculated. A score of more than six points indicates a high risk of CTEPH. Furthermore, the presence of physical impairment or dyspnoea in the clinical course of the index PE was evaluated by reviewing the patient charts by the same two reviewers. The ECG and NT-proBNP measurement with a sex- and age-dependent threshold performed during CTEPH diagnostic work-up in the VUMC were used to apply the rule-out criteria [8, 9]. ECG reading was independently performed by two reviewers as well (Y.E-V, F.K). For calculation of the final CTEPH prediction score and outcome of the rule-out criteria, differences were resolved by consensus.

Study outcome

The primary objective of the study was to evaluate the sensitivity of the screening algorithm in patients diagnosed with CTEPH, that is, the number of patients with confirmed CTEPH that would have been correctly identified according to this strategy. The secondary aim of the study was to assess the interobserver agreement for calculating the prediction score, right-to-left ventricle (RV/LV) diameter ratio measurement, and ECG reading.

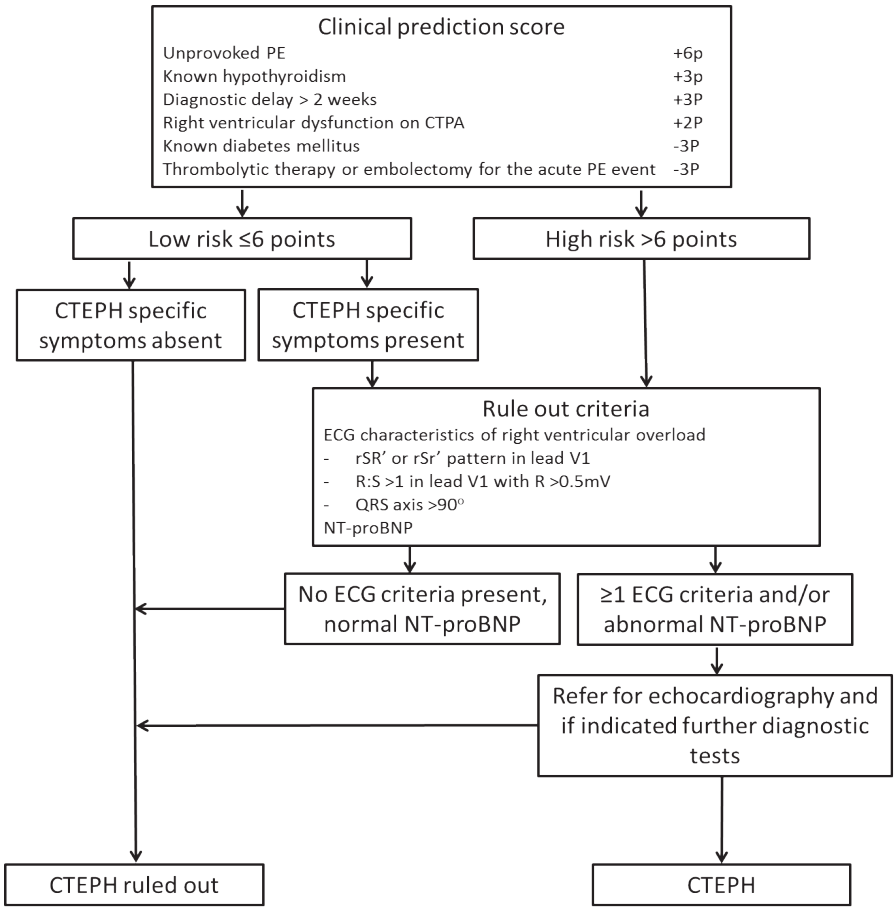

Figure 1. Screening algorithm for CTEPH after acute PE consisting of the CTEPH prediction score, CTEPH specific symptoms and the rule out criteria.
Note: CTEPH: chronic thromboembolic pulmonary hypertension; PE: pulmonary embolism; ECG: electrocardiography; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Statistical analysis

Based on the available number of patients in the allocated time frame a sample size of at 50 patients was chosen. The sensitivity of the CTEPH screening algorithm was determined with its corresponding 95% confidence interval (CI). A sensitivity of more than 90% was predefined as adequate. Interobserver agreement for assessment of the prediction score, RV/LV diameter ratio measurement on CT pulmonary angiography (CTPA), as well as, ECG reading was evaluated by calculating Cohen's kappa-statistics [11]. The kappa value for agreement was interpreted as follows: poor (< 0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or very good (0.81–1.00). All analyses were performed using SPSS software version 23 for Windows IBM Corporation.

RESULTS

Patients

A total of 68 consecutive patients diagnosed with CTEPH in the period of 2014-2016 in the VUMC were eligible for inclusion. Of these, 14 patients were excluded because a documented previous episode of acute PE was lacking (13 patients) or detailed information of the index PE diagnosis was unavailable (one patient), leaving a total of 54 patients for the current analysis. Their baseline characteristics are shown in **Table 1**. Mean age of the included patients at time of CTEPH diagnosis was 63 ± 15 years and 26 (48%) patients were male. The mean pulmonary artery pressure (mPAP) by RHC was 42 mmHg (±standard deviation (SD) 12 mmHg). Of those, 18 patients had a mPAP of less than 35 mmHg and 11 patients had a mPAP of greater than 50 mmHg. The median time between last PE diagnosis and CTEPH presentation was 9 months (inter quartile range (IQR) 5-15). Twenty patients were referred to the VUMC for CTEPH diagnostic work-up within 6 months after the last PE diagnosis. A total of 48 patients (89%) were treated with vitamin K antagonists and six (11%) with direct oral anticoagulants. Twenty two (41%) patients had a history of recurrent venous thromboembolism (VTE).

Clinical prediction score

The complete prediction score could be calculated in 44 patients. In 10 patients the clinical prediction score was incomplete, although based on the available data these patients could be indicated as low or high risk based on a definitive score of below or above six points. The index PE episode was unprovoked in 47 patients (87%). Three patients had known hypothyroidism at the moment of the index PE diagnosis. The diagnostic delay for the index PE was longer than 2 weeks in 45 patients. This latter information could not be retrieved for three patients. The majority of patients (44) had signs of right ventricular dysfunction as defined by a right-to-left ventricle (RV/LV) diameter ratio of ≥ 1.0 on CTPA. Information of the RV function was not available for nine patients, of whom two had been subjected to ventilation perfusion scintigraphy to diagnose the PE. The original CTPA images could not be retrieved for the remaining seven. Five of the included patients had known diabetes mellitus and one patient received thrombolytic therapy. Based on the available data, 46 of 54 patients (85%, 95%CI 73-93%) had a total score of at least more than six points indicative of high risk of CTEPH, and eight had a score of a maximum of six points or lower, allowing for a definite score result in all 54 patients.

Fifty patients had reported persistent dyspnoea or physical impairment within the first 6 months following the index PE diagnosis. Of the eight patients with a score of six points or less indicating low-probability, six patients had persistence of symptoms and would therefore have been subjected to the rule-out criteria according to the algorithm (**Figure 1**).

Table 1. patient characteristics.

	Patients (n=54)
Age at CTEPH diagnosis (years, SD)	63 (15)
Male sex (n,%)	26 (48)
mPAP at diagnosis of CTEPH (average mmHg, SD)	42 (12)
Number of VTE events (median, IQR)	1 (1-2)
Treatment of last PE	
Vitamin K antagonist (n,%)	48 (89)
DOAC (n,%)	6 (11)
Duration of last PE to CTEPH diagnosis (median months, IQR)	9 (5-15)
Comorbidities at the moment of CTEPH diagnostic work-up	
COPD (n,%)	11 (20)
Chronic left heart failure (n,%)	1 (2)
Rheumatic diseases (n,%)	7 (13)
Malignancy (n,%)	8 (15)
Splenectomy (n,%)	2 (4)
Prior infected pace maker lead (n,%)	0
Known antiphospholipid syndrome (n,%)	2 (4)

Note: CTEPH: chronic thromboembolic pulmonary hypertension; SD: standard deviation; mPAP: mean pulmonary artery pressure; IQR: inter quartile range; VTE: venous thromboembolism; PE: pulmonary embolism; DOAC: direct oral anticoagulants; IQR: inter quartile range; COPD: chronic obstructive pulmonary disease.

Rule out criteria

The rule out criteria were evaluated in all 52 patients with either high pre-test probability or specific symptoms of CTEPH. In one of these patients, the ECG was not available. Because the NT-proBNP level was abnormal, we were able to confirm the indication for echocardiography in this patient. Of the 51 patients with an available ECG, 33 (65%) had one or more ECG criteria positive and 15 (29%) patients scored two or more ECG criteria positive. The median NT-proBNP level in all patients was 906 ng/l (IQR 145-235410). In 35 (67%) of the 52 patients, the NT-proBNP level was abnormal. Forty-nine patients (49/52; 94%, 95%CI 84-99%) scored positive on at least one of the rule out criteria.

Sensitivity of the screening algorithm

According to the screening algorithm, a total of 49 out of 54 patients were correctly identified by the algorithm, implicating a sensitivity of 91% (95%CI 79-97%). This indicates that 27 of 30 cases of CTEPH would have been detected when applying the screening algorithm to 1000 random PE survivors with a 3% CTEPH incidence (projected negative predictive value 99.7%; 95%CI 99.1-99.9%).

Detailed characteristics of the five patients who were not identified by the algorithm are shown in **Table 2**. Two patients with a malignancy related provoked PE were not

identified as high risk according to the clinical prediction score. Both patients developed CTEPH specific symptoms only after a long follow-up period of 2 and 9 years after the index PE episode, respectively. The other three patients had normal ECG and NT-proBNP blood levels. Based on the diagnostic procedures performed during the CTEPH diagnostic work-up, these three patients had a normal RV function and no RV dilatation at echocardiography, CTPA and cardiac magnetic resonance imaging (MRI). Two of the three had an elevated estimated pulmonary artery pressure which was the reason for right heart catheterisation. The last patient was referred for right heart catheterisation because of the combination of extensive abnormalities on the ventilation perfusion scintigraphy and severe clinical symptoms (**Table 2**).

Interobserver variability

The Cohen Kappa statistic between the two reviewers was 0.96 for calculating the prediction score, 0.95 for measuring the RV/LV diameter ratio based on a ratio of <1 or ≥1 and 0.89 for ECG reading.

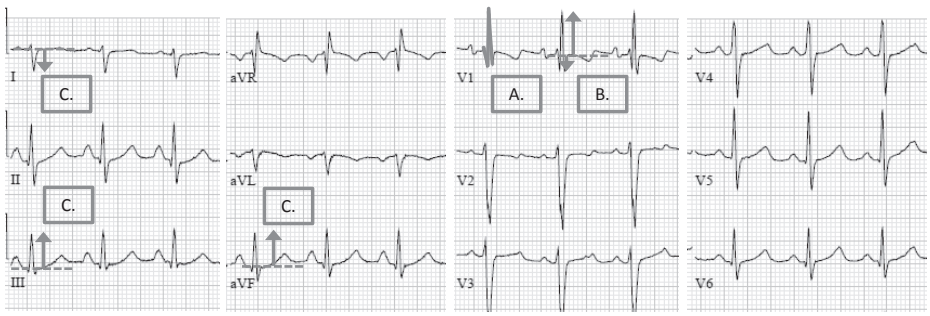

Figure 2. ECG demonstrating the three electrocardiographic signs of the rule out criteria
A) In lead V1 a right bundle branch block: rSR' or RSr' pattern with a QRS duration ≥ 120ms; B) in lead V1 R:S >1 with R>0.5mV and C) Right QRS axis deviation QRS axis >90°.
Note: CTEPH: chronic thromboembolic pulmonary hypertension; ECG: electrocardiography.

DISCUSSION

With this study we could demonstrate that by using a simple non-invasive CTEPH screening algorithm, 49 out of 54 CTEPH patients could have been correctly identified early after the PE diagnosis. The sensitivity of the screening algorithm in this population was thus 91% (95%CI 79-97%). The screening algorithm proved highly reproducible as well, with Cohen's kappa-statistics of 0.96, 0.95 and 0.89 for calculating the prediction score, RV/LV diameter ratio measurement and ECG reading, respectively.

Table 2. Characteristics of the 5 patients who were not identified according to the screening algorithm.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at CTEPH diagnosis	76	86	62	65	65
Sex	male	female	male	male	female
NYHA classification at the time of CTEPH referral	3	4	3	2	2
Number of previous VTE events	2012: provoked PE (post-surgery, malignancy related)	1994 provoked PE, malignancy related	1999 unprovoked PE 2014 unprovoked PE	2002 unprovoked PE 2012 unprovoked DVT	2014 unprovoked PE
Referral to the VUMC (months after PE diagnosis)	23	240	6	151	6
Cardiopulmonary comorbidities	none	COPD	none	none	none
Other risk factors for CTEPH[¥]	none	Splenectomy	none	none	Rheumatoid arthritis
Clinical prediction score	2 points	5 points	11 points	9 points	11 points
Persistence of symptoms after index PE	In 2014 new, progressive symptoms of dyspnoea	In 2013 new, progressive symptoms of dyspnoea	Yes	Yes	Yes
Rule out criteria	abnormal	abnormal	normal	normal	normal
NT-proBNP ng/L[^]	1694 (<486)	9082 (<738)	101 (<210)	56 (<376)	148 (<301)
ECG items†	1 item	2 items	none	none	none
Echocardiography (at diagnosis of CTEPH)	Dilated RV, severe PH	Dilated RV, severe PH	RV not dilated, normal function, signs of PH based on a slightly dilated right atrium and a SPAP of > 44 mmHg	RV not dilated, normal function signs of PH based on midsystolic notching of the pulmonary valve and a SPAP of >55mmHg	RV not dilated, normal function, no signs of PH. RHC performed because of severity of symptoms and the extensiveness of the abnormalities on V/Q lung scintigraphy
RHC MPAP (mmHg) / PVR (dynes-sec-cm^{-5})	56/554	49/577	36/329	31/400	32/376

Note: CTEPH: chronic thromboembolic pulmonary hypertension; NYHA: New York Heart Association ; VTE: venous thromboembolism; VUMC: VU university medical Center Amsterdam; PE: pulmonary embolism; PM: pacemaker; NT-proBNP: N-terminal pro-brain natriuretic peptide; ng/L: nanograms per litre; ECG: electrocardiography; PH: pulmonary hypertension; SPAP: systolic pulmonary artery pressure; RHC: right heart catheterisation; V/Q : ventilation/perfusion lung scintigraphy; MPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance.

[¥] splenectomy, infected PM leads, autoimmune diseases; [^] age and sex adjusted; † Right bundle branch block: rSR' or RSr' pattern in lead V1 with a QRS duration ≥ 120ms, R:S >1 in lead V1 with R>0.5mV or right QRS axis deviation QRS axis >90°.

Early CTEPH diagnosis is of relevance for optimal treatment and patient outcome of patients suffering from this disease. Although randomized trials comparing early and later CTEPH diagnosis and treatment initiation are not available, it is reported in the European registry that performing PEA was the strongest predictor of survival (hazard ratio 0.37; 95%CI 0.24-0.58; P<0.0001) underlining the importance of early CTEPH diagnosis [3]. Until now, however, strategies for earlier CTEPH diagnosis are rarely reported in the literature and are underreported in relevant guidelines [12]. The median time between last reported PE event and referral for CTEPH diagnostic work-up in this cohort was 9 months.

Based on the screening algorithm evaluated in this analysis, only five of 54 CTEPH patients would have been missed. Two of these patients suffered provoked PE many years before the CTEPH diagnosis, and had full physical recovery before new symptoms suggestive of CTEPH occurred. A recent study suggested that CTEPH often is an already ongoing disease in patients diagnosed with acute PE [13]. In this study it was shown that five of seven CTEPH patients from 146 patients with PE already had signs of CTEPH at echocardiography during initial PE diagnosis and all seven had signs of CTEPH on retrospective CTPA evaluation. Our two patients may either have developed a secondary vasculopathy caused by redistribution of the blood flow after PE with a long symptom-free honeymoon period or developed subclinical recurrent PE as start of developing CTEPH [14, 15].

The three other patients who were not identified by the algorithm had a high risk according to the CTEPH prediction score, displayed characteristic symptoms of CTEPH, but had normal ECG and NT-proBNP levels. Interestingly, echocardiography, CTPA and cardiac MRI performed during CTEPH diagnostic work-up showed a normal RV function and no RV dilation in all three patients. This may be explained by the process of RV adaptation to the increased vascular load [16]. During this stage of pulmonary hypertension which is also referred to as 'coupling', the right ventricle adapts by increasing contractility and muscle wall thickness to maintain flow [17]. In the natural course of disease, 'uncoupling' will ultimately occur, causing RV dilatation and eventually RV failure. The fact that two of the three patients were referred within 6 months after the PE diagnosis suggests that these patients were indeed identified early in the course of disease. Considering this, we conclude that patients in very early stages of CTEPH may be missed by the rule-out criteria, as was shown in the derivation study of the criteria. Even so, the majority (18/20) of patients referred within the first 6 months after PE diagnosis and most (16/18) patients with mild increased mPAP (<35 mmHg) were correctly identified by the algorithm.

The strength of this study lies in the large cohort of consecutive patients diagnosed with CTEPH after a previously documented episode of acute PE, as well as the ability to assess the interobserver variability of all individual items of the screening algorithm.

This study also had some limitations. The design of this study does not allow us to estimate the specificity of the algorithm. Also, only limited data with regard to index PE event of patients referred to VUMC before 2014 was available. Therefore, we were not able to include more patients in this study. Based on the available data from the referral centers, it was not possible to evaluate the complete screening algorithm in all CTEPH patients. We were nonetheless able to include 10 patients with an incomplete clinical prediction score with definitely more than six or definitely less than six points. The patient with a missing ECG had an abnormal NT-proBNP level, allowing for full assessment of the rule-out criteria in all patients. Another limitation is that the median time between the last PE diagnosis and referral to the VUMC for CTEPH diagnostic work-up was 9 months. We used ECGs and NT-proBNP measurements at the time of referral and not the required 3 to 6 months following acute PE, which could have influenced our outcome. Lastly although the screenings algorithm is assessed for the early diagnosis of CTEPH, the sensitivity was tested in prevalent patients, some with advanced disease.

In conclusion, 91% of the evaluated CTEPH patients would have been identified by the proposed screening algorithm, underlining its adequate sensitivity. All components of the algorithm proved to be highly reproducible as well. The few patients who would have been missed by the algorithm had either a very long 'honeymoon period' or were diagnosed with very early disease. The results of the ongoing prospective validation of the algorithm in consecutive PE patients will provide more definite proof of sensitivity and also the accuracy and applicability of the algorithm in daily clinical practice.

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Chapter 5

Accuracy and reproducibility of CT right-to-left ventricular diameter measurement in patients with acute pulmonary embolism

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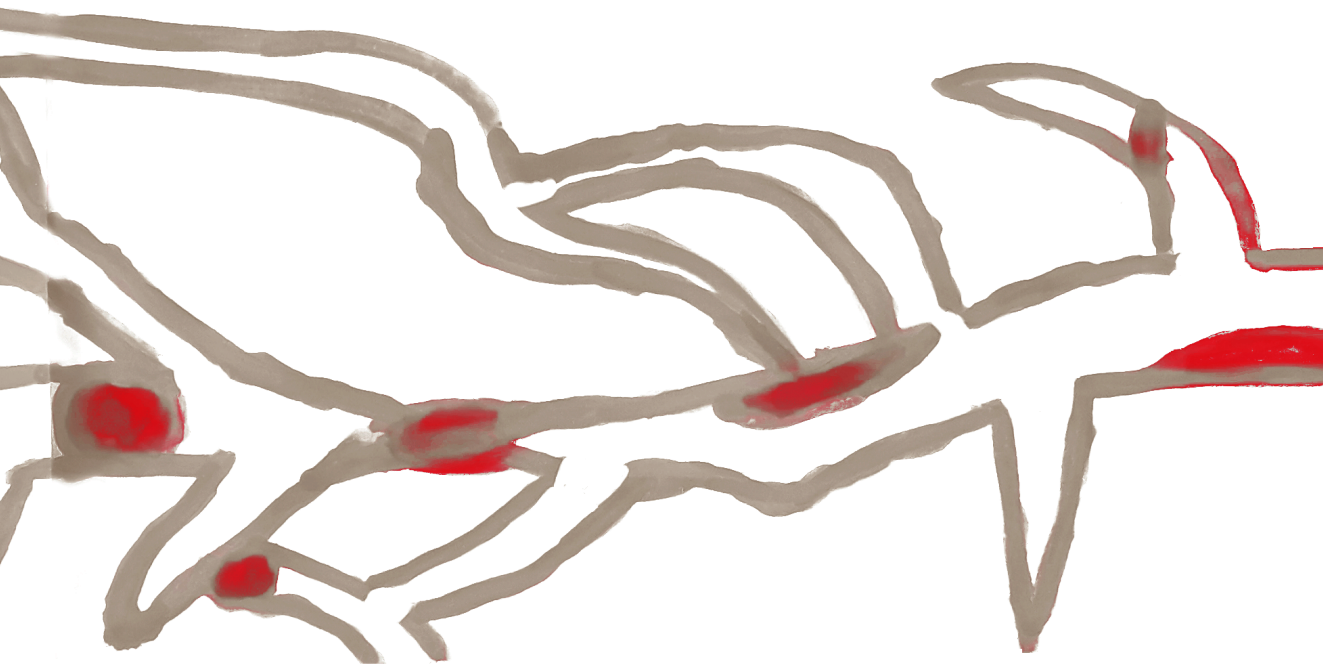

ABSTRACT

Background: Right ventricular (RV) dysfunction caused by acute pulmonary embolism (PE) is associated with poor short- and long-term prognosis. RV dilatation as a proxy for RV dysfunction can be assessed by calculating the right-to-left ventricle diameter (RV/LV) ratio on standard computed tomography pulmonary angiography (CTPA) images. It is unknown whether dedicated training is required to accurately and reproducibly measure RV/LV ratio therefore we aimed to assess these parameters in residents internal medicine without experience in CTPA reading.

Methods: CTPA images of 100 patients with PE were assessed by three residents after single instruction, and one experienced thoracic radiologist. Maximum diameters were evaluated in the axial view by measuring the distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis of the heart. RV dilatation was defined as a ratio of ≥1.0. Interobserver accuracy and reproducibility was determined using Kappa statistics, Bland-Altman analysis and Spearman's rank correlation.

Results: The kappa statistic for the presence of RV dilatation of the residents compared to the experienced radiologist ranged from 0.83-0.94. The average interobserver difference in calculated RV/LV ratio's (±SD) between the three residents was: -0.01 (SD0.11), 0.07 (SD0.14) and 0.06 (SD0.18) with an overall mean RV/LV diameter ratio of 1.04. In line with this, Spearman's rank correlation coefficients were 0.92, 0.88 and 0.85 respectively indicating very good correlation ($p<0.01$ for all).

Conclusion: After simple instruction, RV/LV diameter ratio assessment on CTPA images by clinical residents is accurate and reproducible, which is of help in identifying PE patients at risk.

INTRODUCTION

Right ventricular (RV) dysfunction caused by acute pulmonary embolism (PE) is associated with poor short and long-term prognosis, i.e. higher risk of PE related mortality and chronic thromboembolic pulmonary hypertension (CTEPH) [1-3]. Several methods to determine RV dysfunction have been proposed and validated [4, 5]. RV dilatation based on right-to-left ventricle (RV/LV) diameter ratio on computed tomographic pulmonary angiography (CTPA) as a measure of RV dysfunction correlates well with echocardiographic parameters [6-8]. RV dilatation on CTPA has been shown to predict a higher 30-day mortality risk (OR 2.08; 95% confidence interval (CI) 1.63-2.66) in 4661 patients presenting with PE and even in 2254 haemodynamically stable patients (OR 1.64; 95%CI 1.06-2.52) [9]. The advantage of RV/LV diameter ratio measurement on CTPA compared to echocardiography is that it obviates the need of a second imaging test in addition to the diagnostic test applied to confirm the PE diagnosis.

International guidelines do not recommend standard RV/LV diameter ratio measurement in all patients with acute PE, although the initial risk assessment of PE also involves the measurement of RV function [1, 10]. Specifically, the presence of RV dysfunction as well as of biomarkers of cardiac overload and ischemia help differentiating between patients at intermediate-low risk of adverse outcome and patients at intermediate-high risk. The latter is an indication for close hemodynamic monitoring due to the 5.6% risk of hemodynamic deterioration in the first days after diagnosis [11]. RV/LV diameter ratio assessment may thus be useful in day-to-day clinical practice and especially in circumstances that echocardiography is not readily available.

The inter- and intra-observer agreement and reproducibility of RV/LV diameter ratio measurement by trained radiologists is reported to be very good with a Cohen's Kappa statistic ranging from 0.80 to 0.87 [12-15]. The accuracy and reproducibility of RV/LV diameter ratio measurements by non-radiologist clinicians without dedicated training and expertise in CT reading is unknown. We aimed to assess the accuracy and reproducibility of CTPA RV/LV diameter ratio measurement by three residents in internal medicine without prior dedicated training in CT reading.

METHODS

Study population

This is a post hoc analysis of a previously published observational prospective outcome study aimed at assessing the incremental value of ventricular function measurement with ECG-synchronized cardiac CTPA scanning over standard CTPA measured RV/LV ratio for predicting the short term prognosis in patients with acute PE [16, 17]. Consecutive,

normotensive patients with suspected acute PE, based on a likely clinical probability by the Wells rule and/or an abnormal D-dimer test, were eligible for inclusion. Patients with renal function impairment, age < 18 years, pregnancy or allergy to contrast were excluded. A total of 430 consecutive haemodynamic stable patients were included and underwent standard CTPA and ECG-synchronized cardiac CT scanning, of whom 113 (26%) were diagnosed with acute PE [16, 17]. For the current analysis, the first 100 consecutive patients with confirmed PE were selected. Institutional review board (IRB) approval was obtained and written informed consent provided by all patients for the original study. The IRB of the LUMC waived the need for informed consent for this post-hoc analysis.

CTPA reading

The standard CTPA scans were reviewed chronologically by one expert thoracic radiologist (reviewer 1 (L.K)) with over 15 years of experience in pulmonary CTPA reading, two residents (reviewer 2 and 4 (Y.E-V and I.M)) and one senior resident with experience in VTE research (reviewer 3 (F.K.)), without specific training in CTPA reading. The experienced thoracic radiologist provided the following written instructions to the three residents: 1) evaluate the ventricle diameters in the standard axial view, 2) Measure the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis of the heart, and 3) Use the maximum dimensions for both ventricles which may be found at different levels [12, 18]. In addition one RV/LV diameter ratio measurement was demonstrated (**Figure 1**). All four reviewers were blinded to the findings of the other reviewers. RV dilatation was defined as a RV/LV diameter ratio of ≥1.0 [1].

Study aim

The primary aim of the study was to evaluate the accuracy of assessing the presence or absence of RV dilatation, defined as an RV/LV diameter ratio of ≥1.0, by three residents in internal medicine without dedicated training in CT reading compared to the ruling of an experienced thoracic radiologist. The secondary aims of the study were to compare mean differences in the measured RV/LV diameter ratio in the individual study patients between the three residents internal medicine.

The primary endpoint was the kappa statistic for the presence or absence of RV dilatation measured by the three residents compared to the experienced thoracic radiologist. The secondary endpoint was the correlation coefficient between RV/LV ratio measurements among the three residents.

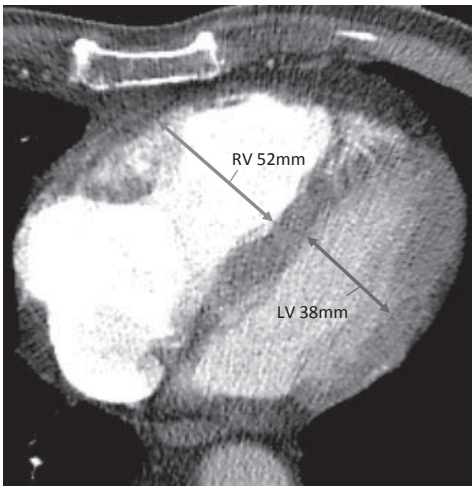

Figure 1. CTPA demonstrating the RV/LV ratio measurement.
Note: CTPA: computed tomography pulmonary angiography; RV/LV: right-to left ventricle diameter ratio in this patient was 1.4.

Statistical analysis

Based on previous studies on this subject, we set our sample size at 100 CTPAs [12-15]. Baseline characteristics of the patients are provided with corresponding frequencies. Interobserver reproducibility for the dichotomous variable, i.e. a RV/LV diameter ratio of ≥ 1.0, of the thoracic radiologist compared to each of the three residents and among the residents was determined by using Cohen's kappa-statistics. The kappa value for agreement was interpreted as follows: poor (< 0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or very good (0.81–1.00) [19]. Further, Bland and Altman plots were used to represent the mean difference between the RV/LV diameter ratio measurements by the three residents [20]. We predefined adequate interobserver agreement on the Bland and Altman plot by a mean difference between 2 readers <0.1. Correlations between the measurements in individual patients were determined by Spearman's rank correlation. A correlation coefficient of 1 indicates a positive correlation while a coefficient of 0 represents no correlation. All analyses were performed using SPSS software version 23 for Windows IBM Corporation.

RESULTS

Patients

One-hundred haemodynamically stable consecutive patients diagnosed with symptomatic acute PE were selected for the current analysis [16, 17]. Patient characteristics are provided in **Table 1**. Their mean age was 55 ± 16 years and 51 (51%) of the patients were male. Twenty-one patients (21%) had a history of venous thromboembolism,

38 patients (38%) had an unprovoked PE (bases on the absence of immobility, recent surgery, postpartum period or use of oral contraceptives or active malignancy). Twenty-four (24%) had an active malignancy.

Table 1. Patient characteristics.

	Patients (n=100)
Age (years ± SD)	55 ± 16
Male sex (n,%)	51 (51)
Previous PE/DVT (n,%)	21 (21)
Immobility, surgery, trauma, postpartum, estrogen use (n,%)*	49 (49)
Active malignancy (n,%)*	24 (24)
Unprovoked PE (n,%)	38 (38)
Inpatient (n,%)	17 (17)
Left sided heart failure	3 (3)

Note: PE: pulmonary embolism; DVT: deep vein thrombosis; n: number; SD: standard deviation.
* 11 patients had an active malignancy and immobility, surgery, trauma, postpartum or estrogen use.

Accuracy of the RV/LV diameter ratio assessment

According to the measurement of the experienced radiologist, the RV was dilated (RV/LV diameter ratio of ≥1.0) in 42 CTPA scans, and the RV was not enlarged in 58 scans. Each resident individually measured the RV/LV diameter ratio of 93 (93%; 95%CI 86-97), 97 (97%; 95%CI 91-99) and 92 (92%; 95%CI 85-96) CTPA scans in accordance with the experienced radiologist resulting in a Cohen Kappa statistic of 0.86 (95%CI 0.75-0.96), 0.94 (95%CI 0.87-1.00) and 0.83 respectively (95%CI 0.72-0.94) (**Table 2**). The Cohen Kappa statistics between the residents internal medicine were 0.88 (95%CI 0.78-0.97; Reviewer 2 – Reviewer 3), 0.85 (95%CI 0.75-0.96; Reviewer 2 – Reviewer 4) and 0.85 (95%CI 0.75-0.96; Reviewer 3 – Reviewer 4). All discrepancies between the 3 residents concerned patients with RV/LV diameter ratio close to 1.0.

Interobserver variability among the three residents internal medicine

The average RV/LV diameter ratio in the 100 measured CTPA scans by the three residents internal medicine was 1.06 (standard deviation (SD) 0.35), 1.07 (SD 0.29) and 1.00 (SD 0.26) respectively. On Bland Altman analysis, the mean difference in the calculated RV/LV diameter ratio's (±SD) was -0.01 (SD 0.11) (reviewer 2 and 3), 0.06 (SD 0.18) (reviewer 2 and 4) and 0.07 (SD 0.14) (reviewer 3 and 4) (**Figure 2**). The Spearman's rank correlation coefficient was 0.92, 0.88 and 0.85 respectively ($p<0.001$ for all). The outlines in the Bland Altman plots were all in patients with RV/LV diameter ratio of larger than 1.5, i.e. those patients in whom RV overload is undoubtedly present. The differences in the RV/LV diameter ratio in these patients were mainly caused by variance in identification of the wall of the ventricular endocardium.

Table 2. Cohen kappa statistic of the experienced thoracic radiologist reviewer 1 and the three residents internal medicine reviewer 2-4.

	Kappa
Reviewer 1 – reviewer 2	0.86 (95%CI 0.75-0.96)
Reviewer 1 – reviewer 3	0.94 (95%CI 0.87-1.00)
Reviewer 1 – reviewer 4	0.83 (95%CI 0.72-0.94)
Reviewer 2 – reviewer 3	0.88 (95%CI 0.78-0.97)
Reviewer 2 – reviewer 4	0.85 (95%CI 0.75-0.96)
Reviewer 3 – reviewer 4	0.85 (95%CI 0.75-0.96)

Note: CI: confidence interval.

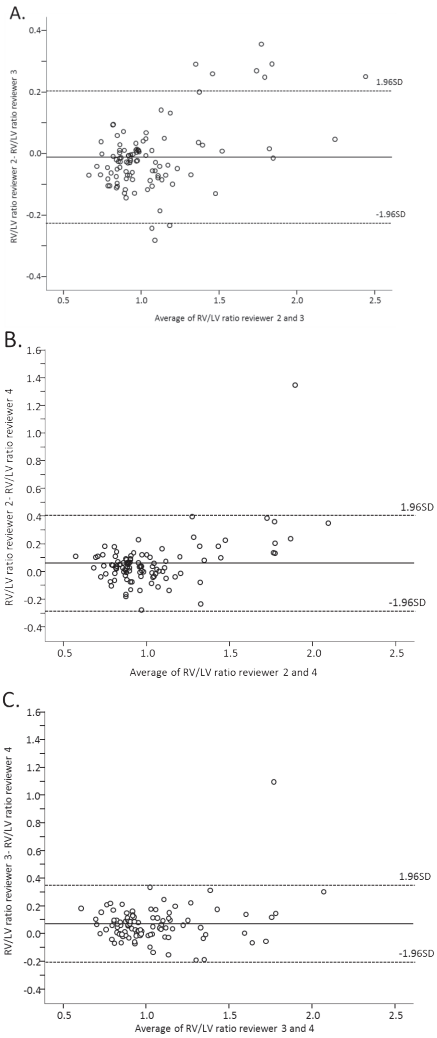

Figure 2. Bland and Altman analysis of the RV/LV diameter ratio measured by three residents internal medicine.
Figure 2a. reviewer 2 and 3, figure 2b reviewer 2 and 4, figure 2c reviewer 3 and 4.
Note: RV/LV: right-to left ventricle diameter ratio.

Table 3. Studies evaluating the interobserver RV/LV diameter ratio agreement.

	Number of patients	Type of PE patients	Years of radiology experience	Kappa RV/LV ≥1/<1	Bland and Altman mean difference (SD)	Correlation coefficient
Jimenez *et al* 2012 [12]	96	Haemodynamically stable	Trained and certified radiologists	0.8	0.03 (0.23)	n.a.
Cok *et al* 2013 [13]	61	No selection	8 and 5 years	0.83-0.96*	n.a.	0.72-0.94*‡ (P<0.001)
Javadrashid *et al* 2015 [14]	63	haemodynamically stable and no pre-existing comorbidity	>10 years	0.87	n.a.	n.a.
Kang *et al* 2011 [15]	173	Haemodynamically stable	7 and 5 years	0.81	n.a.	0.89 (P<0.001) ¥
Kang *et al* 2010 [22]	50	No selection	6 and 3 years	n.a.	0.01 (0.20)	0.88 (P<0.001) ‡
Kumamaru *et al* 2012 [23]	30	No selection	Both 5 years	n.a.	n.a.	0.88 (P<0.001) ‡
Aribas *et al* 2014 [7]	120	Haemodynamically stable	5 and 12 years	n.a.	n.a.	0.85 (P<0.001) ‡
Ouriel *et al* 2017 [24]	10	RV/LV diameter ratio of ≥0.9	Experienced radiologist	n.a.	n.a.	0.98 (P<0.001) ‡
Becattini *et al*, 2011 [21]	260	No selection	Expert radiologist and a physician with experience on CTPA reading	0.88#	n.a.	0.91¥

Note: PE: pulmonary embolism; RV/LV: right-to left ventricle diameter ratio; SD: standard deviation; n.a.: not applicable.
*different measurements including the RV/LV diameter ratio were mentioned within these numbers; # kappa based on a RV/LV ratio of ≥0.9 or <0.9; ‡ Spearman rank correlation coefficient; ¥ intra-class correlation coefficient.

DISCUSSION

With the results of this study, we have shown that after a single focussed instruction, residents internal medicine without dedicated training and expertise in CT reading were able to accurately determine the presence or absence of RV dilatation as defined by a RV/LV diameter ratio of ≥ 1.0 on CTPA images in patients diagnosed with acute PE. Also, the mean difference in calculated RV/LV diameter ratio's by the residents was very low (-0.01, 0.07 and 0.06 respectively), which was underlined by the very good correlation from the Spearman's rank test (0.92, 0.88 and 0.85 respectively (p<0.01 for all)).

RV dilatation on CTPA is an indicator of RV dysfunction that can be useful in selecting PE patients with a high risk of an adverse short and long term outcome [1]. Even in haemodynamically stable patients, it has been clearly shown (OR of 1.64 (95%CI 1.06-

2.52)) that an enlarged RV/LV diameter ratio on CTPA is associated with an increased risk of death at 30 days [9]. As for the long term prognosis, right ventricular dilatation at the moment of a PE diagnosis is an independent risk factor for CTEPH with a reported OR of 4.1 (95%CI 1.4-12) [2]. Alternative methods to assess RV dysfunction such as echocardiography are more time consuming, expensive and may not be available around the clock in all hospitals. With CTPA being the most commonly used method to diagnose acute PE, it is likely that this is the most simple and economic method to assess cardiac function at moment of diagnosis as well as post-hoc when patients visit the outpatient clinic for counselling on their long term prognosis.

Previous studies reported a good to very good inter- and intra-agreement on the CTPA RV/LV diameter ratio measurement between experienced radiologists (**Table 3**) using axial images. In four studies that evaluated a total of 393 patients with PE, the Cohen's Kappa statistic for CT assessment of the presence of RV overload has ranged from 0.80 to 0.87 for trained radiologists with 5 to over 10 years of experience [12-15]. The first study retrospectively evaluated 61 unselected PE patients including 12 patients with massive PE and reported a kappa of at least 0.83 [13]. The remaining three studies were restricted to haemodynamic stable patients, with kappa statistics between 0.8 and 0.87 [12, 14, 15]. A fifth study evaluated the agreement between an experienced radiologist and a clinical physician with experience in CTPA reading for PE. In this study 460 unselected PE patients were included of which 49 were haemodynamically instable. The kappa statistic for a RV/LV diameter ratio of ≥0.9 was 0.88 [21].

Two further studies assessed differences in the measured ratios using axial images. In the first study 96 haemodynamically stable patients were evaluated by trained and certified radiologists whose measurements of the RV/LV ratio differed only 0.03 (SD 0.23) on average [12]. The second study included 50 unselected PE patients, of whom 10 were haemodynamically instable, and found a mean difference of the measured ratios of 0.01 (SD 0.20) between 2 radiologists with 3 and 6 years of experience [22]. A final five studies covering a total of 444 PE patients whose CTPA images were read by radiologists with 3-12 years of experience, reported Spearman rank or intra-class correlation coefficients of 0.72 to 0.98 ($P<0.001$ for all), indicating a clear correlation between the measured ratio's [13, 15, 22-24].

One earlier study described the interobserver agreement between radiologists and clinicians without specific training in chest CT reading [25]. This study described the interobserver agreement of the RV/LV diameter ratio on 113 CTPA scans of patients with suspected acute PE between two radiologists with 14 and 15 years of experience and inexperienced radiology residents [25]. The inter-reader variability as assessed by using interclass coefficients was 0.95.

To our knowledge, this study is the first study evaluating the accuracy and reproducibility of CTPA RV/LV diameter ratio measurement in PE patients by residents in internal

medicine who did not have dedicated training or expertise in CT reading. This is relevant for daily clinical practice because in many cases clinical residents internal medicine, cardiology, pulmonology or emergency medicine are responsible for both the initial risk assessment and treatment as well as long term follow-up of patients with PE. This simple method is of help to the clinician in identifying the patient presenting with acute PE who is at higher risk of mortality in the acute moment [9] and on the long term of the development of CTEPH [2].

The main limitation of this study is that other signs of RV failure on CTPA such as enlargement of the pulmonary truncus and backflow of contrast in the vena cava were not studied but may be relevant as well in the evaluation of RV function on CTPA. Only haemodynamically stable patients were included making our results only applicable to that patient category. The RV/LV diameter ratio depends on the diameter of the LV as well. In patients with a pathologically enlarged LV, as was present in 3 patients of this current analysis, RV dilatation based on RV/LV diameter ratio could have been missed. This was a post hoc analysis of patients diagnosed with PE in our centre from an observational multicenter study. Therefore, a formal power analysis was not performed and the sample size was based on previous studies on this subject (**Table 3**). Also, three residents internal medicine were selected to perform all measurements. We did not formally prove that our results can be translated to residents from other hospitals or countries, or form other specialties (cardiology, pulmonology), although we would not expect relevant differences.

In conclusion, the presence of RV dilatation on CTPA in patients with acute PE were accurately assessed by clinical residents without dedicated training in CT reading but after simple instruction. This is of help in identifying PE patients at higher risk of short and long term adverse outcome.

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Chapter 6

Usefulness of standard computed tomography pulmonary angiography performed for acute pulmonary embolism for identification of chronic thromboembolic pulmonary hypertension: results of the InShape III study

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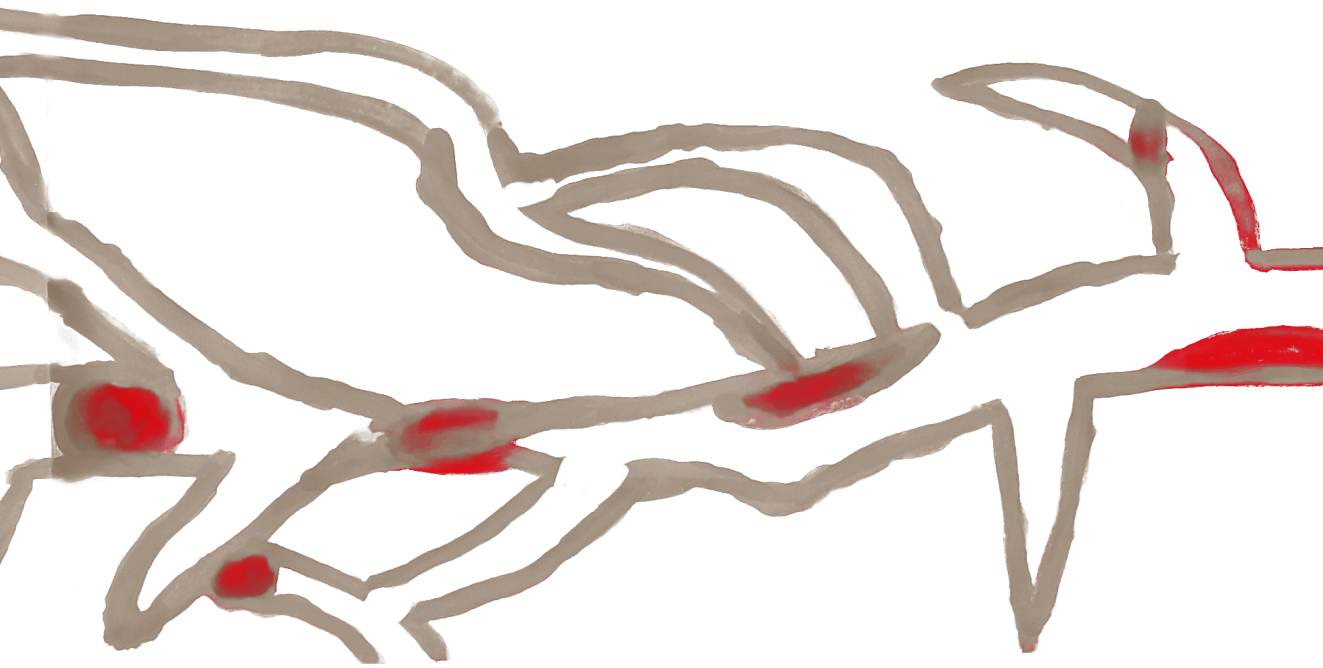

ABSTRACT

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is often diagnosed after a long delay, even though signs of CTEPH may already be present on the CT pulmonary angiography (CTPA) used to diagnose a preceding acute pulmonary embolism (PE). In this setting of suspected acute PE, we evaluated the diagnostic accuracy of dedicated CTPA reading for the diagnosis of already existing CTEPH.

Methods: Three blinded expert radiologists scored radiological signs of CTEPH on initial CTPA scans with confirmed acute PE in 50 patients who were subsequently diagnosed with CTEPH during follow-up (cases), and in 50 patients, in whom sequential echocardiograms performed more than two years after the acute PE diagnosis did not show any signs of pulmonary hypertension (controls). All 50 control CTPA scans had signs of right ventricular (RV) overload. Sensitivity and specificity of expert CTPA reading was calculated, and best predicting radiological parameters were identified.

Results: The overall expert reading yielded a sensitivity of 72% (95%CI 58-84) and a specificity of 94% (95%CI 83-99%) for CTEPH diagnosis. Multivariate analysis identified six radiological parameters as independent predictors: intravascular webs, pulmonary artery retraction or dilatation, bronchial artery dilatation, RV hypertrophy and interventricular septum flattening. The presence of ≥3 of these parameters was associated with a sensitivity of 70% (95%CI 55-82), a specificity of 96% (95%CI 86-100%) and a c-statistic of 0.92.

Conclusion: Standardized reading of CTPA scans performed for acute PE can be useful for the diagnosis of CTEPH when structured identification of 6 characteristics are employed during interpretation. The use of this technique may help reduce diagnostic delay of CTEPH.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious, though potentially curable long-term complication of acute pulmonary embolism (PE), occurring in approximately 3.2% of PE survivors [1-4]. Relevance of optimal treatment and prognosis is clear [1, 2], yet early CTEPH diagnosis is a major clinical challenge as a median diagnostic delay of 14 months (inter quartile range (IQR) 7.5-32.8) was recently demonstrated in 679 patients included in the International CTEPH registry [5].

It has been suggested that a relevant proportion of patients with CTEPH with a prior history of acute PE already had radiological signs of pre-existing CTEPH on the initial computed tomography pulmonary angiography (CTPA) performed to diagnose the acute PE. Guerin et al showed in a retrospective evaluation of the initial CTPA scan of 146 acute PE patients, that all seven patients with an ultimate diagnosis of CTEPH had several radiological signs of CTEPH at the initial CTPA [6].

CTPA is the imaging test of choice for patients with suspected acute PE [7] and can be helpful in the diagnostic work-up of suspected CTEPH as well. Data from the Aspire registry assessing the spectrum of pulmonary hypertension (PH) showed that CTPA yielded a high sensitivity of 94% (95%CI 0.85-0.98) and high specificity of 98% (95%CI 0.88-0.99) for CTEPH in patients with clinically suspected CTEPH [8]. Typical CTPA parameters for right ventricular (RV) overload such as a right-to-left ventricle diameter (RV/LV) ratio >1.0 are often present in patients with acute PE [9]. More specific radiological clues for CTEPH include intravascular webs or bands, and wall-adherent thrombi. Mosaic attenuation and dilated bronchial arteries are less specific for CTEPH and can also be seen in other types of pulmonary hypertension [1, 10-13]. In contrast, on CTPA acute PE can manifest as a complete arterial occlusion, or centrally located in the vessel with contrast material present between the thrombus and the arterial wall, or as an eccentric filling defect that forms an acute angle with the arterial wall [14, 15]. Confirmation of the findings of Guerin et al [6] should prompt (more) targeted reading of CTPA scans performed for suspected acute PE, since recognition of concurrent signs of CTEPH may greatly help in achieving earlier CTEPH diagnosis.

We set out to evaluate the accuracy of extensive reading of CTPA scans performed in the setting of suspected acute PE, to assess concomitant CTEPH diagnosis. Moreover, we aimed to identify the most predictive radiological parameters for this purpose.

METHODS

Study population

Patient selection occurred post-hoc from the local registry of the VU university medical Center (VUmc) (cases) and previous prospective studies (controls) [9, 16, 17]. The assessment of the CTPA scans was performed prospectively. The cases consisted of 50 consecutive patients who were referred to the VUmc, Amsterdam, in the period between 2014 and 2016 for treatment of CTEPH, and had a prior diagnosis of acute PE. The CTEPH diagnosis was confirmed by right heart catheterisation (RHC) and pulmonary angiography in all patients, in accordance with current guideline recommendations [1]. The second group consisted of 50 control patients diagnosed in the Leiden University Medical Center (LUMC), Leiden, with acute PE and associated RV overload, defined as RV/LV diameter ratio of >1.0 as shown by the CTPA made for PE diagnosis, who had thereafter not developed CTEPH over the course of at least 2 years. These latter 50 patients were selected out of two prior studies and were prospectively subjected to baseline ECG-synchronized cardiac CTPA scanning at the moment of PE diagnosis and sequential echocardiography during a follow-up period of at least two years [9, 16, 17]. The echocardiograms did not show any signs of PH. We only included controls with signs of RV overload at baseline to minimize bias, since patients without any signs of RV overload at the moment of acute PE diagnosis are very unlikely to have concurrent CTEPH.

All initial CTPA scans for PE diagnosis were performed using a CT scanner with at least 64 slices and generally a reconstructed slice thickness of 1-3 mm. The institutional review board (IRB) of both the LUMC and VUmc approved the study protocol and waived the need for informed consent due to the observational nature of the study. All controls had previously provided oral and written informed consent for inclusion in the two prior studies that included assessment of all clinical and radiological parameters used in the current study [9, 16-18].

Study procedures

The CTPA images for PE diagnosis of both cohorts were collected and anonymized. All relevant information of the date of the CTPA scan and the specific scanner used were removed, as were additional image sequences and reformatted series other than the original axial data-set. All CTPA studies were distributed among three expert thoracic radiologists, who were unaware of the case or control status, patient characteristics or other clinical outcome. All three radiologists have broad expertise on diagnosis of acute PE and CTEPH (L.M, L.K and L.B). Each radiologist independently scored the presence of radiological parameters of both chronic thrombus remnants as well as of PH on a predesigned adjudication form according to predefined criteria. Moreover, after reading the scan and scoring all items, they were forced to classify each patient as having CTEPH or not.

The following radiological parameters were scored as 'yes, present' or 'no, not present' for assessment as indicators of PH: right atrial (RA) dilatation, RV dilatation, RV hypertrophy, flattening or inversion of the interventricular septum, dilatation of the main pulmonary artery, dilated bronchial arteries and the presence of mosaic perfusion. The following radiological parameters were scored for the presence of chronic thrombus remnants: intravascular webs, residual thrombus attached to the vascular wall, complete arterial occlusion, arterial retraction, post-stenotic vascular dilatation, pulmonary infarction and parenchymal bands (**Figures 1, 2 and 3**) [19, 20]. The presence of RA dilatation was visually determined, RV dilatation was defined as a RV/LV diameter ratio of >1.0, RV hypertrophy as a wall thickness of > 4mm or visually determined and main pulmonary artery dilatation was based on a diameter of > 30mm or a diameter larger than the diameter of the aorta. The readers scored each of the above mentioned items as present or not present.

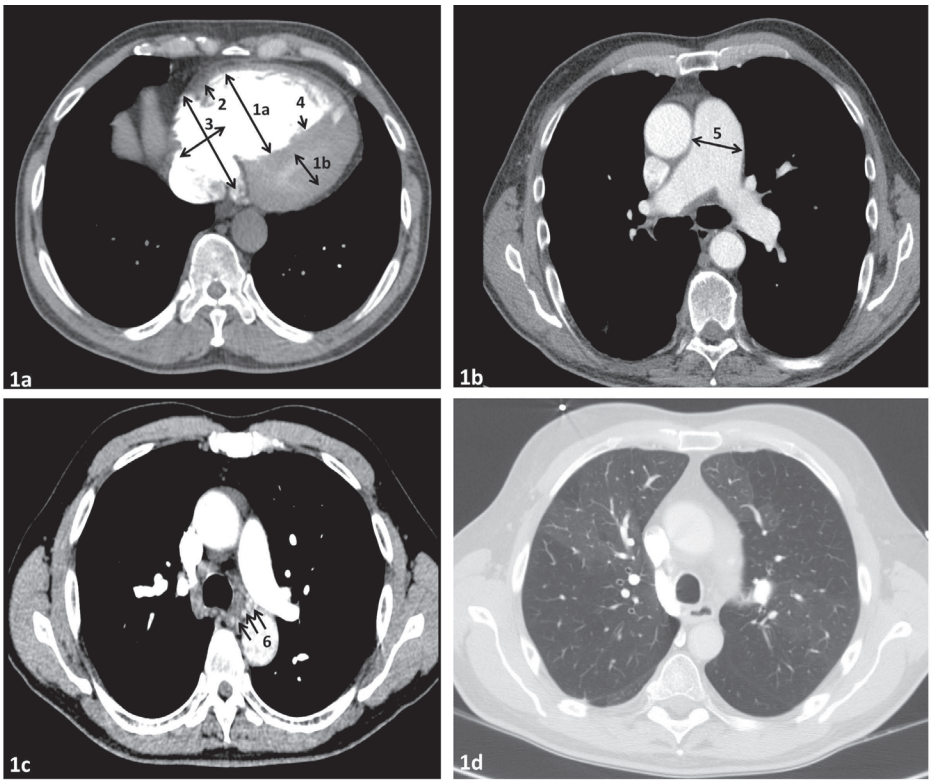

Figure 1. Pulmonary hypertension characteristics found on axial CTPA images.
Fig 1a: 1. Right ventricle dilatation based on right (1a) -to- left (1b) ventricle diameter ratio of >1.0; 2. Right ventricle hypertrophy ; 3. Right atrial dilatation ; 4. Flattening/inversion of the interventricular septum.
Fig 1b: 5. Dilatation of the main pulmonary artery.
Fig 1c: 6. Dilated bronchial arteries.
Fig 1d: Mosaic perfusion.
Note: CTPA: computed tomography pulmonary angiography.

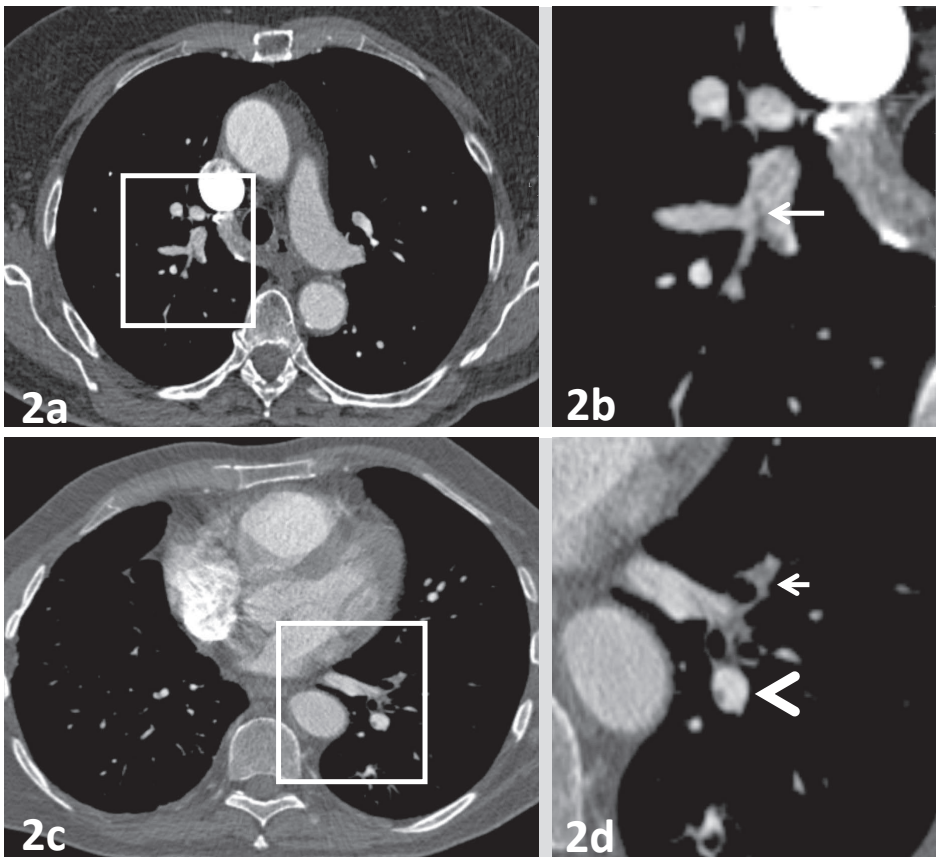

Figure 2. Chronic thrombus remnants characteristics found on axial CTPA images.
Fig 2a and b (zoomed-in): Intravascular webs in the right upper lobe artery (arrow).
Fig 2c and d (zoomed-in): Retraction of the anterobasal segment artery of the left lower lobe (arrow), note the difference in size compared with the segmental posterior artery of the left lower lobe (arrrowhead).
Note: CTPA: computed tomography pulmonary angiography.

Study outcome and definitions

The primary aim of the study was to assess whether careful reading of CTPA scans performed for suspected acute PE can differentiate patients with acute PE without CTEPH from those with already existing CTEPH. The secondary aims of the study were: 1) to evaluate the interobserver agreement of the three expert radiologists for the diagnosis of CTEPH and 2) to identify the best (set of) predictive radiological signs of CTEPH on CTPA for acute PE. To avoid misclassification bias, the radiological signs of CTEPH were indicated as predictive for CTEPH diagnosis, as it is impossible to prove that these patient already had CTEPH at that moment.

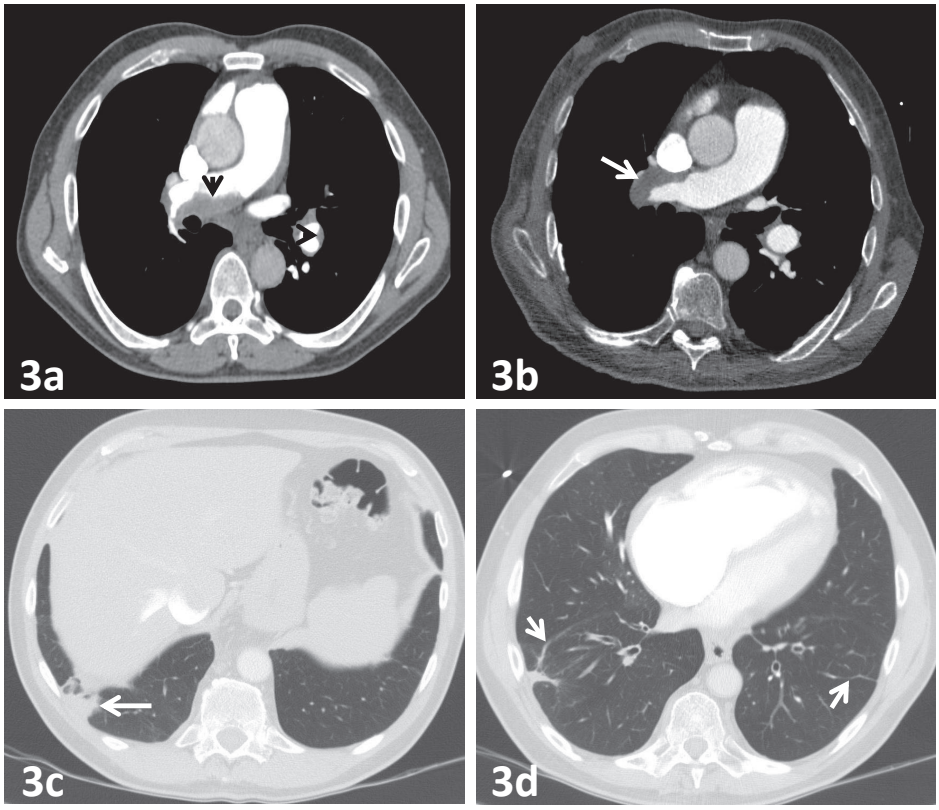

Figure 3. Chronic thrombus remnants characteristics found on axial CTPA images.
Fig 3a: Residual thrombus attached to the vascular wall (arrows).
Fig 3b: Total occlusion of the right pulmonary artery (arrow).
Fig 3c: Pulmonary infarction in the laterobasal segment of the right lower lobe (arrow).
Fig 3d: Parenchymal bands in the laterobasal segments of the left- and right lower lobe (arrows).
Note: CTPA: computed tomography pulmonary angiography.

Statistical analysis

Baseline characteristics of the patients are provided with corresponding frequencies. Differences between the two cohorts with regard to categorical variables were calculated using odds ratios (OR) with corresponding 95% confidence intervals (95%CI). Final patient allocation by the radiologists was based on majority rule. Odds ratio, sensitivity and specificity of the patient allocation were calculated with corresponding 95%CI. We predefined a sensitivity >80% and/or a specificity >80% as 'relevant' accuracy. The interobserver agreement for allocation of the patients in either of the two groups was determined by using Cohen's kappa-statistics. The kappa value for agreement was interpreted as follows: poor (< 0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or very good (0.81–1.00) [21].

Next, we determined the accuracy of all individual radiological signs studied for a future CTEPH diagnosis in univariate analysis by calculating ORs with corresponding 95%CI. The 10 strongest predictors from univariate analysis were included in a multivariable backward conditional stepwise logistic regression model. All items left in the final model were considered to be independently associated with a CTEPH diagnosis in the clinical course of acute PE. The predictive accuracy of the combination of the identified independent predictors was evaluated using receiver operating characteristic (ROC) curve analysis in all 100 study patients. Optimal threshold of the number of radiological signs for patients at high risk was determined based on comparison of the area under the curves (AUC). The sensitivity and specificity of this threshold was calculated for the complete study population. All analyses were performed using SPSS software version 23 for Windows IBM Corporation.

RESULTS

Patients

The patient characteristics at the moment of the initial CTPA scan for the PE diagnosis are provided in **Table 1.** Mean age at the time of PE diagnosis was 61 ± 15 years in cases and 56 ± 15 years in controls. A total of 43 (86%) cases had an unprovoked acute PE event and 20 (40%) had recurrent venous thromboembolism (VTE). In the control cohort, these numbers were 29 (58%) and 10 (20%) respectively for ORs of 5.2 (95%CI 2.0-14) and 2.7 (95%CI 1.1-6.5), respectively. Symptom onset was >2 weeks before PE diagnosis in 43 (86%) cases compared with 6 (12%) controls for an OR of 45 (95%CI 14-145). The median RV/LV diameter ratio at the time of the PE diagnosis was 1.5 ± 0.4 for the cases and 1.1 ± 0.2 for the controls. The cases were referred for CTEPH diagnosis after a median of 7.1 months (IQR 4.7-12.3) following the initial CTPA scan performed for diagnosing PE.

CTPA scan quality

Twelve of the 100 CTPA scans were judged to be of suboptimal quality due to motion artefacts and/or inadequate contrast timing for diagnosing acute PE. One of these latter CTPA scans could not be assessed for the presence of chronic thrombus remnants at all because of completely insufficient scan timing. This patient was therefore allocated to the control cohort by all three expert readers. All 100 scans were included in the primary analysis.

Table 1. Patient characteristics.

	Cases (patients diagnosed with CTEPH during follow-up after PE) (n=50)	Controls (patients who did not develop CTEPH after PE) (n=50)	Differences
Age at PE diagnosis (mean, SD)	61 (15)	56 (15)	0.04[#]
Male sex (n, %)	23 (46)	17 (34)	1.7 (0.74-3.7)[^]
Unprovoked PE (n, %)	43 (86)	27 (54)	5.2 (2.0-14)[^]
Recurrent VTE	20 (40)	10 (20)	2.7 (1.1-6.5)[^]
Onset of symptoms > 2 weeks before PE diagnosis	43 (86)[*]	6 (12)	45 (14-145)[^]
Comorbidities at the moment of PE			
COPD (n, %)	10 (20)	4 (8)	2.9 (0.84-9.9)[^]
Chronic left heart failure (n, %)	4 (8)	3 (6)	1.4 (0.29-6.4)[^]
Malignancy (n, %)	7 (14)	14 (28)	0.42 (0.15-1.1)[^]

Note: CTEPH: chronic thromboembolic pulmonary hypertension; PE: pulmonary embolism; SD: standard deviation; VTE: venous thromboembolism; COPD: chronic obstructive pulmonary disease.
Differences calculated by using: [#]students T test; [^]OR with corresponding 95% confidence interval; [*]missing in 3 patients.

Distinction of CTEPH from acute PE

The results of CTPA scoring are displayed in **Table 2.** A total of 39 patients were diagnosed as having CTEPH and 61 as not having CTEPH. The OR for a CTEPH diagnosis during follow-up for those former 39 patients was 40 (95%CI 11-151). This final diagnosis yielded a sensitivity of 72% (95%CI 58-84) and a specificity of 94% (95%CI 83-99%). Of the 50 CTEPH cases, any sign of acute PE was identified in 37 (74%) patients and signs of chronic thrombus remnants in 44 (88%). A total of 31 (62%) patients were scored as having both acute PE and chronic thrombus remnants. For the control cohort, these numbers of acute PE and chronic thrombus remnants were 46 (92%) and 11 (22%), respectively.

A total of 14 CTEPH cases were not identified. The CTPA scan in one of them was technically inadequate for diagnosis of CTEPH as described above. Moreover, in those 14 patients, the median duration between PE diagnosis and referral to the VUMC was 11 (IQR 4.9-19) months. In the 36 patients correctly identified, this time period was 6.7 (IQR 4.5-16) months (P=0.13 for difference). None of the patient characteristics available for analysis were associated with incorrect allocation (**Supplement 1**).

Radiological parameters for future CTEPH diagnosis

All radiological parameters for chronic thrombus remnants and PH were highly associated with a future CTEPH diagnosis in univariate analysis, with ORs ranging from 4.4 to

Table 2. Results of CTPA scoring by three expert radiologists based on majority rule.

	Signs of chronic thrombus remnants (n, %)	Signs of acute PE (n, %)	Signs of acute PE and chronic thrombus remnants (n,%)	Signs of PH (n,%)	Overall judgment CTEPH yes/no (n, %)
Cases: patients diagnosed with CTEPH during follow-up after PE (n=50)	44 (88)	37 (74)	31 (62)	43 (86)	36 (72)
Controls: patients who did not develop CTEPH after PE (n=50)	11 (22)	46 (92)	10 (20)	9 (18)	3 (6)

Note: PE: pulmonary embolism; PH: pulmonary hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; CTPA: computed tomography pulmonary angiography.

infinite (**Table 3**)**.** The latter indicates that the specific radiological parameter was not identified in any of the controls but in at least one of the cases. Signs of chronic thrombus remnants with the highest predictive value for CTEPH diagnosis were: presence of intravascular webs (OR 48; 95%CI 13-177), thrombus adherent to the vascular wall (OR 44; 95%CI 9.2-207), complete arterial occlusion (OR 5.0; 95%CI 1.8-14), arterial retraction (OR 26; 95%CI 8.0-82) and post-stenotic vascular dilatation (OR infinite). Signs of PH with the highest predictive value for a future CTEPH diagnosis were: dilatation of the main pulmonary artery (OR 18; 95%CI 6.2-55), RV hypertrophy (OR infinite), flattening of the interventricular septum (OR 18; 95%CI 6.1-55), mosaic perfusion (OR 20; 95%CI 6.0-69) and dilated bronchial arteries (OR 13; 95%CI 4.0-39).

Multivariate regression analysis revealed the following six radiological parameters to be independent predictors for a future CTEPH diagnosis: presence of intravascular webs (adjusted OR 209; 95%CI 4.2->1000), retraction (adjusted OR 47; 95%CI 1.9->1000), dilatation of the bronchial arteries (adjusted OR 19; 95%CI 0.71-516), dilatation of the pulmonary arteries (adjusted OR 14; 95%CI 0.82-248), RV hypertrophy (adjusted OR infinite) and flattening of the interventricular septum (adjusted OR 9.9; 95%CI 0.61-161). The overall AUC of the ROC curve for these six variables was 0.99 (95%CI 0.97-1.0). The most optimal threshold for a future CTEPH diagnosis was three or more of these radiological parameters, for a C-statistic of 0.92 (95%CI 0.86-0.99). Patients with three or more of these radiological parameters had a higher risk of a future CTEPH diagnosis than those with less than three parameters, for an OR of 56 (95%CI 12-261). This model yielded a sensitivity of 70% (95%CI 55-82) and a specificity of 96% (95%CI 86-100). Kappa values for the assessment of the individual 6 independent predictors of CTEPH ranged between 0.53 and 0.83, with 75% of all kappa's ≥ 0.7.

Table 3. Univariate and multivariate analysis on radiological parameters of a future CTEPH diagnosis in the clinical course of acute PE.

Scored radiological parameter	Scored in number of cases n=36	Scored in number of controls n=50	Univariate analysis		Multivariate analysis	
			OR	95%CI	OR	95%CI
Signs of chronic PE						
Intravascular webs	29	4	48	13-177	209	4.2->1000
Thrombus attached to the vascular wall	34	14	44	9.2-207		
Complete arterial occlusion	30	25	5.0	1.8-14		
Arterial retraction	28	6	26	8.0-82	47	1.9->1000
Post-stenotic vascular dilatation	2	0	Infinite			
Pulmonary infarction	21	12	4.4	1.8-11		
Parenchymal bands	10	4	4.4	1.3-16		
Signs of PH						
Dilatation of the main pulmonary artery	28	8	18	6.2-55	14	0.82-248
RV hypertrophy	14	0	Infinite		Infinite	
Flattening of the interventricular septum	27	7	18	6.1-55	9.9	0.61-161
Dilated bronchial arteries	21	5	13	4.0-39	19	0.71-516
Mosaic perfusion	23	4	20	6.0-69		

Note: OR: odds ratio; CI: confidence interval; PE: pulmonary embolism, PH: pulmonary hypertension; RV: right ventricular.

DISCUSSION

In this study we have demonstrated that expert radiologists were able to identify 36 of 50 patients with acute PE who were later diagnosed with CTEPH and correctly excluded CTEPH in 47 out of 50 patients from those who did not develop CTEPH after at least 2 years of follow-up, based on close reading of the CTPA scan performed for the initial PE diagnosis. The interobserver agreement between the three expert radiologists for the majority of the best predictive radiological parameters was good. The presence of three or more of these best predicting parameters was strongly predictive of a CTEPH diagnosis.

Our findings have two main explanations. First, it is likely that CTEPH was already present at the moment of the initial PE diagnosis but that CTEPH characteristics were not recognized when not sought for. Second, chronic thrombus remnants may increase

the risk of future CTEPH development. Although the design of our study does not allow differentiation between the two, we consider the first explanation the most likely. First, we found high diagnostic accuracy for all evaluated radiological parameters of CTEPH. This could not be explained by any other fact than that CTEPH was already developing or present, especially since the specificity we found in our cohort approximates the established specificity of CTPA for CTEPH [8]. Importantly, we did not set out to find *new* radiological signs for CTEPH but only evaluated established ones. Second, the vast majority of cases reported to have symptoms of dyspnoea for longer than two weeks before diagnosis of acute PE, in contrast to the controls. This is an argument supporting the presence of CTEPH in addition to acute PE as well [22, 23].

Interestingly, almost all cases had radiological signs of acute PE as well, which supports the validity of this diagnosis of 'acute on chronic' PE in these patients. On the other hand, a small number of the controls had signs of chronic thrombus remnants and/or PH as well, although PH was not confirmed by sequential echocardiography after 2 years of follow-up. Earlier studies also suggested that the prevalence of radiological parameters of chronic thrombus remnants and/or PH is 20% in patients who do not have echocardiographic signs of CTEPH after a 2-year follow-up period [6]. The clinical relevance of these findings is unknown, especially since it is unclear if these patients develop CTEPH beyond the first two years from the acute PE event.

How can our findings be useful for clinical practice? It seems clear that specific radiological findings on CTPA may accurately predict CTEPH diagnosis, or the concurrent presence of CTEPH. Several considerations need however to be taken into account. The control patients were selected based on RV dilatation to force the radiologist to focus on the subtle aspects of thrombus remnants and to prevent bias towards overestimation of our primary endpoint. The results of this study are therefore only applicable to PE patients with signs of RV overload. Nevertheless, it is not likely that PE patients without RV overload have CTEPH. Also, the interobserver agreement between the expert thoracic radiologists was mostly good. The performance for less specialized radiologists may be less, and additional training may be needed for them.

Strong points of this study are the blind assessment of the CTPA scans by three independent expert radiologists, the relative large number of patients with CTEPH and the selection of the controls based on RV dysfunction. Also, the fact that not all CTPA scans were of excellent technical quality underlines the fact that our study truly represents daily practice rather than trial circumstances, favouring external validity of our findings.

The main study limitation is that we studied clear-cut cases of patients with CTEPH and PE patients with right ventricular overload who did not develop CTEPH after 2 years of follow-up, while in clinical practice, the presentation of CTEPH is heterogeneous and the diagnosis is often challenging, for instance considering other conditions that may cause PH such as left sided heart failure and/or chronic obstructive pulmonary disease

[24, 25]. Moreover, the prevalence of CTEPH in the cohort was 50%, while this number is much lower in clinical practice. This may have influenced the predictive value of the identified radiological parameters.

In conclusion, we showed that expert radiologists are able to accurately identify patients who were later on diagnosed with CTEPH based on careful reading of the CTPA scan performed in the setting of suspected acute PE. We identified six radiological parameters that proved to be independent predictors of definite CTEPH diagnosis in the clinical course of acute PE. The presence of three or more of these radiological parameters was associated with a 56-fold higher incidence of CTEPH, with a sensitivity of 70% and a specificity of 96%. Our findings support the hypothesis that dedicated CTPA reading in patients with acute PE with integral focus on signs of chronic thrombus remnants and PH may help to detect CTEPH earlier, which may improve the prognosis of these patients with CTEPH [26].

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Supplement 1. Patient characteristics of the cases identified versus those not identified.

	Cases identified as CTEPH (n=36)	Cases not identified as CTEPH (n=14)	Difference
Age at moment of PE diagnosis (mean, SD)	62 (15)	64 (16)	0.79[#]
Male sex (n, %)	17 (47)	6 (43)	0.83 (0.24-2.9)[^]
Unprovoked PE (n, %)	31 (86)	12 (86)	0.97 (0.16-5.7)[^]
Recurrent VTE (n, %)	14 (39)	6 (43)	1.2 (0.34-4.1)[^]
Duration between PE diagnosis and referral to VUMC (month; median, IQR)	6.7 (4.5-16)	10.5 (4.9-19)	0.13[‡]
Malignancy (n, %)	4 (11)	3 (21)	2.2 (0.42-11)[^]
Cardiopulmonary comorbidity (n, %)	10 (28)	4 (29)	1.0 (0.26-4.1)[^]

Note: PE: pulmonary embolism; VTE: venous thromboembolism; VUMC: VU university medical Center Amsterdam.

[#] Independent sample t-test; [^]OR with corresponding 95% confidence interval; [‡]Mann Whitney U test.

Chapter 7

Healthcare utilisation in chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

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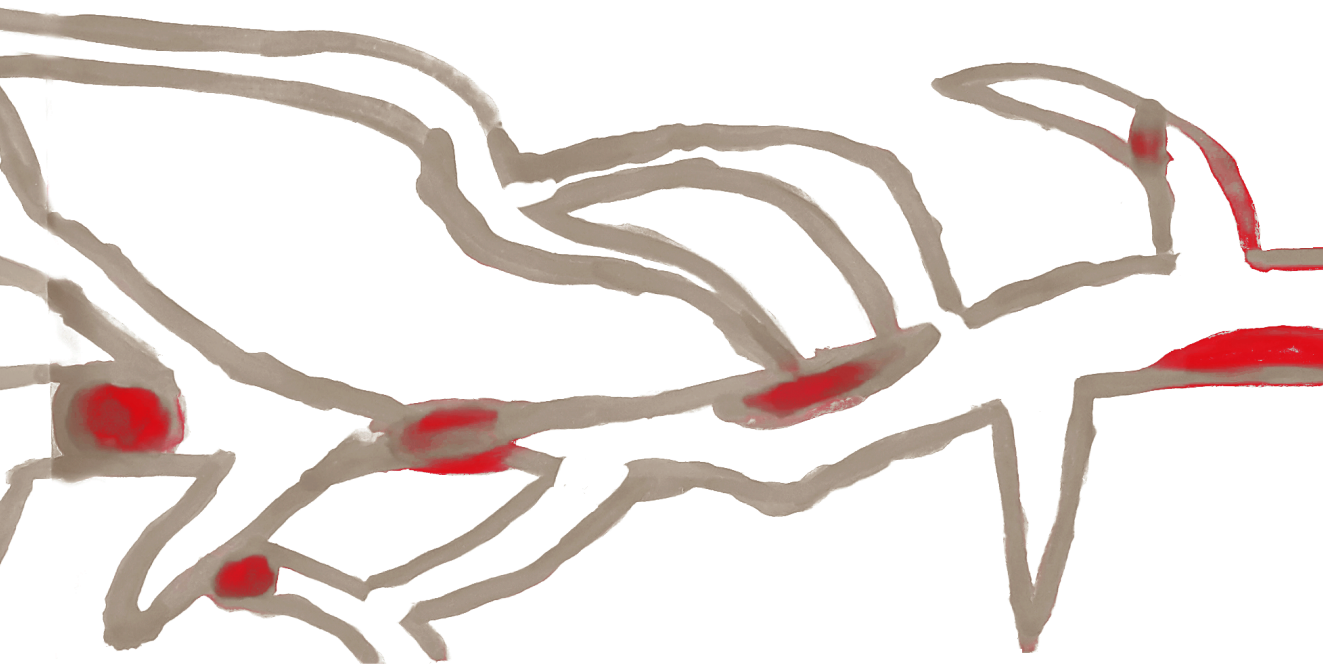

ABSTRACT

Background The median diagnostic delay of chronic thromboembolic pulmonary hypertension (CTEPH) is 14 months, which may affect prognosis. We aimed to explore healthcare utilisation of patients diagnosed with CTEPH after acute pulmonary embolism (PE) and to identify the causes of diagnostic delay.

Methods We collected all data of patient's symptoms, medical specialist referrals and ordered diagnostic tests to reconstruct the clinical pathways of 40 patients referred to the VU University Medical Center Amsterdam (VUMC, the Netherlands) for CTEPH treatment. Diagnostic delay was defined as the time between first symptom onset and referral to the VUMC. Correlations of patient specific characteristics and diagnostic delay were evaluated.

Results Patients consulted four (median) different physicians for a median of 13 (inter quartile range [IQR] 10-18) consultations before the correct diagnosis was made. The median diagnostic delay was 21 (IQR 12-49) months. Echocardiographic results suggestive of CTEPH were not always followed by an adequate work-up; most patients were not subjected to ventilation/perfusion scanning. Prior cardiopulmonary comorbidity and recurrent venous thromboembolism were predictors of a longer delay.

Conclusion Healthcare utilisation in patients before their final CTEPH diagnosis was far from optimal, contributing to a considerable diagnostic delay. Better education and higher awareness of CTEPH among PE caretakers may lead to faster diagnosis.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially curable long term complication of acute pulmonary embolism (PE), occurring in ~3.2% of PE survivors [1]. CTEPH is caused by persistent obstruction of the pulmonary arteries by major vessel thromboembolism and vascular remodelling that result in increasing vascular resistance and progressive right heart failure [2]. CTEPH can be cured by surgical removal of these chronic thrombi by pulmonary endarterectomy (PEA) [2, 3]. However, when PEA is not feasible, owing to advanced distal pulmonary artery remodelling or the patient's performance status, the prognosis is poor [3-5]. Therefore, early CTEPH diagnosis and referral to an expert center are both crucial for optimal treatment [2, 3, 6]. Notably, the often nonspecific and insidious clinical presentation of CTEPH requires a high level of suspicion in patients presenting with unexplained new or persisting symptoms suggestive of CTEPH in the clinical course of acute PE [7]. Early CTEPH diagnosis has already been proven to be a major clinical challenge as demonstrated by a median diagnostic delay of 14 months in the International CTEPH registry [8].

In clinical practice, the diagnostic process of CTEPH after a PE diagnosis may take some time, and often involves multiple healthcare providers from different clinical specialties [2, 3, 8, 9]. This diagnostic process may even be longer in patients without a previous acute PE diagnosis. Prior research has consistently identified a gap between what is identified as "best practice" by scientific evidence and recommended by the guidelines, and patterns of clinical practice [3, 10, 11]. It was shown that only 33-54% of 1748 patients diagnosed with CTEPH underwent a ventilation perfusion (V-Q) lung scan during diagnostic work-up, and that only 25-44% were referred to a dedicated multidisciplinary CTEPH team [10], although both are indicated [3].

An improved understanding of healthcare utilisation, including diagnostic testing and referral patterns, among patients diagnosed with PE with new or persistent dyspnoea would be an important first step in further optimizing the diagnostic process for CTEPH. The aim of this study was to explore the healthcare utilisation of PE patients who were diagnosed with CTEPH, and to identify causes of diagnostic delay.

METHODS

Study population

Consecutive patients diagnosed at the VU University Medical Center Amsterdam (VUMC) with CTEPH between 2014 and 2016, were eligible for inclusion. Because the VUMC is the primary referral center for CTEPH in the Netherlands, we consider the patients studied to be a representative sample for the Dutch situation. CTEPH was diagnosed according

to the most recent guidelines [3], based on the results of right heart catheterisation (RHC) and pulmonary angiography in all patients. Patients with no previous diagnosis of acute PE, those below 18 years of age or those with any psychological condition that would preclude completion of the study were excluded from participation. This study was approved by the institutional review board of the VUMC, and all patients provided informed consent.

Study procedures

To evaluate healthcare utilisation from first symptom onset to referral to the CTEPH expertise center, all patients were subjected to an extensive and structured interview by one of the investigators (Y.E-V). Moreover, original medical charts were scrutinized. During the interview, patients were questioned on their medical history, including the number of previous PE and deep vein thrombosis (DVT) events, the moment of symptom onset, the course of symptoms before and after the diagnosis of acute PE, the clinical course of symptoms related to CTEPH, the first physician visited for these symptoms, the diagnostic tests performed, and the number and type of clinical referrals.

On the basis of the information provided by the patients, all relevant medical charts from relevant departments and hospitals were collected and scrutinized for the number and type of physicians consulted, the dates when they were consulted, the date of PE diagnosis, and the dates and results of imaging and/or functional tests performed, including echocardiography and V-Q lung scans. Data from the charts and the interview were correlated and combined in the study database, and the healthcare utilisation from the moment of symptom onset up to the moment of referral to the VUMC was reconstructed.

Study outcome and definitions

The primary aim of this study was to assess the health care utilisation for each individual patient from moment of first symptom onset to referral to the VUMC for CTEPH diagnosis. We also aimed to evaluate whether the following patient-specific characteristics were associated with diagnostic delay: age, sex, body mass index (BMI), number of prior venous thromboembolic (VTE) events and the presence of cardiopulmonary comorbidities, including chronic obstructive pulmonary disease (COPD), pulmonary infections, cardiac ischemia, and left-sided heart failure. To assess the potential presence of CTEPH at the moment of the index PE diagnosis, we also evaluated the presence of chronic PE or pulmonary hypertension (PH) on the computed tomography pulmonary angiogram (CTPA) performed for PE diagnosis. This evaluation was based on the original CTPA report and -if the original scan images were available- on a retrospective evaluation of the CTPA scan by an expert radiologist (L.J.M.).

Statistical analysis

Baseline characteristics of the patients are provided with corresponding frequencies. The median numbers with corresponding inter quartile range (IQRs) of consulted physicians, consultations and diagnostic tests performed were calculated. Three specific forms of delay were considered: 1) patient delay, i.e. the time between the onset of the first symptoms of CTEPH to first contact with a physician; 2) doctor delay, defined as the time between first contact with the first consulted physician to referral to the VUMC; and 3) overall diagnostic delay combining both periods. All three were reported in median number of months with corresponding IQRs.

The association of patient-specific characteristics with the predefined categories of patient, doctor and overall diagnostic delay was assessed with univariate logistic regression analyses. For this analysis the 25% of patients with the longest delay were compared with the remaining patients. A P-value of <0.05 was considered statistically significant. All analyses were performed using SPSS software version 23 for Windows IBM Corporation.

RESULTS

Patients

A total of 64 patients were diagnosed with CTEPH in the VUMC between 2014 and 2016. Of these 64 patients, 12 had no documented previous acute PE event and two could not be reached. Ten patients refused participation because of lack of time (n=6), lack of detailed memory (n=3), and hearing impairment (n=1), leaving 40 patients signing informed consent. The baseline patient characteristics are presented in **Table 1**. The mean age at the moment of referral to the VUMC was 65 ±15 years and 21 (53%) of the patients were male. A total of 16 (40%) patients were diagnosed with recurrent VTE before the CTEPH diagnosis. Anticoagulation treatment for the acute PE consisted of vitamin K antagonists in 38 (95%) patients. Two (5.0%) patients were treated with direct oral anticoagulants.

Of the 40 patients, 39 patients reported that the onset of CTEPH symptoms preceded the diagnosis of acute PE, and none of these patients completely recovered, despite anticoagulant treatment: 36 (90%) patients reported persistence of dyspnoea, seven (18%) persistence of pain, seven (18%) persistence of palpitations and 21 (53%) persistence of fatigue following the index PE diagnosis.

In nine of the 40 patients, the presence of chronic PE had already been suggested by the radiologist on the original report of CTPA performed for acute PE diagnosis. After re-evaluation of the CTPA scans, signs of chronic PE and/or PH were identified in an additional 23 patients. One CTPA scan could not be assessed for this purpose, owing to inadequate contrast timing, and the remaining seven scans were unavailable for re-evaluation.

Table 1. Patient characteristics.

	Patients (n=40)
Age at CTEPH referral (mean, SD)	65 (15)
Male sex (n, %)	21 (53)
BMI (mean, SD)	26 (4)
Number of patients with 1 VTE event (n,%)*	21 (53)
Number of patients with 2 VTE events (n,%) *	15 (38)
Number of patients with 3 VTE events (n,%) *	4 (10)
Number of patients with a DVT diagnosis concomitant to the index PE (n,%)	4 (10)
Treatment of last PE event	
Vitamin K antagonist (n,%)	38 (95)
DOAC (n,%)	2 (5.0)
Comorbidities at the moment of CTEPH referral	
COPD (n,%)	8 (20)
Pulmonary infection	2 (5.0)
Cardiac ischemia (n,%)	2 (5.0)
Rheumatologic diseases (n,%)	5 (13)
Malignancy (n,%)	5 (13)
Splenectomy (n,%)	0
Prior infected pace maker lead (n,%)	0
Known antiphospholipid syndrome (n,%)	1 (2.5)

Note: CTEPH: chronic thromboembolic pulmonary hypertension; SD: standard deviation; BMI: body mass index; PE: pulmonary embolism; IQR: inter quartile range; DVT: deep vein thrombosis; VTE: venous thromboembolism; DOAC: direct oral anticoagulants; COPD: chronic obstructive pulmonary disease.
* Number of VTE events at the time of symptom onset.

Health care utilisation

The first physician that the patient consulted after symptom onset was the general practitioner (GP) for 37 (93%) patients, a rheumatologist for two (5.0%) patients, and a cardiologist for one patient (2.5%). A complete overview of the order of consulted physicians per specialty and per hospital is presented in **Figure 1.** Six patients consulted physicians in two or more different hospitals before referral to the VUMC.

Before referral to the VUMC, patients consulted a median number of four (IQR 4-5) different physicians for a median number of 13 (IQR 10-18) consultations. All 40 patients were evaluated by at least a GP and a cardiologist during the diagnostic process. Of the 40 patients, 24 consulted one GP and 16 patients consulted more than 1 GP. Thirty-one patients consulted one cardiologist, and nine consulted more than one cardiologist. Thirty-nine (98%) patients consulted a pulmonologist, and 17 patients consulted more than one pulmonologist. Nine (23%) patients consulted an internist (**Supplement 1**).

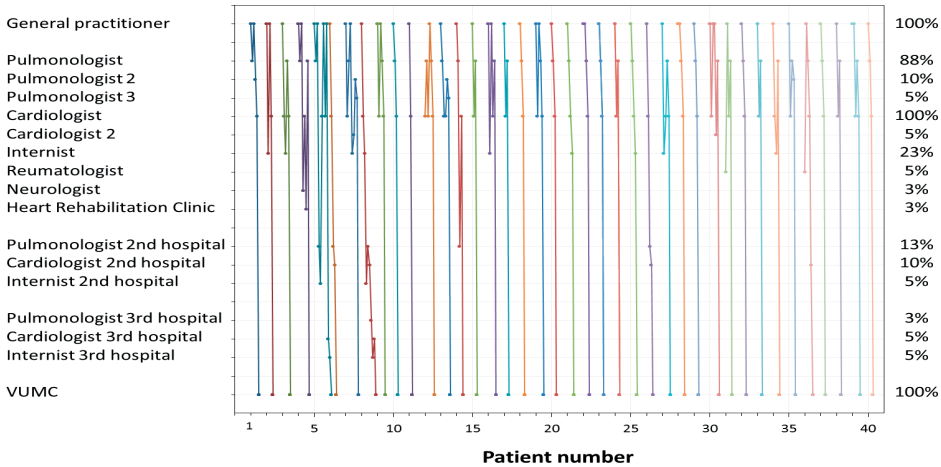

Figure 1. Overview of consulted physicians per patient.
The y-axis represents the number of physicians per specialty and per hospital that were consulted for each individual patient before referral to the VU University Medical Center Amsterdam. The z-axis represents the overall percentage of patients who visited the specific specialist.

Thirty-seven patients were referred to the VUMC by a pulmonologist, two by a cardiologist and one patient by an internist.

During the diagnostic process, all 40 patients underwent echocardiography; 13 had one echocardiogram, and 11 patients had three or more echocardiograms. PH was concluded not to be present in nine patients on the first echocardiogram. However, in retrospect, some of these latter patients had subtle signs of PH on the echocardiogram, such as an enlarged right ventricle, a short acceleration time over the pulmonary valve, or a slightly elevated mean pulmonary arterial pressure. Therefore, it is quite possible that these patients already had CTEPH at that specific moment. For these nine patients, the median time between the first normal echocardiogram and the first echocardiogram with PH was 8 months (IQR 2-59). In all 40 patients, the median time between the first abnormal echocardiogram and referral to the VUMC was 4 months (IQR 1-12). In 16 (40%) patients, this latter period was longer than 6 months.

A V-Q lung scan was performed in 26 (52%) patients before referral to the VUMC, and showed perfusion defects in all. The median time between an abnormal V-Q lung scan and referral to the VUMC was 0.63 (0.23-5.5) months. RHC was performed in 11 (22%) patients before referral to the VUMC. The median time between an abnormal RHC and referral to the VUMC was 1.7 (IQR 0.43-3.8) months.

Patient, doctor and overall diagnostic delay

The median patient delay, from the first symptoms of CTEPH to the first contact with a physician, was 3.3 months (IQR 0.47-8.9) (**Table 2**). The median doctor delay, defined as

Table 2. Patient, doctor and overall diagnostic delays; the evident longer median overall diagnostic delay than the combined median patient delay and doctor delay was caused by large individual differences in patient- and doctor delay per patient.

		Patients (n=40)
Patient delay months (median, IQR)		3.3 (0.47-8.9)
	< 14 days (n,%)	10 (25)
	14 days-1 month (n,%)	4 (10)
	1-6 months (n,%)	12 (30)
	>6 months (n,%)	14 (35)
Doctors delay months (median, IQR)		15 (7.7-28)
	<6 months (n,%)	8 (20)
	6-12 months (n,%)	7 (17)
	12-24 months (n,%)	14 (35)
	>24 months (n,%)	11 (28)
Total diagnostic delay months (median, IQR)		21 (12-49)
	<6 months (n,%)	2 (5.0)
	6-12 months (n,%)	7 (16)
	12-24 months (n,%)	12 (30)
	>24 months (n,%)	19 (48)

Note: IQR: inter quartile range.

the moment of first physician contact after symptom onset until referral to the VUMC was 15 months (IQR 7.7-28). The median overall diagnostic delay was 21 months (IQR 12-49). This evident longer median overall diagnostic delay than the combined medians of each delay is caused by considerable individual differences in patient and doctor delay per patient, with skewed distribution of both doctor and patient delays.

In the 39 patients with persistent functional limitation or pain after the acute PE, the median time between first symptoms and the index PE diagnosis was 9.5 months (IQR 3.9-33), the time between first physician contact and the index PE diagnosis was 3.0 months (IQR 0.15-8.7) and the time between the index PE diagnosis and referral to the VUMC was 6.7 months (IQR 4.2-16).

Patient-specific factors associated with delay

The median patient delay of patients in the upper quartile of delay was 33 months (IQR 26-39), and that in patients in the first to third quartile was 1 month (IQR 0.34-3.8). None of the studied patient characteristics showed a correlation with longer patient delay (**Table 3**).

The median doctor delay of patients in the upper quartile of delay was 69 months (IQR 44-109), and that in patients in the first to third quartile was 12 months (IQR 5.6-17). Cardiopulmonary comorbidity (odds ratio [OR] 7.5; 95% confidence interval [CI] 1.5-37)

Table 3. Univariate regression analysis of patient-specific factors associated with longer delay.

	Patient delay OR* (95%CI)	Doctor delay OR# (95%CI)	Overall diagnostic delay OR^ (95%CI)
Age >65year	2.7 (0.57-12.3)	0.85 (0.21-3.7)	0.88 (0.21-3.7)
Male sex	3.5 (0.75-16.3)	0.38 (0.08-1.7)	1.1 (0.27-4.8)
BMI >30	0.56 (0.06-5.4)	1.6 (0.25-10.6)	1.6 (0.25-10.6)
Cardiopulmonary comorbidity	2.2 (0.48-10.0)	7.5 (1.5-36.7)†	4.0 (0.87-18.4)
VTE>1 event¥	2.0 (0.47-8.4)	6.9 (1.2-39)†	6.9 (1.2-39)†

Note: OR: Odds ratio; CI: confidence interval; BMI: body mass index; PE: pulmonary embolism; DVT: deep vein thrombosis; VTE: venous thromboembolism;
*25% of patients with the longest patient delay were selected; #25% of patients with the longest doctors delay were selected; ^25% of patients with the longest diagnostic delay were selected. †Statistically significant at p<0.05; ¥ One or more recurrent VTEs (regardless of when the patient developed symptoms of CTEPH).

and a recurrent VTE event (OR 6.9; 95%CI 1.2-39) were significantly associated with a longer doctor delay.

The median overall diagnostic delay of the patients in the upper quartile of delay was 72 months (IQR 62-132) and that in the remaining patients was 16 months (IQR 9.0-26). A recurrent VTE event (OR 6.9; 95%CI 1.2-39) was the only predictor of a longer overall diagnostic delay.

DISCUSSION

In this study, we evaluated the health care utilisation in obtaining the correct diagnosis of 40 patients with CTEPH after a diagnosis of acute PE. Our main finding was that patients consulted a large number of different physicians for many consultations before the correct diagnosis was made. The median overall diagnostic delay was 21 months, and consisted mostly of doctor delay. Moreover, abnormal diagnostic tests suggestive of CTEPH were not always followed by further evaluation, as recommended by current guidelines. Prior cardiopulmonary comorbidity and recurrent VTE were associated with longer delay, but age, sex and BMI were not. Finally, radiological signs of CTEPH were already present on the first available CTPA of the index PE diagnosis in the majority of patients, and many patients reported symptoms compatible with CTEPH long before the index PE diagnosis. This probably indicates that they already had CTEPH at the moment of the index diagnosis of PE, which was misclassified as an acute PE. Although recall bias may limit the validity of this observation, similar findings from a French study support this hypothesis [12]. In this study, a retrospective evaluation of the initial CTPA scan for signs of CTEPH at the moment of PE diagnosis showed that all seven patients diagnosed

with CTEPH already had several clear radiological signs of CTEPH at the moment of the PE diagnosis. Moreover, we speculate that the fact that recurrent VTE was associated with longer overall diagnostic delay may also be explained by diagnostic misclassification of CTEPH.

By reconstructing the health care utilisation of the 40 patients diagnosed with CTEPH and included in this study, we demonstrated an overall median diagnostic delay of 21 months (IQR 12-49), which is even longer than the 14 months reported in the International registry, although IQRs do overlap [8]. Patients experienced symptoms for a median of 3.3 months (IQR 0.47-8.9) before they contacted a physician. In comparison, patients diagnosed with idiopathic pulmonary hypertension were found to have a median diagnostic delay of 44 months (IQR 21-65) from first symptom onset to diagnosis [13]. In this particular study, patients consulted their GP a mean number of 5.3 ± 3.8 times and were seen by 3.0 ± 2.1 specialists before referral to a PH expertise center.

Recurrent VTE was an independent predictor of longer delay. One possible explanation for this is that, as we outlined above, the VTE recurrence was not an actual recurrence but a misclassified CTEPH. Unfortunately, we did not have all original radiological images available to confirm this hypothesis. In addition to recurrent VTE, prior cardiopulmonary comorbidity was identified as a relevant predictor of a longer doctor delay. A possible explanation for this may be the clinical assumption that the reported signs and symptoms were caused by these cardiopulmonary comorbidities, so that CTEPH was not considered immediately. From the International CTEPH registry, it is known that many patients with CTEPH have a concomitant diagnosis of coronary disease (12% of patients) and COPD (9.5% of patients) [8]. Hence, a CTEPH diagnosis should be considered in all patients who do not completely recover after an acute PE event, even in the presence of other conditions that may explain the presentation of the patient.

Doctor delay contributed for a larger extent then patient delay to the overall diagnostic delay. It took a median of 13 consultations by four different physicians to reach the correct diagnosis. We have two explanations for this phenomenon. First, CTEPH has a low incidence and often has an insidious presentation. The number of patients reporting persisting symptoms such as dyspnoea after an acute PE largely exceeds the number of patients who have or develop CTEPH [7, 14-18]. Second, both CTEPH awareness and knowledge of the diagnostic work-up among PE caretakers seems suboptimal, as diagnostic clues from abnormal echocardiograms were not followed by adequate further diagnostic work-up by V-Q lung scan and direct referral to a CTEPH expertise center. A recent large retrospective international study evaluating the diagnostic management of CTEPH in both non-PH and PH centers showed poor adherence to the guideline recommendations as well, with echocardiography being performed in 81-98% of patients but V-Q lung scanning being performed in only 33-54% before CTEPH diagnosis [10]. More-

over, in our study, it took a median of 4 months from the moment PH was suggested on echocardiogram to the moment of actual referral to a CTEPH expertise center.

An important limitation of this study is the retrospective nature of the data acquisitions. With this study design, we were not able to reconstruct the actual diagnostic reasoning of the involved physicians, which could have introduced bias. Even so, we were able to find and analyse detailed data on performed tests and referrals. Second, the evaluation of the total patient delay is subjective and likely suffers from recall bias. Third, Echocardiography or other hemodynamic data obtained at the moment of the acute PE diagnosis were not available, and could have provided a better indication of the presence of CTEPH at that moment. Fourth, only patients referred to the VUMC for CTEPH diagnosis after a previous acute PE diagnosis were included in current study, and not patients without a previous acute PE diagnosis or those who remained undiagnosed or were not referred: the diagnostic delay might even be much longer in these patients. This challenges the external validity of our findings. Fifth, as we did not adjudicate the VTE recurrences reported in our study, or the other comorbid conditions included in the multivariate analysis, we cannot exclude biases in this part of our study. Finally, as only patients referred to the VUMC in the Netherlands were evaluated, health care utilisation in other countries may be different.

In conclusion, we observed a considerable diagnostic delay of 21 months for CTEPH diagnosis, and a far-from-optimal use and interpretation of diagnostic tests performed in the clinical course after the acute PE diagnosis. In many patients, CTEPH was probably already present at the moment of the index PE diagnosis but was not recognized. In line with this observation, we found that most of the diagnostic delay was attributable to doctor delay. Specifically, patients with prior cardiopulmonary comorbidity and recurrent VTE had the longest doctor delay. On the basis of these findings, we underline the need for better knowledge and higher awareness of CTEPH among PE caretakers. This may be the best way to improve health care utilisation and ultimately achieve earlier CTEPH diagnosis. Every PE patient with persistent dyspnoea after three months of follow-up should be evaluated for the presence of CTEPH according to the guidelines, and correct interpretation of the diagnostic test results suggestive of CTEPH is essential. Particular vigilance is required in patients with signs of chronic PE or PH on the initial CTPA performed to confirm the diagnosis of acute PE.

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Supplement 1. Contacted physicians, number of consultations per physician and number of different physicians before referral to the VUMC.

Total number of contacted physicians (median, IQR)	4 (4-5)
Total number of consultations (median, IQR)	13 (10-18)
Number of patients contacted a GP (N, %)	40 (100)
Number of GP consultations in 40 patients (median, IQR)	3 (1-4)
Number of different consulted GP's in 40 patients (median, IQR)	1 (1-2)
Number of patients consulted >1 GP (n,%)	16 (40)
Number of patients contacted a pulmonologist (N, %)	39 (98)
Number of pulmonologist consultations in 39 patients (median, IQR)	4.5 (3-9)
Number of different consulted pulmonologists in 39 patients (median, IQR)	1 (1-2)
Number of patients consulted >1 pulmonologist (n,%)	17 (44)
Number of patients contacted a cardiologist (N, %)	40 (100)
Number of cardiologist consultations in 40 patients (median, IQR)	3 (2-6)
Number of different consulted cardiologists in 40 patients (median, IQR)	1 (1-1)
Number of patients consulted >1 cardiologist (n,%)	9 (23)
Number of patients contacted an internist (N, %)	9 (23)
Number of internist consultations in 9 patients (median, IQR)	4 (3-6.5)
Number of different consulted internists in 9 patients (median, IQR)	1 (1-2.5)
Number of patients consulted >1 internist (n,%)	3 (33)
Number of patients contacted a rheumatologist (N, %)	2 (5)
Number of rheumatologist consultations in 2 patients (median, IQR))	1 (1-1)
Number of different consulted rheumatologist in 2 patients (median, IQR)	2.5 (2-3)
Number of patients consulted >1 rheumatologist (n,%)	0 (0)

Note: VUMC: VU university Medical Center Amsterdam; IQR: inter quartile range; GP: general physician.

Chapter 8

Post-thrombotic syndrome: short and long-term incidence and risk factors

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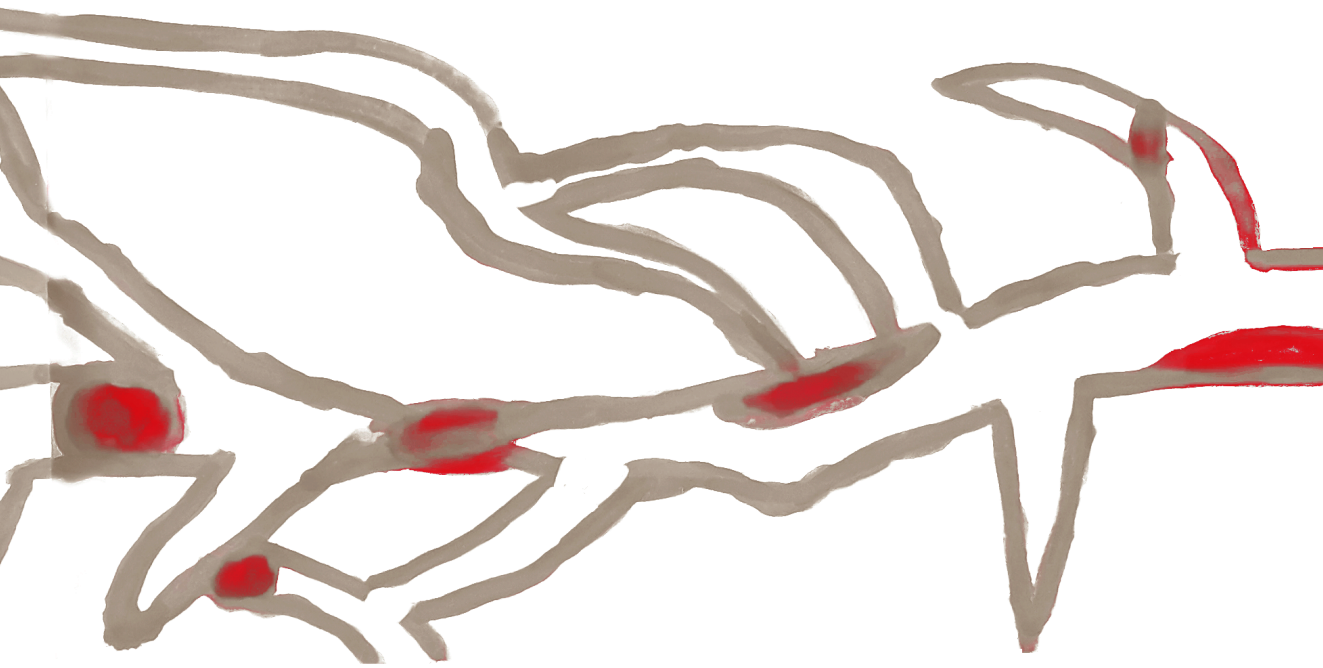

ABSTRACT

Background: The reported incidences of post-thrombotic syndrome (PTS) after deep vein thrombosis (DVT) vary. Further, PTS symptom development over time and its long-term incidence are unknown.

Methods: Patients included in the MEGA study were interviewed at 1 year and completed a questionnaire at 8 years of follow-up regarding symptoms and signs of PTS based on the Villalta score after a first DVT diagnosis. The cumulative incidence of PTS at 0-1 and 1-8 year, changes in PTS classification and the effect of possible clinical and laboratory risk factors were determined.

Results: After 1 year, 361 out of 1657 patients diagnosed with DVT were classified as having PTS, for a 0-1 year cumulative incidence of 21.8% (95%CI 19.9-23.8), out of whom 92 (5.6%) had severe PTS. After 8 years 633 patients without previous PTS completed the second questionnaire, of whom 44 were classified as having PTS, for a 1-8 year cumulative incidence of 7% (95%CI 5.2-9.2); of these 13 (2.1%) were classified as severe PTS. During follow-up PTS complaints improved in 69% and worsened in 7% of patients. At 1 year, risk factors were female sex (RR 1.5; 95%CI 1.2-1.9) and obesity (RR 1.5; 95%CI 1.2-7.9), with the same effect sizes at 8 years. Provoked/unprovoked DVT, thrombus location, pregnancy, hormone use and several laboratory parameters did not affect risk of PTS, either at 1 or 8 years.

Conclusion: The incidence of PTS remained substantial up to 8 years after a first DVT. Symptoms improved in a large proportion of the cases. The short and long term risks were highest in women and obese patients.

INTRODUCTION

Approximately 20-50% of patients with a deep venous thrombosis (DVT) develop post-thrombotic syndrome (PTS) within 2 years despite treatment with anticoagulation [1-5]. The pathophysiology of PTS is complex and has not yet been fully characterised. Chronic venous hypertension caused by outflow obstruction and reflux by valvular incompetence appear to play a central role in PTS development [6, 7]. PTS diagnosis is mostly based on the Villalta scale as recommended by the current guidelines and should be deferred until 3-6 months after the acute phase when initial pain and swelling associated with acute DVT have resolved [1, 8].

Patients with PTS present a various spectrum of symptoms and signs of chronic venous insufficiency such as pain, feeling of heaviness, oedema, skin pigmentation and in more severe cases, venous ulcers. Patients usually develop these symptoms and signs within the first months to the first years after DVT diagnosis [9, 10]. Little is known on the development of these symptoms and signs more than 2 years after initial DVT diagnosis [4, 11].

Recent studies identified older age, obesity (body mass index (BMI) >30 kg m^{-2}), proximal DVT location and recurrent ipsilateral DVT as risk factors for PTS. According to the current literature there is no agreement regarding several other possible risk factors such as sex, provoked-, unprovoked DVT or inherited or acquired hypercoagulability [1, 12]. This discrepancy in possible risk factors is mainly caused by different studied populations and the heterogeneous design of several studies.

In the current study we aimed to evaluate 0 to 1- and 1 to 8-year PTS cumulative incidence in patients diagnosed with a first DVT, and to determine how these symptoms and signs evolved over time (how many patients with PTS improved, worsened or stayed the same). Furthermore, we aimed to assess the effect of several risk- and treatment factors on PTS development after both 1-year and after 8-years of follow-up. This study is a continuation with additional information on a previously published study into the 1-year cumulative incidence and the assessment of several risk factors of PTS in patients included in the Multiple Environmental and Genetic Assessment (MEGA) study [5].

METHODS

Study population

For this study we used data of patients diagnosed with a first DVT event available from the MEGA study. The MEGA study is a population-based case-control study into risk factors for venous thromboembolism (VTE). Between March 1999 and August 2004 consecutive patients aged between 18 and 70 years with an objectively diagnosed first VTE

event and signed informed consent were included from six participating anticoagulation clinics. Patients with any psychological condition that would not permit completion of the study or who could not speak Dutch were excluded. Further details of the MEGA study have been described previously [13].

According to the protocol of the MEGA study all patients received a first questionnaire regarding known risk factors for VTE within a few weeks after VTE diagnosis. Most patients were treated with oral anticoagulation for a period of 3 to 6 months. Patients who discontinued to use oral anticoagulation were invited to the anticoagulation clinic three months after they discontinued oral anticoagulation. At the anticoagulation clinic the patients were seen by a research assistant who was not involved in the patient's treatment for an interview and blood sample collection. Patients who continued to use oral anticoagulation treatment were invited at 1 year of treatment for the interview and blood sample collection. Blood sample collection was requested until June 2002.

Between June 2008 and July 2009 all patients included in the MEGA study were evaluated for the development of a recurrent VTE in the previous period (the MEGA follow-up study). Additionally all patients received a second questionnaire that contained questions regarding risk factors for recurrent VTE and symptoms of PTS.

Study definitions

The 0-1 year cumulative incidence of PTS was defined as the incidence of PTS at the moment of the interview within 1 year after DVT diagnosis and the 1-8 year cumulative incidence of PTS was defined as the incidence of PTS during the MEGA follow-up study, starting from the first PTS assessment.

PTS classification was assessed during the interview with the research assistant and based on a questionnaire in the follow-up study. The patients were asked for five symptoms and four signs based on the Villalta score (**Supplement 1**) [5, 8]. For the presence of each sign or symptom the patient scored one point. A total score of 0 to 3 points indicated no PTS, a score of 4 to 6 points indicated moderate PTS and a score of 7 or more points or the presence of a venous ulcer indicated severe PTS. Previously it was shown that this post-thrombotic score and the Villalta score had an excellent relation (kappa 0.88; 95% confidence interval (CI) 0.79-0.96) [5].

Thrombus localisation was considered proximal when present in the femoral, iliac or inferior vena cava; popliteal when present in the popliteal vein and distal when the thrombus was limited to the calf veins [8]. A DVT was defined as provoked when it occurred in the presence of one or more of the following risk factors: surgery, minor injury, plaster cast, bedridden at home or in the hospital during the last 3 months before DVT diagnosis, active malignancy, female hormone use or pregnancy at the time of thrombosis or when a patient gave birth within 3 months prior to the thrombotic event as reported by the patient during the first questionnaire. Body mass index (BMI; weight/

height^2) was classified as follows: <18.5kg m^{-2} as underweight, between 18.5 and 25kg/m^2 as normal, between 25 and 30kg/m^2 as overweight and >30kg/m^2 as obesity.

Laboratory measurements

Blood samples were drawn from the antecubital vein into vacuum tubes containing 0.106mol L^{-1} trisodium citrate. High molecular weight DNA was isolated form leukocytes using a standard salting-out procedure and stored at -20 °C until amplification. The following laboratory parameters were determined according to previously described methods: protein C, protein S and antithrombin (AT), FV Leiden (G1691A), prothrombin (G20210A) and FXIII Val34Leu mutation, level of FVIII, clot lysis time (CLT), high sensitive C reactive protein (HsCRP) and d-dimer [5, 14, 15].

Statistical analysis

The 0-1- and 1-8 year cumulative incidences and their corresponding 95%CIs were estimated by dividing the number of patients with a PTS score of > 3 points at 1 respectively 8 years of follow-up by the total number of patients who completed all questions regarding PTS at 1 respectively 8 years. For estimation of the 1-8 year cumulative incidence only the patients who did not have PTS at 1 year (based on a PTS score <4 points) were selected. To evaluate how PTS classification evolved over time, all patients who were classified as PTS after 1 year and who completed all questions regarding PTS at 8 years of follow-up were selected.

The effect of several risk factors, treatment factors and laboratory parameters on PTS was assessed by calculating the risk ratios (RR) and their 95%CI. Adjusted RRs were calculated by fitting a generalized linear model with a log link function and a binomial distributed outcome. We adjusted for sex and age in all analyses and for height in all except for the risk factors sex, age and BMI. For assessment of the effect of risk factors at 1 year all patients who completed the first questionnaire regarding PTS were selected. For this analysis at 8 years of follow-up all patients who completed the second questionnaire regarding PTS and who did not have PTS at 1 year of follow-up were selected.

We could not determine the effect of a recurrent VTE on PTS incidence at 1 year. Since PTS is not a condition with a clear onset it was unknown whether the patients classified as PTS at this time point already had PTS before development of a recurrent VTE event. Nevertheless, we could evaluate the effect of a recurrent VTE event within 1 year on long-term incidence of PTS.

As blood sample collection took place at 6 months to 1-year of follow-up, the effect of the laboratory parameters on occurrence of subsequent PTS (CLT, HsCRP, d-dimer, protein C, protein S and AT) could only be assessed in patients who did not have PTS before this time point.

In approximately 50% of cases there were some missing data. Therefore, as a sensitivity analysis, we repeated all analyses regarding clinical and laboratory risk factors on PTS after conducting multiple imputation for all missing data. For evaluation at 1 year all patients diagnosed with a first episode of DVT in the lower extremity were selected for multiple imputation and at 8 years the patients who completed all questions regarding PTS during the interview and did not have PTS at 1 year. Ten datasets were imputed and the results were pooled according to Rubin's combination rules [16].

All analyses were performed using Stata 14.0 (Stata Corp., College Station, TX USA).

RESULTS

Patients

Out of 3153 patients included in the MEGA study who were diagnosed with a DVT of the lower extremity, 1912 (60.6%) of these patients answered one or more questions regarding PTS. In 1657 (52.6%) patients all questions regarding PTS after 1 year could be completed. At 8 years of follow up 846 (65.2%) out of 1296 patients without PTS after 1 year answered at least one question regarding PTS in the second questionnaire. Of these 1296 patients, 633 (48.8%) completed all questions regarding PTS at 8 years of follow-up (**Figure 1**). There were no differences in baseline characteristics between patients who completed all questions regarding PTS, after 1 year of follow-up compared with those

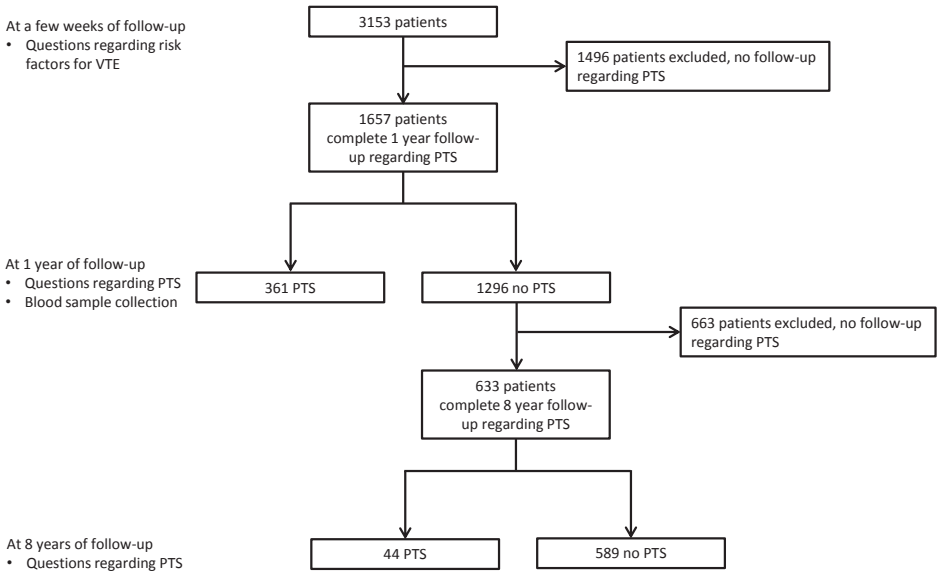

Figure 1. Flow chart of patient inclusion.
Note: VTE: venous thromboembolism; PTS: post-thrombotic syndrome.

who also completed all questions after 8 years of follow-up. The baseline characteristics are shown in **Table 1.**

Table 1. Patient characteristics.

	Included for evaluation at 1 year of follow-up	Not included for evaluation at 1 year of follow-up	Included for evaluation at 8 years of follow-up	Not included for evaluation at 8 years of follow-up
Patients (n)	1657	1496	633	663
Age at DVT diagnosis (years, SD)	48 (13)	49 (13)	48 (12)	50 (14)
Male sex (n,%)	785 (47)	749 (50)	298 (47)	351 (53)
Height (m; mean, SD)	1.75 (0.09)	1.75 (0.09)	1.75 (0.09)	175 (0.1)
Weight (kg; mean, SD	83 (17)	82 (16)	82 (16)	83 (16)
BMI (kg m^{-2}; mean, SD)	27 (4.8)	27 (4.7)	27 (4.6)	27 (4.5)
DVT location				
Proximal vein (n,%)	408 (25)	345 (23)	151 (24)	159 (24)
Popliteal vein (n,%	528 (32)	377 (25)	204 (32)	212 (32)
Distal vein (n,%)	202 (12)	137 (9)	83 (13)	80 (12)
Unknown n,%)	519 (31)	637 (43)	195 (31)	212 (32)
Provoked (n,%)	1201 (72) ^	1094 (73) *	466 (74)#	199 (30) $
Unprovoked (n,%)	441 (27) ^	380 (25) *	164 (26)#	457 (69) $
Duration of anticoagulation treatment (month; median, IQR)	5.6 (3.3-7.0)	5.6 (3.2-7.3)	5 (3.3-6.5)	5.9 (3.3-7.1)

DVT: deep vein thrombosis; SD: standard deviation; m: meter; kg: kilogram; BMI body mass index.
^ unknown in 15 patients; *unknown in 22 patients # unknown in 3 patients $ missing in 7 patients.

Short and long term PTS cumulative incidence

At 1 year, 361 out of 1657 patients were classified as having PTS for a cumulative incidence of 21.8% (95%CI 19.9-23.8). Ninety-two of these patients (5.6%) had severe PTS, of whom 47 (2.8%) patients reported to have a venous ulcer. After 8 years of follow-up, an additional 44 out of 633 patients, previously free of PTS, were classified as having PTS, for a cumulative incidence of 7.0% (95%CI 5.2-9.2). Of these, 13 of 633 (2.1%) were classified as severe PTS of whom 12 (1.9%) patients reported a venous ulcer (**Table 2**)**.** The most frequently reported symptoms and signs at 1 year of follow-up were heaviness of the leg (37%), swelling of the foot or calf (35%) and spontaneous pain in the calf (26%). At 8 years of follow-up the most frequent symptoms and signs were newly formed varicose veins (30%), heaviness of the leg (22%) and swelling of the foot or calf (21%) (**Table 3**).

Table 2. 1-year and 1-8 years PTS cumulative incidence.

	1 year 1657 (n)	Cumulative incidence	1-8 year 633 (n)	Cumulative incidence
PTS	361	22% (95%CI 20-24)	44	7.0% (95%CI 5.2-9.2)
Moderate PTS	269	16 (95%CI 15-18)	31	4.9 (95%CI 3.5-6.9)
Severe PTS	92	5.6 (95%CI 4.5-6.8)	13	2.1 (95%CI 1.2-3.5)
Venous ulcer	47	2.8 (95%CI 2.1-3.8)	12	1.9 (95%CI 1.1-3.3)

Note: PTS: post-thrombotic syndrome; CI: confidence interval.

Table 3. Post thrombotic symptoms and signs at 1 year and at 8 years of follow-up.

Symptoms / signs	1 year 1657 (n,%)	1-8 year 633 (n,%)
Spontaneous pain in the calf	429 (26)	60 (9.4)
Spontaneous pain on walking	239 (14)	29 (4.6)
Spontaneous pain on standing	291 (18)	22 (3.5)
Pain worsening during the day	388 (23)	43 (6.8)
Heaviness of leg	618 (37)	138 (22)
Newly formed varicose veins	217 (13)	193 (30)
Swelling of foot or calf	572 (35)	136 (21)
Skin changes, pigmentation, discoloration	415 (25)	81 (13)
Skin changes with venous ulcer	47 (2.8)	12 (1.9)

PTS symptoms development

A total of 195 patients classified as PTS at 1 year completed all questions regarding PTS at 8 years of follow-up. PTS classification improved after 8 years of follow-up in 134 (69%) patients. Of these patients, a total of 97 originally classified with moderate and 28 originally diagnosed with severe PTS were not classified as having PTS after 8 years. In 9 patients PTS classification changed from severe to moderate. In 42 (22%) patients classified as moderate and 6 (3.1%) patients classified as severe PTS, PTS classification did not change over time. PTS classification became worse in 13 (6.7%) patients (**Figure 2**).

Risk factors for PTS development after 1 and 8 years of follow-up

At 1 year of follow-up the cumulative incidence of PTS was 27% in women and 16% in men. Women had a 1.7 times higher risk of PTS occurrence (RR 1.7; 95%CI 1.4-2.0) which remained elevated after adjustment for age (RR 1.5; 95%CI 1.2-1.9). The 1-8 year cumulative incidences of PTS in women and in men were 7.8% and 6.0% respectively, for an adjusted RR of 1.2 (95%CI 0.64-2.3) (**Table 4**). The absence of a long- term sex difference remained after multiple imputation (RR 1.1 (95%CI 0.75-1.6)) (**Supplement 2**).

The cumulative incidence of PTS was 13% in patients over 60 years of age while it was 25% in patients below 30 (RR 0.50; 95%CI 0.34-0.73). This difference persisted after

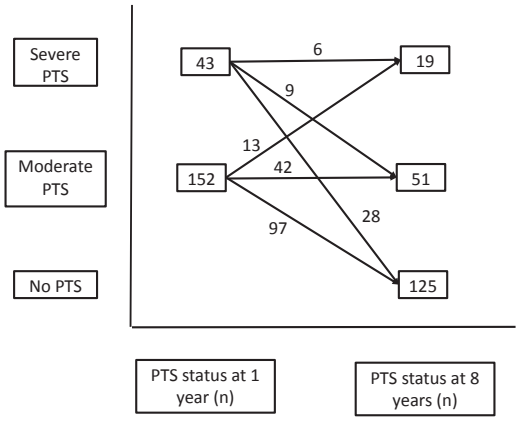

Figure 2. Change of PTS classification over time.
Note: PTS: post-thrombotic syndrome.

adjustment for sex (RR 0.61; 95%CI 0.41-0.90). We did not find this age effect at 8 years of follow-up.

At 1 year patients shorter than 1.65m compared with a height of 1.65-1.80m had a higher risk of PTS development (adjusted RR 1.5; 95%CI 1.2-1.9). Patients who weighted 86-100kg and more than 100kg had a higher risk of PTS development than those weighing 65-85kg (adjusted RR 1.3; 95%CI 1.1-1.7 and adjusted RR 1.6; 95%CI 1.2-2.1 respectively). Obese patients had a 1.5 (95%CI 1.2-7.9) times higher risk of PTS compared to patients with a normal BMI. At long term follow-up compared with short term follow-up, the effect size was the same for obesity (adjusted RR of 1.5; 95%CI 0.70-3.5). After multiple imputation the adjusted RR for obesity at the long term follow-up was also 1.5 (95%CI 1.0-2.4) (**Supplement 2**).

Thrombus location or whether the inciting DVT was provoked or unprovoked or associated with pregnancy or female hormone use did not affect the risk of PTS, either at 1 or at 8 years. A recurrent VTE during the first year of follow-up possibly affected the risk of PTS on the long term (RR 1.7 (95%CI 0.63-4.4)). Multiple imputation did not reveal any differences in these RRs (**Table 4, Supplement 2**).

Treatment factors associated with PTS development after 1 and 8 years of follow-up

Patients with PTS at 1 year had used oral anticoagulation for a longer time period. The adjusted RR for duration of use of 6-12 months was 1.3 (95%CI 1.1-1.6) and for > 12 months 1.4 (95%CI 1.1-1.9) compared with the reference of 3-6 months use. At 8 years the same effect sizes were found in the complete data as well as after multiple imputation for a duration of > 12 months (adjusted RR 1.7; 95%CI 0.7-4.0 and 1.5; 95%CI 1.0-2.3 respectively) (**Supplement 2**). At 1- and at 8 years follow-up, patients with PTS had worn elastic compression stockings more frequently, for an adjusted RR of never versus

Table 4. Risk factors associated with PTS 1 and 8 years after DVT diagnosis.

		1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*	8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*
Sex									
	Men	785	127	1 (ref)	1 (ref)	298	18	1 (ref)	1 (ref)
	Women	872	234	1.7 (1.4-2.0)	1.5 (1.2-1.9)	335	26	1.3 (0.72-2.3)	1.2 (0.64-2.3)
Age									
	18-29	179	45	1 (ref)	1 (ref)	58	7	1 (ref)	1 (ref)
	30-39	287	71	1.0 (0.71-1.4)	1.0 (0.75-1.45)	120	8	0.55 (0.21-1.4)	0.58 (0.22-1.5)
	40-49	386	111	1.1 (0.85-1.5)	1.2 (0.92-1.66)	158	10	0.52 (0.21-1.3)	0.55 (0.22-1.4)
	50-59	463	91	0.8 (0.57-1.1)	0.90 (0.66-1.2)	190	12	0.52 (0.22-1.3)	0.56 (0.22-1.4)
	60-69	342	43	0.50 (0.34-0.73)	0.61 (0.41-0.90)	107	7	0.54 (0.20-1.5)	0.61 (0.20-1.9)
Height (m)		#				¢			
	<1.65	203	68	1.6 (1.3-2.0)	1.5 (1.2-1.9)	65	2	0.42 (0.10-1.7)	0.38 (0.09-1.6)
	1.65-1.80	993	207	1 (ref)	1 (ref)	406	30	1 (ref)	1 (ref)
	>1.80	413	73	0.85 (0.67-1.1)	1.1 (0.80-1.5)	150	9	0.8 (0.39-1.7)	1.0 (0.41-2.3)
Weight (kg)		^				¢			
	<65	122	31	1.3 (0.92-1.8)	1.1 (0.73-1.5)	64	1	0.21 (0.03-1.5)	0.21 (0.03-1.5)
	65-85	879	174	1 (ref)	1 (ref)	327	24	1 (ref)	1 (ref)
	86-100	432	93	1.1 (0.87-1.4)	1.3 (1.1-1.7)	165	10	0.83 (0.40-1.7)	0.85 (0.40-1.8)
	>100	185	53	1.4 (1.1-1.8)	1.6 (1.2-2.1)	65	5	1.0 (0.42-2.6)	1.0 (0.40-2.7)
BMI (kg m^{-2})		%				T			
	Underweight	15	4	1.3 (5.7-3.2)	1.3 (0.55-3.0)	4	0	n.a.	n.a.
	Normal	544	108	1 (ref)	1 (ref)	225	12	1 (ref)	1 (ref)
	Overweight	699	131	0.94 (0.75-1.2)	1.0 (0.83-1.3)	269	18	1.3 (0.62-2.5)	1.3 (0.64-2.7)
	Obese	340	101	1.5 (1.2-1.9)	1.5 (1.2-7.9)	121	10	1.5 (0.69-3.5)	1.6 (0.70-3.5)

Table 4. Risk factors associated with PTS 1 and 8 years after DVT diagnosis. (continued)

	1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*	8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*
Unprovoked	&				£			
no	1201	282	1 (ref)	1 (ref)	466	36	1 (ref)	1 (ref)
yes	441	15	0.72 (0.58-0.91)	0.96 (0.74-1.2)	164	7	0.55 (0.25-1.2)	0.60 (0.25-1.4)
DVT location	$				≠			
Proximal vein	408	100	1.2 (0.92-1.5)	1.2 (0.93-1.5)	151	10	1.0 (0.44-2.1)	0.92 (0.43-2.0)
Popliteal vein	528	111	1 (ref)	1 (ref)	204	14	1 (ref)	1 (ref))
Distal vein	202	37	0.87 (0.62-1.2)	0.86 (0.61-1.2)	83	3	0.53 (0.16-1.8)	0.49 (0.14-1.7
Female hormone use								
no	340	84	1 (ref)	1 (ref)	107	8	1 (ref)	1 (ref)
yes	532	147	1.1 (0.86-1.4)	1.0 (0.77-1.3)	228	18	1.1 (0.47-2.4)	0.85 (0.37-2.0)
Pregnancy	ƛ				ø			
no	740	202	1 (ref)	1 (ref)	294	22	1 (ref)	1 (ref)
yes	8	4	1.8 (0.91-3.7)	1.8 (0.91-3.7)	2	0	n.a.	n.a.
Duration of oral anticoagulation								
< 3 months	60	8	0.70 (0.36-1.3)	0.70 (0.36-1.4)	26	1	0.56 (0.08-3.9)	0.59 (0.08-4.2)
3-6 months	820	157	1 (ref)	1 (ref)	347	24	1 (ref)	1 (ref)
6-12 months	595	149	1.3 (1.1-1.6)	1.3 (1.1-1.6)	204	13	0.92 (0.48-1.8)	0.94 (0.47-1.9)
>12 months	182	47	1.3 (1.0-1.8)	1.4 (1.1-1.9)	56	6	1.5 (0.66-3.6)	1.7 (0.71-4.0)
Frequency of elastic compression stockings	†				÷			
Always	1079	243	1 (ref)	1 (ref)	394	32	1 (ref)	1 (ref)
Most of the time	188	46	1.1 (0.83-1.4)	1.0 (0.80-1.4)	29	3	1.3 (0.41-3.9)	1.4 (0.44-4.2)
Sometimes	100	31	1.4 (1.0-1.9)	1.4 (1.0-1.8)	19	2	1.3 (0.33-5.0)	0.69 (0.10-4.8)
Never	280	39	0.62 (0.45-0.84)	0.64 (0.47-0.88)	166	6	0.45 (0.19-1.0)	0.40 (0.16-1.0)

Table 4. Risk factors associated with PTS 1 and 8 years after DVT diagnosis. (continued)

	1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*	8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*
Duration of elastic compression stockings use	‡				Þ			
0 months	304	43	0.50 (0.36-0.70)	0.50 (0.36-0.71)	150	4	0.26 (0.09-0.73)	0.26 (0.09-0. 73)
< 3 months	113	18	0.56 (0.35-0.90)	0.56 (0.35-0.89)	17	1	0.57 (0.08-4.0)	0.56 (0.08-3.9)
3-6 months	286	53	0.66 (0.48-0.90)	0.65 (0.47-0.88)	41	2	0.47 (0.12-1.9)	0.42 (0.10-1.7)
6-12 months	690	171	0.88 (0.69-1.1)	0.83 (0.65-1.0)	76	4	0.51 (0.18-1.4)	0.36 (0.11-1.2)
>12 months	244	69	1 (ref)	1 (ref)	233	24	1 (ref)	1 (ref)
Recurrent VTE								
No	n.a.	n.a.	n.a.	n.a.	597	40	1 (ref)	1 (ref)
Yes	n.a.	n.a.	n.a.	n.a.	36	4	1.7 (0.63-4.4)	1.9 (0.71-5.1)
FV Leiden	+				ĉ			
GG	1300	281	1 (ref)	1 (ref)	496	37	1 (ref)	1 (ref)
AG / AA	315	74	1.1 (0.87-1.4)	1.1 (0.89-1.4)	131	6	0.61 (0.26-1.4)	0.67 (0.29-1.6)
prothrombin 20210A mutation	¥				ĉ			
GG	1525	330	1 (ref)	1 (ref)	594	38	1 (ref)	1 (ref)
AG /AA	91	25	1.3 (0.90-1.8)	1.3 (0.90-1.8)	33	5	2.4 (1.0-5.6)	2.6 (1.1-6.2)
FXIII mutation					ĉ			
GG	923	196	1 (ref)	1 (ref)	349	19	1 (ref)	1 (ref)
GT	585	141	1.1 (0.94-1.4)	1.2 (1.0-1.4)	236	22	1.7 (0.95-3.1)	1.7 (0.90-3.1)
TT	106	18	0.8 (0.52-1.2)	0.8 (0.50-1.2)	42	2	0.87 (0.21-3.6)	0.94 (0.23-3.9)
Factor VIII activity	ħ				ĩ			

Table 4. Risk factors associated with PTS 1 and 8 years after DVT diagnosis. (continued)

	1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*		8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*
< 25th percentile; <111	362	87	1 (ref)	1 (ref)	<109	146	7	1 (ref)	1 (ref)
25-50th percentile; 111-137	355	80	0.94 (0.72-1.2)	0.92 (0.71-1.2)	109-135	146	6	0.86 (0.30-2.5)	0.74 (0.24-2.3)
50-75th percentile; 137-167	351	83	1.0 (0.76-1.3)	1.0 (0.78-1.3)	135-163	145	16	2.3 (1.0-5.4)	2.4 (1.0-5.8)
>75th percentile; 167-437	342	63	0.77 (0.57-1.0)	0.77 (0.57-1.0)	163-361	138	11	1.7 (0.66-4.2)	1.9 (0.75-4.9)
D-dimer (ng/ml)						ĩ			
	n.a.	n.a.	n.a.	n.a.	<213	144	10	1 (ref)	1 (ref)
	n.a.	n.a.	n.a.	n.a.	213-319	143	10	1.0 (0.43-2.3)	1.1 (0.46-2.7)
	n.a.	n.a.	n.a.	n.a.	319-534	144	9	0.90 (0.38-2.1)	1.0 (0.40-2.5)
	n.a.	n.a.	n.a.	n.a.	534-3142	144	11	1.1 (0.48-2.5)	1.2 (0.50-3.0)
CLT						ĩ			
< 25th percentile	n.a.	n.a.	n.a.	n.a.	<60	143	12	1 (ref)	1 (ref)
25-50th percentile	n.a.	n.a.	n.a.	n.a.	60-68	143	7	0.58 (0.24-1.4)	0.67 (0.27-1.7)
50-75th percentile	n.a.	n.a.	n.a.	n.a.	68-78	145	9	0.74 (0.32-1.7)	0.87 (0.37-2.1)
>75th percentile	n.a.	n.a.	n.a.	n.a.	>78	143	12	1 (0.46-2.2)	1.1 (0.49-2.6)
HsCRP (mg/L)						ĩ			
< 25th percentile	n.a.	n.a.	n.a.	n.a.	<0.8	144	9	1 (ref)	1 (ref)
25-50th percentile	n.a.	n.a.	n.a.	n.a.	0.8-1.8	147	9	1.0 (0.40-2.4)	1.2 (0.46-2.9)
50-75th percentile	n.a.	n.a.	n.a.	n.a.	1.8-4.0	140	13	1.5 (0.66-3.4)	1.7 (0.72-4.0)
>75th percentile	n.a.	n.a.	n.a.	n.a.	>4.0	143	9	1.0 (0.41-2.5)	1.0 (0.38-2.6)
Protein C activity (%, 100%=1IU/ml))						ģ			
normal	n.a.	n.a.	n.a.	n.a.		556	38	1 (ref)	1 (ref)
Decreased (<mean-2SD)	n.a.	n.a.	n.a.	n.a.		17	2	1.7 (0.45-6.6)	0.87 (0.13-6.0)
Protein S antigen (U/dl)						ĭ			

Table 4. Risk factors associated with PTS 1 and 8 years after DVT diagnosis. (continued)

		1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*	8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*
	Normal	n.a.	n.a.	n.a.	n.a.	518	38	1 (ref)	1 (ref)
	Decreased (<mean-2SD)	n.a.	n.a.	n.a.	n.a.	10	0	n.a.	n.a.
Antithrombin activity						ĩ			
	normal	n.a.	n.a.	n.a.	n.a.	556	38	1 (ref)	1 (ref)
	Decreased (<mean-2SD)	n.a.	n.a.	n.a.	n.a.	19	2	1.5 (0.40-5.9)	1.6 (0.40-6.1)

Note: PTS: post-thrombotic syndrome; RR: risk ratio; CI: confidence interval; m: meter; kg: kilogram; BMI: body mass index; DVT: deep vein thrombosis; VTE: venous thromboembolism; CLT: clot lysis time; HsCRP high sensitive C reactive protein.

*Adjusted for sex, age and height when possible; # missing in 48 patients; ^ missing in 39 patients; % missing in 59 patients; & missing in 15 patients; $ missing in 519 patients; ƛ missing in 124 woman; † missing in 10 patients; ‡ missing in 20 patients; + missing in 42 patients; ¥ missing in 41 patients; ħ missing in 247 patients; ¢ missing in 12 patients; Ŧ missing in 14 patients; £ missing in 3 patients; ≠ missing in 195 patients; ø missing in 39 women; ÷ missing in 25 patients; Þ missing in 116 patients; ĉ missing in 6 patients; ĩ missing in 58 patients; ģ missing in 60 patients; ĭ missing in 105 patients

always use of 0.64; 95%CI 0.47-0.88 at 1 and 0.40; 95%CI 0.16-1.0 at 8 years follow-up. Furthermore, at 1 year of follow-up, patients with PTS had worn elastic compression stockings for a longer time period with an adjusted RR of 0.50 (95%CI 0.36-0.71) for none use and 0.65 (95%CI 0.47-0.88) for a duration of 3-6 months compared to the reference of more than 12 months. After 8 years of follow-up the same association was found with an adjusted RR of 0.26 (95%CI 0.09-0.73) in patients who had worn elastic compression stockings for 0 months compared to the reference of more than 12 months (**Table 4**).

Laboratory parameters associated with PTS development after 1 and 8 years of follow-up

At neither follow-up moment did the presence of Factor V Leiden, prothrombin 20210A, FXIII mutation or factor FVIII levels affect the risk of PTS. Levels of CLT, HsCRP, d-dimer, protein C, protein S and AT did not affect the risk of PTS at 8 years of follow-up (**Table 4**). After multiple imputation we did not find any changes to these RRs (**Supplement 2**).

DISCUSSION

We showed that in patients with a first DVT, the 1- year PTS cumulative incidence was 22% while an additional 7% developed PTS between 1-to-8 years after DVT diagnosis. Between 1 and 8 years, PTS classification improved in 69%, stayed the same in 25% and became worse in 7% of patients during follow-up. Risk factors for PTS development at 1 year were female sex, shorter height and obesity, while elderly patients appeared to have a lower risk of PTS. Only obesity showed to be a relevant risk factor for the long term follow-up. We further demonstrated that patients with PTS had more often been treated with oral anticoagulants for a period of >6 months and had worn elastic compression stockings more frequently and for a longer duration. Whether or not the patient's DVT was provoked or unprovoked, thrombus location and several laboratory parameters were not associated with PTS development either at 1 and 8 years.

The 0-1-year PTS cumulative incidence of 22% we found is in accordance with previously reported 1- year incidences of between 17%-27% in patients after a first DVT [17-20]. Several studies reported on PTS incidence during long term follow-up. A prospective cohort study of 528 patients after a first DVT diagnosis showed a PTS cumulative incidence of 24.5% after 2 years, of 29.6% after 5 years and of 29.8% after 8 years [4]. A second study reported PTS incidences of 14.9% at 1 year and 19.5% after 5 years in 167 patients [21]. Another study reported on PTS incidence after 1, 2 and 6 years of follow-up based on the CEAP classification in 93, 65 and 48 patients. This study showed much higher cumulative incidences of 49% after 1 year, 55% after 2 years and 56% after 6 years of follow-up, although PTS diagnosis was based on a different score and a limited num-

ber of patients was followed [22]. In these long term studies, changes in PTS symptoms during follow-up were not reported while these numbers are relevant in evaluating the development of PTS over time. In our study we have shown that between 1 and 8 years of follow-up PTS classification improved in 69% and worsened in 7% of patients. This is in line with a prospective multicentre follow-up study in 387 patients diagnosed with DVT who were scored according to the Villalta score at 1, 2, 8, 12 and 24 months [9]. Approximately half of the 49 patients with moderate or severe PTS patients after 1 year improved to none or mild at the end of the follow-up period. In a subsequent study, it might be worthwhile evaluating these changes every 1 or 2 years in order to obtain more detailed insight into long term PTS development.

According to our findings at 1 year, women had a 1.5 times higher risk of PTS than men. The literature, however, shows no consistent relationship with sex [1]. We were further able to confirm obesity, as previously described, as a risk factor for PTS development [1]. Interestingly, at 1 year of follow-up, patients with PTS reported to use oral anticoagulation for a longer time period than patients without PTS. A possible explanation for this might be that patients with symptoms and signs of PTS were treated for a longer period of time because of their complaints. Another likely explanation is that these patients were interviewed at a later moment and therefore had a longer period of time to develop PTS. A previous randomized trial on duration of anticoagulation treatment and PTS development, however, showed that anticoagulation treatment for 6 weeks compared with 6 months did not affect the risk of PTS after 10 year of follow-up [11]. A second study also observed no influence of duration of anticoagulation treatment on the risk of PTS after at least 18 months of follow-up [23]. The same explanation is probably true for our finding that patients with PTS wore elastic compression stockings more frequently and for a longer period of time than patients without PTS. Studies regarding the use of elastic compression stockings on PTS development are not consistent due to differences in study design and PTS definition [10, 19, 24-27].

None of the analysed laboratory parameters were associated with PTS development. A recent meta-analysis also did not find an effect of factor V Leiden, deficiencies of protein S, C and AT or levels of factor VIII on PTS development [28]. As reported in a recent systematic review, the literature is conflicting regarding an association between D-dimer at presentation and PTS development as well as for D-dimer measured in the early-subacute phase (1-4months after DVT diagnosis) and the late-subacute phase (5-12 months after DVT diagnosis) on PTS. However, these results were based on very heterogeneous data [29]. In the current study we showed that D-dimer determined at 1 year of follow-up did not affect the risk of PTS on the long term.

The strength of this study lies in the large unselected cohort of patients followed for a long time period which gave us the opportunity to evaluate the cumulative incidence of

PTS at 1 and at 1-8 year of follow-up and to assess the clinical course of PTS over time as well as the effect of several risk factors.

This study also had some limitations. First, PTS diagnosis was based on symptoms and signs as reported by the patient based on the Villalta score and not objectively evaluated by a clinician as recommended in the guidelines. Based on a previously reported excellent relation of this post-thrombotic score and the Villalta score [5] we assume this might have influenced our data only minimally. Second, PTS evaluation did not take place at the same time point for every patient: for the 0-1 year cumulative incidence this was between 6 months and 1 year and for the 1-8 year cumulative incidence this was at some point during follow-up. Further it was unknown at what point in time patients began to develop symptoms and signs of PTS, for which reason we could not evaluate incidences within finer time frames. Further, it is unknown whether the symptoms and signs reported by the patient were due to PTS or already present before DVT diagnosis. This is nevertheless a limitation of all studies in this field because it is difficult to classify PTS before DVT diagnosis. Fourth, we could only determine the effect of several laboratory parameters (CLT, HsCRP, d-dimer, protein C, protein S and AT) on long-term PTS development because they were not measured before PTS development at one year of follow-up. Fifth, the missing data at 1- and 8–years of follow-up may not have been completely random and could have introduced selection bias. Lastly, only a limited number of patients completed the long term follow-up questionnaire which led to smaller subgroups and wider 95%CIs. Nevertheless, the effect sizes were largely the same as for the risk factors during 0-1 year of follow-up.

We conclude that in our study population, the incidence of PTS remained substantial up to eight years after a first DVT and that PTS symptoms improved in almost 70% of PTS patients and worsened in 7%. The risk of PTS development is highest in women and obese individuals.

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Supplement 1. Symptoms and signs of post-thrombotic syndrome asked in the questionnaire.

Symptoms	Signs
Spontaneous pain in the calf	Newly formed varicose veins
Spontaneous pain in the leg during walking	Swelling of the foot or calf
Spontaneous pain in the leg while standing	Any skin changes, pigmentation or discoloration
Pain in the leg worsening during the day	Skin changes with open wounds
A tired or heavy feeling in the leg	

Supplement 2: Risk factors associated with PTS 1 and 8 years after DVT diagnosis in imputed data.

	1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*	8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*
Sex								
Men			1 (ref)	1 (ref)			1 (ref)	1 (ref)
Women			1.6 (1.3-1.9)	1.5 (1.2-1.9)			1.1 (0.78-1.6)	1.1 (0.75-1.6)
Age								
18-29			1 (ref)	1 (ref)			1 (ref)	1 (ref)
30-39			0.93 (0.72-1.2)	1.0 (0.77-1.3)			0.77 (0.44-1.3)	0.77 (0.44-1.4)
40-49			1.0 (0.74-1.3)	1.0 (0.79-1.4)			0.73 (0.44-1.2)	0.74 (0.44-1.2)
50-59			0.77 (0.58-1.0)	0.89 (0.766-1.2)			0.62 (0.36-1.1)	0.64 (0.36-1.1)
60-69			0.59 (0.42-0.82)	0.71 (0.50-1.0)			0.77 (0.41-1.4)	0.79 (0.41-1.5)
Height (m)								
<1.65			1.3 (1.1-1.7)	1.2 (1.0-1.5)			0.80 (0.45-1.4)	0.73 (0.39-1.4)
1.65-1.80			1 (ref)	1 (ref)			1 (ref)	1 (ref)
>180			0.84 (0.69-1.0)	1.1 (0.84-1.4)			1.2 (0.75-1.8)	1.4 (0.78-2.7)
Weight (kg)								
<65			1.2 (0.86-1.6)	1.0 (0.71-1.4)			0.76 (0.38-1.6)	0.77 (0.39-1.5)
65-85			1 (ref)	1 (ref)			1 (ref)	1 (ref)
86-100			1.1 (0.91-1.3)	1.3 (1.0-1.5)			1.1 (0.75-1.6)	1.1 (0.75-1.6)
>100			1.3 (1.1-1.7)	1.5 (1.2-1.9)			1.5 (0.89-2.6)	1.5 (0.79-2.7)
BMI (kg m^{-2})								
Underweight			1.1 (0.47 -2.5)	1.0 (0.45-2.3)			1.1 (0.15-7.6)	1.1 (0.15-7.5)
Normal			1 (ref)	1 (ref)			1 (ref)	1 (ref)
Overweight			1.0 (0.80-1.1)	1.0 (0.87-1.2)			1.3 (0.88-1.9)	1.3 (0.91-1.9)
Obese			1.4 (1.1-1.7)	1.4 (1.1-1.7)			1.5 (1.0-2.4)	1.5 (1.0-2.4)
Unprovoked								

Supplement 2: Risk factors associated with PTS 1 and 8 years after DVT diagnosis in imputed data. (continued)

	1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*	8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*
no			1 (ref)	1 (ref)			1 (ref)	1 (ref)
yes			0.76 (0.63-0.92)	1.0 (0.75-1.2)			0.88 (0.56-1.4)	0.94 (0.56-1.6)
DVT location								
Proximal vein			1.1 (0.86-1.4)	1.1 (0.87-1.4)			1.0 (0.69-1.5)	1.0 (0.7-1.5)
Popliteal vein			1 (ref)	1 (ref)			1 (ref)	1 (ref))
Distal vein			0.87 (0.59-1.3)	0.86 (0.58-1.3)			0.70 (0.37-1.3)	0.72 (0.37-1.4)
Duration of oral anticoagulation								
< 3 months			0.76 (0.43-1.3)	0.78 (0.44-1.4)			0.71 (0.22-2.3)	0.71 (0.22-2.3)
3-6 months			1 (ref)	1 (ref)			1 (ref)	1 (ref)
6-12 months			1.2 (1.0-1.4)	1.2 (1.0-1.4)			1.0 (0.68-1.4)	1.0 (0.69-1.5)
>12 months			1.2 (1.0-1.5)	1.3 (1.0-1.6)			1.5 (1.0-2.2)	1.5 (1.0-2.3)
Frequency of elastic compression stockings								
Always			1 (ref)	1 (ref)			1 (ref)	1 (ref)
Most of the time			1.0 (0.76-1.2)	1.0 (0.74-1.2)			0.85 (0.34-2.1)	0.87 (0.36-2.1)
Sometimes			1.2 (0.87-1.6)	1.1 (0.84-1.5)			1.0 (0.46-2.0)	1.0 (0.48-2.0)
Never			0.63 (0.46-0.85)	0.63 (0.47-0.85)			0.53 (0.27-1.0)	0.53 (0.27-1.0)
Duration of elastic compression stockings use								
0 months			0.49 (0.34-0.72)	0.49 (0.33-0.72)			0.46 (0.22-0.94)	0.45 (0.22-0.93)
< 3 months			0.61 (0.39-1.0)	0.62 (0.40-0.96)			0.53 (0.12-2.3)	0.51 (0.12-2.3)
3-6 months			0.63 (0.45-0.87)	0.62 (0.45-0.85)			0.50 (0.15-1.7)	0.48 (0.14-1.6)
6-12 months			0.86 (0.69-1.1)	0.84 (0.68-1.04)			0.57 (0.29-1.0)	0.55 (0.29-1.1)
>12 months			1 (ref)	1 (ref)			1 (ref)	1 (ref)
Female hormone use								
no			1 (ref)	1 (ref)			1 (ref)	1 (ref)

Supplement 2: Risk factors associated with PTS 1 and 8 years after DVT diagnosis in imputed data. (continued)

	1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*		8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*
yes			1.18 (1.0-1.5)	1.0 (0.79-1.3)				1.0 (0.53-1.8)	0.89 (0.49-1.6)
FV Leiden									
GG			1 (ref)	1 (ref)				1 (ref)	1 (ref)
AG/AA			1.1 (0.88-1.4)	1.1 (0.88-1.4)				0.84 (0.46-1.5)	0.85 (0.46-1.57)
prothrombin 20210A mutation									
GG			1 (ref)	1 (ref)				1 (ref)	1 (ref)
AG			1.2 (0.85-1.6)	1.2 (0.83-1.7)				1.4 (0.81-2.5)	1.5 (0.83-2.6)
FXIII mutation									
GG			1 (ref)	1 (ref)				1 (ref)	1 (ref)
GT			1.0 (0.87-1.3)	1.05 (0.88-1.3)				1.1 (0.75-1.7)	1.1 (0.76-1.7)
TT			0.84 (0.58-1.4)	0.83 (0.58-1.3)				1.0 (0.32-2.9)	0.9 (0.31-2.9)
Factor VIII activity									
< 25th percentile; <111			1 (ref)	1 (ref)	<109			1 (ref)	1 (ref)
25-50th percentile; 111-137			1.0 (0.76-1.2)	1.0 (0.78-1.2)	109-135			0.89 (0.46-1.7)	0.91 (0.48-1.7)
50-75th percentile; 137-167			1.0 (0.77-1.2)	1.0 (0.82-1.3)	135-163			1.2 (0.3-2.0)	1.3 (0.80-2.1)
>75th percentile; 167-437			0.9 (0.69-1.2)	1.0(0.74-1.2)	163-361			1.1 (0.766-2.0)	1.2 (0.75-2.0)
D-dimer (ng/ml)									
< 25th percentile					<213			1 (ref)	1 (ref)
25-50th percentile					213-319			1.0 (0.47-2.0)	1.0 (0.49-2.1)
50-75th percentile					319-534			0.84 (0.40-1.7)	0.87 (0.41-1.8)
>75th percentile					534-3142			1.1 (0.66-1.9)	1.2 (0.74-2.0)
CLT									

Supplement 2: Risk factors associated with PTS 1 and 8 years after DVT diagnosis in imputed data. (continued)

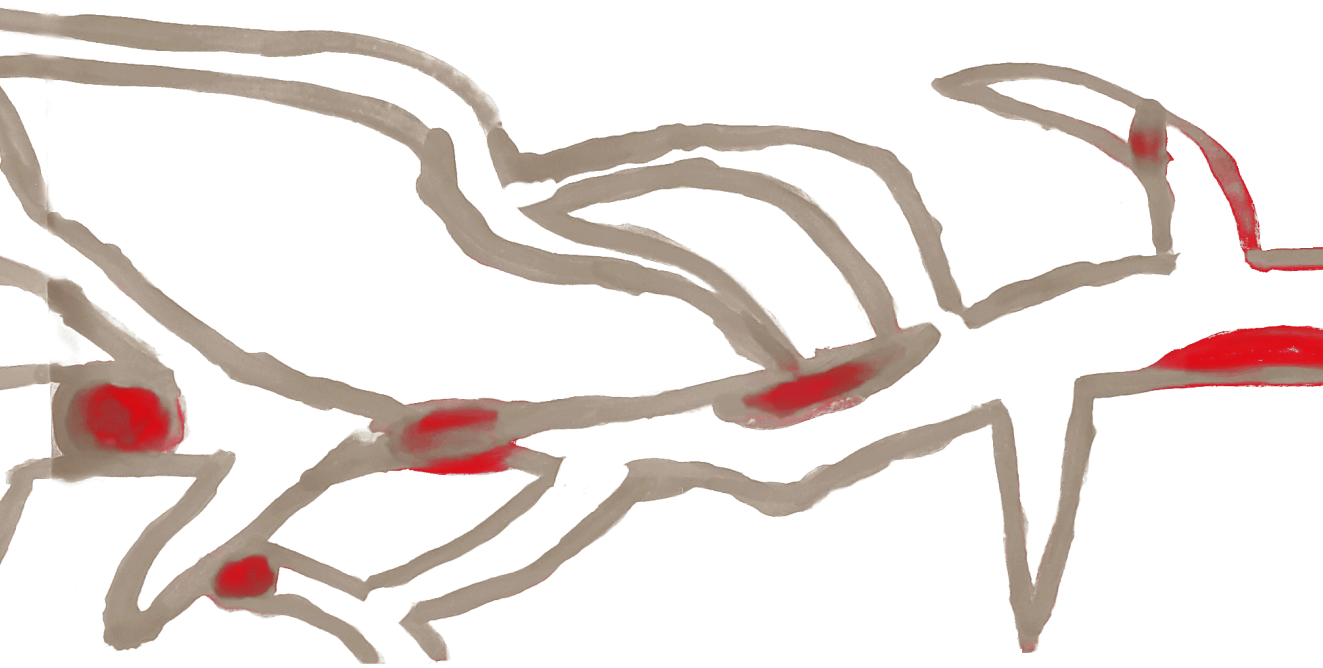
	1 year, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*	8 years, n	PTS, n	RR (95%CI)	RR adjusted (95%CI)*
< 25th percentile					<60		1 (ref)	1 (ref)
25-50th percentile					60-68		0.84 (0.50-1.4)	0.86 (0.51-1.4)
50-75th percentile					68-78		0.85 (0.47-1.6)	0.89 (0.47-1.7)
>75th percentile					>78		1.0 (0.66-1.6)	1.1 (0.66-1.8)
HsCRP (mg/L)								
< 25th percentile					<0.8		1 (ref)	1 (ref)
25-50th percentile					0.8-1.8		1.3 (0.71-2.2)	1.30 (0.74-2.3)
50-75th percentile					1.8-4.0		1.4 (0.78-2.5)	1.4 (0.82-2.6)
>75th percentile					>4.0		1.6 (0.90-2.7)	1.7 (1.0-2.8)
Protein C activity (%, 100%=1IU/ml))								
normal							1 (ref)	1 (ref)
Decreased (<mean-2SD)							2.1 (0.85-4.9)	2.0 (0.83-4.8)
Protein S antigen (U/dl)								
Normal							1 (ref)	1 (ref)
Decreased (<mean-2SD)							1.4 (0.48-4.0)	1.3 (0.43-3.9)
Antithrombin activity								
normal							1 (ref)	1 (ref)
Decreased (<mean-2SD)							0.91 (0.31-2.7)	0.91 (0.31-2.7)

Note: PTS: post-thrombotic syndrome; RR: risk ratio; CI: confidence interval; m: meter; kg: kilogram; BMI: body mass index; DVT: deep vein thrombosis; CLT: clot lysis time; HsCRP: high sensitive C reactive protein.

*Adjusted for sex, age and height when possible; pregnancy was not imputed by the low number of cases; recurrent venous thromboembolism was not imputed by there were no missing cases.

Chapter 9

General discussion and summary



The most feared long term complications of deep vein thrombosis (DVT) and pulmonary embolism (PE) are respectively the post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). The overall aim of this thesis was to provide more accurate estimations of the incidences of post-venous thromboembolism (VTE) syndromes and to evaluate ways to improve the outcomes of these patients by identifying relevant risk factors, proposing risk stratification models and improving health care utilisation. **Chapter 1** provides a general introduction of CTEPH and PTS and an overview of the presented studies.

Chapter 2 reviews the literature on arguments for and against routine screening for CTEPH in patients with acute PE based on the principles for screening of Wilson and Jungner. These principles give guidance in the selection of conditions that might be suitable for screening. Screening for CTEPH fulfils most of these principles. First of all, patients with CTEPH experience a substantially reduced quality of life and have a lower life expectancy than the general population. Second, facilities for CTEPH diagnosis initially involve echocardiography and ventilation perfusion (V/Q) lung scintigraphy, both widely available. If these tests are suggestive of CTEPH, right heart catheterization (RHC) should be performed, preferably in a dedicated pulmonary hypertension (PH) center. Third, there is a potential curative treatment for patients with CTEPH. Pulmonary endarterectomy (PEA) is a surgical procedure in which all thrombotic material is removed from the pulmonary arteries. For patients with inoperable disease, other treatment options are balloon pulmonary angioplasty (BPA), which is a catheter based procedure to open the obstructed lesions in the pulmonary arteries, or pharmacological treatment.

An important principle in the argumentation for and against routine screening for CTEPH that still needs to be answered is the availability of a suitable screening test which should be acceptable for the population. Proposed screening instruments for early CTEPH diagnosis are echocardiography, V/Q lung scintigraphy, CT pulmonary angiography (CTPA), electrocardiography (ECG), measurement of biomarkers and clinical pre-test probability assessment. Importantly, due to factors as cost-ineffectiveness, radiation exposure, lack of experience or lack of sufficient sensitivity these tests are not suitable as a standalone routine screening test for CTEPH. At present, a screening algorithm consisting of a combination of a 'CTEPH prediction score' and a set of 'rule-out criteria' consisting of a combined ECG and measurement of N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) is being evaluated in an international multicentre prospective management study (Clinical Trials.gov identifier NCT02555137). This may prove to be the cost-effective, simple and sensitive screening test that may change clinical practice. An alternative strategy would be to closely assess the index CTPA scan that was the basis for the PE diagnosis for signs of CTEPH.

Other principles in the argumentation for and against screening as defined by Wilson and Jungner that still needs to be answered are 1) whether an earlier CTEPH diagnosis

established by screening is indeed associated with a better treatment outcome and prognosis, and 2) whether screening algorithms for CTEPH prove to be cost-effective. The incidence of CTEPH in the clinical course of acute PE event is also relevant for the evaluation whether routine screening programs for CTEPH may be indicated. In **chapter 3** we describe a systematic review and meta-analysis aiming to gain an accurate overview of the reported CTEPH incidence after PE. In this study three predefined cohort subtypes were evaluated 1) the *all comers* i.e. all consecutive patients with symptomatic PE, no exclusion criteria, 2) the *survivors* i.e. all consecutive patients who survived the initial follow-up period of 3 to 6 months, and 3) the *survivors without major comorbidities* i.e. all consecutive survivors without any major cardiopulmonary, oncologic or rheumatologic comorbidities. The incidence of CTEPH in the *all comers* cohort gives the best representation of the incidence of CTEPH on population level while the incidence of CTEPH in the *survivors* and the *survivors without major comorbidities* cohort is relevant for clinical practice because these are the patients who visit the outpatient clinic of our daily practices. The weighted pooled incidence of CTEPH was 0.56% in 1186 *all comers,* 3.2% in 999 *survivors* and 2.8% in 1775 *survivors without major comorbidities.* We confirmed unprovoked PE (Odds Ratio [OR] 4.1) and recurrent VTE (OR 3.2) as strong risk factors for CTEPH development. Additionally we showed that studies assessing the CTEPH diagnosis with other diagnostic tests than RHC provide an overestimation of the CTEPH incidence (weighted pooled incidence 6.3%).

The relatively low incidence of CTEPH of ~3% in PE survivors makes it difficult to establish the sensitivity of any screening algorithm for this disease, since the negative predictive value will be very high *per definition*. In **Chapter 4** we aimed to evaluate the sensitivity of a recently constructed clinical prediction score in combination with a set of rule out criteria in a cohort of CTEPH patients with a previous acute PE diagnosis. In a total of 54 consecutive patients, the algorithm had a high sensitivity of 91%. This might indicate that when applying this algorithm to 1000 random PE survivors with a 3% CTEPH incidence, 27 out of 30 CTEPH cases could have been detected for a projected negative predictive value as high as 99.7%. Importantly, supporting the potential for wide application of the screening algorithm, the calculated interobserver agreement for calculating the clinical prediction score, right-to-left ventricle (RV/LV) diameter ratio measurement of ≥ 1.0 and ECG reading was excellent.

One item of the clinical prediction score includes the presence of right ventricular dilatation on CTPA at the moment of the acute PE event, based on a RV/LV diameter ratio of ≥ 1.0. In **chapter 5** we describe the accuracy of calculating the RV/LV diameter ratio (≥ 1.0 or <1.0) on CTPA in patients with an acute PE diagnosis by three residents internal medicine compared with an expert thoracic radiologist. This study is of relevance as in many cases the resident internal medicine, cardiology, pulmonology or emergency medicine is responsible for the initial risk assessment and treatment as well as the long

term follow-up of the patients with a PE diagnosis. After a single instruction by the thoracic radiologist the RV/LV diameter ratio was measured in 100 haemodynamically stable patients diagnosed with a symptomatic acute PE event. With a Cohen Kappa statistic of 0.86, 0.94 and 0.83 between the three residents and the thoracic radiologist we showed that after a simple instruction residents internal medicine are able to accurately determine the presence of right ventricular dilatation.

In **chapter 6** we propose an alternative screening strategy for early CTEPH diagnosis achievement based on the suggestion that signs of CTEPH may already be present on the initial CTPA scan performed for a PE diagnosis. In this study three blinded expert thoracic radiologists scored radiological parameters of CTEPH on the initial CTPA scan performed for PE diagnosis of 50 patients who were later on diagnosed with CTEPH and of 50 patients who did not develop CTEPH after a follow-up period of 2 years and who were matched to the cases on RV/LV diameter ratio. Based on the scored radiological parameters, the expert radiologists were able to identify 36 out of 50 patients who were later on diagnosed with CTEPH and correctly excluded CTEPH in 47 out of 50 control patients. The presence of three or more of the following radiological parameters was strongly predictive for CTEPH diagnosis with a sensitivity of 70% and a specificity of 96% (C-statistic of 0.92): intravascular webs, arterial retraction, dilatation of the bronchial arteries, dilatation of the main pulmonary artery, right ventricular hypertrophy and flattening of the interventricular septum. Based on this finding, more careful CTPA reading may prove to be a relevant screening tool for CTEPH as well, and reduce the current diagnostic delay of CTEPH.

The median diagnostic delay of CTEPH is over 1 year. Improved understanding of the health care utilisation of patients diagnosed with CTEPH will provide insight in the diagnostic process before CTEPH diagnosis and in patient specific factors associated with this diagnostic delay. To do this we reconstructed the clinical pathways from the moment of symptom onset to the moment of CTEPH diagnosis in 40 CTEPH patients in **chapter 7.** The most important finding of this study was that the majority of patients consulted a large number of 4 different physicians for a median number of 13 consultations before the correct diagnosis was made. The diagnostic delay of 21 months in these patients was longer than the 14 months reported in the International CTEPH registry. During the diagnostic process test results suggestive for CTEPH (for example an echocardiogram with signs of PH) were not always followed by further diagnostic tests as recommended in the current guidelines. Remarkably, in the majority of patients radiological signs of CTEPH were already present on the CTPA scan made for the initial PE diagnosis. Moreover, almost all patients reported that they experienced symptoms long before the initial PE diagnosis and none of the patients completely recovered after treatment of the PE event. This probably indicates that these patients already had CTEPH at the moment of the index PE diagnosis and were misclassified as having acute PE.

Chapter 8 focuses on the development of PTS in patients after a first episode of DVT in the lower extremity. Patients included in the Multiple Environmental and Genetic Assessment (MEGA) and the MEGA follow-up study completed a questionnaire regarding symptoms and signs of PTS. The 0-1 year cumulative incidence of PTS development was 21.8% in 1657 patients. After approximately 8 years of follow-up an additional 7% of 633 patients who completed the second questionnaire developed PTS. During the follow-up period, signs and symptoms of PTS improved in 69% of patients and worsened in 7% of patients. Relevant risk factors for PTS development at 1 year of follow-up were female sex, shorter height, overweight and obesity. After 1-8 years of follow-up only obesity showed to be a relevant risk factor for PTS development. The results of this study indicates that even one year after the initial DVT diagnosis patients might develop PTS and second that patients with a previous PTS diagnosis might improve over time.

FUTURE PERSPECTIVE

Current evidence suggests that the initial PE event in those patients who were later on diagnosed with CTEPH differs from the 'conventional' acute PE event. Patients with CTEPH generally experienced symptoms long before the PE diagnosis was made and already had signs of CTEPH on the initial CTPA scan made for PE diagnosis. In the current active InShape II study (ClinicalTrials.gov identifier NCT02555137), a novel screening algorithm consisting of a clinical prediction score and a set of rule out criteria to identify those patients with CTEPH early is being prospectively validated. Notably, this algorithm does not involve extensive assessment of the index CTPA other than measurement of RV/LV diameter ratio. For a future study, it would be interesting to evaluate whether the combination of the InShape II algorithm and an extensive assessment of the CTPA images will further contribute to an earlier CTEPH diagnosis. The optimal design for such a study would be a randomized clinical trial comparing screening for CTEPH according to the InShape II algorithm with a combination of the InShape II algorithm and an extensive assessment of the CTPA scan in patients with a PE diagnosis. Moreover, the beneficial effect of earlier CTEPH diagnosis remains to be proven. In order to answer this question I propose a comparative study between patients with CTEPH who were early identified by using a screening algorithm and CTEPH patients who were diagnosed without the use of a screening algorithm, with the combined outcomes of operability, cardiac function, functional status (e.g. 6 minute walking distance) and quality of life at diagnosis and after treatment and overall survival.

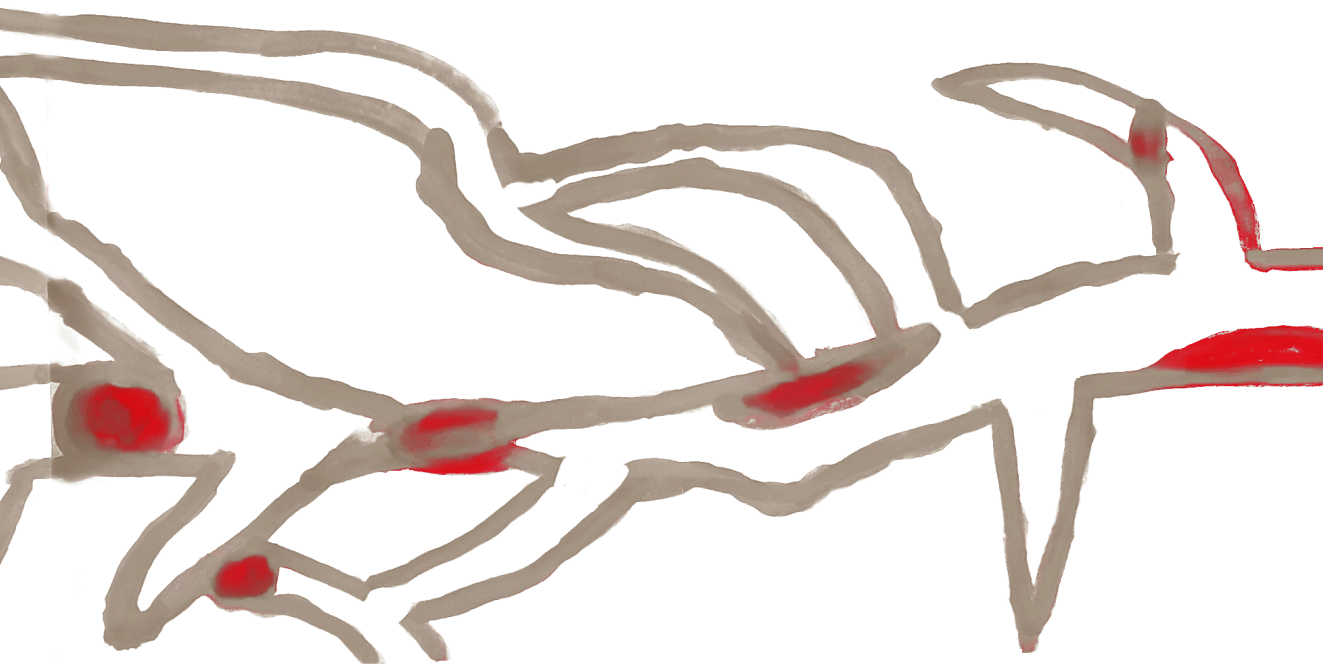
Patients with chronic thromboembolic disease (CTED) have persistent pulmonary vascular obstruction after a PE event, have impaired exercise intolerance without PH at rest and decreased quality of life. These patients may have signs of exercised induced

PH and/or dead space ventilation as main explanation for their functional limitations. Currently there is no recommended treatment option for patients with CTED. Therefore, it would be interesting to evaluate whether these patients should be treated with PEA or BPA. A randomized clinical trial on functional status (e.g. 6 minute walking distance), quality of life and treatment complications in patients with CTED who are randomized between PEA, BPA or no interventional treatment at all is the ideal study design to answer this question.

According to the most recent guidelines on VTE treatment, the majority of patients with a VTE diagnosis are now being treated with a direct oral anticoagulation (DOAC) instead of treatment with vitamin K antagonists . It is suggested that treatment with a DOAC will reduce the incidence of PTS because of a more stable anticoagulation level. Another notable change in these recent guidelines is the recommendation to treat patients with an unprovoked or a recurrent VTE event indefinitely. As we described in this thesis, both an unprovoked VTE event and a recurrent VTE event are risk factors for PTS/CTEPH. It might be that the prevention of a recurrent DVT or PE event by using indefinite anticoagulation reduces the incidence of PTS/CTEPH. A large population level registry is needed to evaluate the incidence of PTS and CTEPH before and after the introduction of VTE treatment with a DOAC.

Chapter 10

Nederlandse samenvatting



Het posttrombotisch syndroom (PTS) en chronische trombo-embolische pulmonale hypertensie (CTEPH) zijn de belangrijkste lange termijn complicaties van respectievelijk een diepeveneuze trombose (DVT) en een longembolie. Het doel van dit proefschrift was het verkrijgen van een accurate weergave van de incidentie van deze post-veneuze trombo-embolische (VTE) syndromen en te evalueren hoe de uitkomst van deze patiënten verbeterd kan worden door 1) identificatie van relevante risicofactoren, 2) ontwerpen van risico stratificatie modellen en 3) verbetering en verkorting van het diagnostisch traject dat patiënten afleggen voordat de diagnose CTEPH gesteld wordt. **Hoofdstuk 1** geeft een algemene introductie van CTEPH en PTS en een overzicht van de beschreven studies.

Hoofdstuk 2 beschrijft een overzicht van de literatuur van argumenten voor en tegen het routinematig screenen naar CTEPH bij patiënten met een acute longembolie gebaseerd op de criteria van Wilson en Jungner. Deze criteria geven richting in de selectie van ziektebeelden die geschikt zouden kunnen zijn voor screening. Screening naar CTEPH voldoet aan de meeste van deze criteria. Ten eerste ervaren patiënten met CTEPH een evidente vermindering van kwaliteit van leven en hebben ze een kortere levensverwachting dan de algemene populatie. Ten tweede zijn de faciliteiten om CTEPH te diagnosticeren makkelijk beschikbaar: echocardiografie en ventilatie perfusie (V/Q) long scintigrafie zijn testen die in ieder ziekenhuis in de Westerse wereld uitgevoerd kunnen worden. Wanneer deze testen aanwijzingen laten zien voor CTEPH dient een rechtskatheterisatie (RHC) te worden verricht, bij voorkeur in een centrum gespecialiseerd in de diagnostiek en behandeling van pulmonale hypertensie (PH). Ten derde is de ziekte goed te behandelen als de diagnose tijdig wordt gesteld. Pulmonalisendarteriëctomie (PEA) is een chirurgische procedure, waarbij het trombotisch materiaal uit de longslagaders wordt verwijderd. Behandelmogelijkheden voor patiënten die niet in aanmerking komen voor PEA zijn ballonpulmonalisangioplastiek (BPA), een procedure waarbij de obstruerende afwijkingen in de longarteriën met een katheter geopend worden, of medicamenteuze behandeling.

Een belangrijke vraag in de argumentatie voor en tegen routinematig screenen naar CTEPH die nog onbeantwoord is, is wat de optimale screeningstest zou zijn. Voorgestelde screeningsmethoden voor vroegtijdige CTEPH diagnose zijn echocardiografie, V/Q long scintigrafie, CT-pulmonalisangiografie (CTPA), elektrocardiogram (ECG), het meten van biomarkers in het bloed en tenslotte klinische risico stratificatie. Vanwege financiële kosten, blootstelling aan röntgenstraling, gebrek aan ervaring of een lage sensitiviteit zijn deze testen onafhankelijk van elkaar niet geschikt als screeningsmethode voor CTEPH. Op dit moment wordt een screeningsalgoritme bestaand uit de combinatie van een klinische beslisregel en een set 'rule out' criteria (ECG en N-Terminal pro-Brain Natriuretic Peptide [NT-proBNP] meting) geëvalueerd in een internationale multicenter

prospectieve management studie (Clinical Trials.gov identifier NCT02555137). Dit zou de kosteneffectieve, eenvoudige en sensitieve screeningstest kunnen zijn die de klinische praktijk gaat veranderen. Een andere methode zou een uitgebreide beoordeling van de index CTPA scan, verricht op het moment van de longembolie diagnose, naar vroege kenmerken van CTEPH kunnen zijn.

De incidentie van CTEPH in het klinisch beloop na een acute longembolie is ook van belang in de discussie of er een indicatie is voor het routinematig screenen naar CTEPH na longembolie. In **hoofdstuk 3** beschrijven we een systematisch review en meta-analyse die als doel had om een accuraat overzicht te geven van de gerapporteerde incidentie van CTEPH na een doorgemaakte longembolie. In deze studie zijn drie van tevoren gedefinieerde subgroepen geëvalueerd: 1) de '*all comers';* dit zijn alle opeenvolgende patiënten met een symptomatische longembolie zonder exclusiecriteria, 2) de *'survivors';* dit zijn alle opeenvolgende patiënten die de initiële follow-up duur van 3-6 maanden hebben overleefd en 3) de *'surivors without major comorbidities';* dit zijn alle opeenvolgende survivors zonder ernstige cardiale, pulmonale, oncologische of reumatologische comorbiditeit. De incidentie van CTEPH in het *all comers* cohort geeft de beste weergave van de incidentie van CTEPH op populatie niveau terwijl de incidentie van CTEPH in het *survivors* en *survivors without major comorbidities* cohort het meest relevant is voor de klinische praktijk omdat dit de patiënten zijn die op de polikliniek teruggezien worden. De gewogen gemiddelde incidentie van CTEPH was 0.56% in 1186 *all comers*, 3.2% in 999 *survivors* en 2.8% in 1775 *survivors without major* comorbidities. Dit betekent dat van de 100 patiënten bij wie een longembolie is gediagnosticeerd en op de polikliniek voor controle worden teruggezien, er 3 CTEPH zullen ontwikkelen. Daarnaast hebben we het doormaken van een niet uitgelokte longembolie (Odds Ratio [OR] 4.1) en een recidief VTE (OR 3.2) als sterke risicofactoren voor het ontwikkelen van CTEPH bevestigd.

De relatief lage CTEPH incidentie van ~3% in de longembolie *survivors* maakt het moeilijk de sensitiviteit van een screeningsinstrument naar deze ziekte vast te stellen, omdat de negatief voorspellende waarde per definitie hoog zal zijn. In **hoofdstuk 4** hebben we de sensitiviteit van een recent ontwikkelde screenings strategie daarom getoetst in een cohort patiënten met CTEPH met een voorgaande diagnose van een acute longembolie. In 54 opeenvolgende patiënten had het algoritme een hoge sensitiviteit van 91%. Dit zou kunnen betekenen dat bij het uitvoeren van dit screeningsalgoritme in 1000 random longembolie *survivors* met een CTEPH incidentie van 3%, 27 van de 30 patiënten met CTEPH gedetecteerd worden met een geprojecteerde negatief voorspellende waarde van 99.7%. Voor een uitgebreide toepassing van het screeningsalgoritme in de klinische praktijk is het van belang dat de berekende overeenstemming voor het invullen van de beslisregel, het meten van de diameter ratio van de rechter ventrikel ten opzichte

van de linker ventrikel (RV/LV) van ≥ 1.0 en het beoordelen van het ECG in deze studie uitstekend bleek met een kappa van respectievelijk 0.96, 0.95 en 0.89.

Een onderdeel van de klinische beslisregel is de aanwezigheid van een verwijd rechter ventrikel op de CTPA scan ten tijde van de acute longembolie gemeten als een RV/LV diameter ratio van ≥ 1.0. In **hoofdstuk 5** beschrijven we een studie naar de accuraatheid van het meten van de RV/LV diameter ratio (≥ 1,0 of <1,0) in CTPA scans van patiënten met een acute longembolie diagnose door drie arts assistenten interne geneeskunde vergeleken met een ervaren thorax radioloog. Deze studie is van belang omdat bij veel patiënten bij wie de diagnose longembolie gesteld wordt, de arts assistent interne geneeskunde, cardiologie, longziekten of eerste hulp geneeskunde verantwoordelijk is voor het vaststellen van het risicoprofiel van de patiënt. Deze vaak nog relatief onervaren artsen hebben geen jarenlange training in het beoordelen van CTPA scans gehad. Na een eenmalige instructie door de thorax radioloog is de RV/LV diameter ratio gemeten in de CTPA scans van 100 hemodynamisch stabiele patiënten met een symptomatische longembolie. Met een kappa coëfficiënt van 0,86, 0,94 en 0,83 tussen de 3 arts assistenten en de thorax radioloog hebben we aangetoond dat arts assistenten interne geneeskunde na een simpele instructie in staat zijn de aanwezigheid van een verwijding van de rechter ventrikel accuraat vast te stellen.

In **hoofdstuk 6** stellen we een andere manier van screenen naar CTEPH voor, gebaseerd op aanwijzingen dat er op de initiële CTPA scan gemaakt voor de longembolie diagnose al kenmerken van CTEPH aanwezig zouden zijn. In deze studie hebben drie geblindeerde ervaren thoraxradiologen radiologische kenmerken van CTEPH gescoord op de initiële CTPA scan gemaakt ten tijde van de longembolie diagnose van 50 patiënten bij wie later de diagnose CTEPH gesteld werd en van 50 patiënten die geen CTEPH kregen. De CTPA scans van deze twee groepen patiënten waren gematched op basis van RV/LV diameter ratio om classificatie bias te voorkomen. Met de gescoorde radiologische kenmerken hebben de expert radiologen 36 van de 50 patiënten die later de diagnose CTEPH kregen geïdentificeerd, en werd CTEPH in 47 van de 50 controle patiënten correct uitgesloten. De aanwezigheid van drie of meer van de volgende radiologische kenmerken was met een sensitiviteit van 70% en een specificiteit van 96% (C-statistic 0,92) sterk voorspellend voor de diagnose CTEPH: intravasculaire webs, arteriële intrekkingen, verwijding van de bronchiaal arteriën, verwijding van de long arterie, hypertrofie van de rechter ventrikel en afplatting van het septum tussen de ventrikels. Op basis van deze resultaten zou een meer uitgebreide beoordeling van de CTPA scan ook een relevant screeningsinstrument naar CTEPH kunnen zijn om de huidige vertraging in CTEPH diagnose kunnen verminderen.

De mediane diagnostische vertraging in CTEPH diagnose is vaak langer dan 1 jaar. Zo'n vertraging is voor geen enkele dodelijk hart- en vaatziekte acceptabel. Meer inzicht in

het diagnostisch traject dat patiënten voorafgaande aan de diagnose CTEPH doorlopen zal meer duidelijkheid geven in het proces en in patiënt specifieke factoren geassocieerd met deze diagnostische vertraging. Hiervoor hebben we in **hoofdstuk 7** het traject dat 40 CTEPH patiënten doorlopen hebben vanaf het moment van eerste klachten tot het moment waarop de diagnose CTEPH is gesteld gereconstrueerd. De belangrijkste bevinding van deze studie was dat de meerderheid van de patiënten 4 verschillende artsen heeft geconsulteerd met een mediaan aantal van 13 polibezoeken voordat de correcte diagnose werd gesteld. Met een mediaan van 21 maanden was het diagnostisch traject in deze patiënten veel langer dan elders gerapporteerd. Tijdens het diagnostisch traject werden testresultaten, die kunnen wijzen op CTEPH (bijvoorbeeld een echocardiogram met tekenen van PH), niet altijd gevolgd door aanvullende diagnostische testen, zoals aanbevolen wordt in de huidige richtlijnen. Het was opmerkelijk dat in de meerderheid van deze patiënten er radiologische aanwijzingen waren voor CTEPH op de initiële CTPA scan gemaakt ten tijde van de longembolie diagnose. Daarnaast ervaarden bijna alle patiënten al klachten lang voordat de diagnose longembolie gesteld werd en de patiënten herstelden niet volledig na behandeling van de longembolie. Dit betekent dat deze patiënten waarschijnlijk al CTEPH hadden ten tijde van de longembolie diagnose.

Hoofdstuk 8 gaat over de ontwikkeling van PTS bij patiënten met een eerste DVT in de onderste extremiteit. Patiënten geïncludeerd in de Multiple Environmental and Genetic Assessment (MEGA) en de MEGA follow-up studie hebben 1- en 8 jaar na DVT diagnose vragen beantwoord over kenmerken en symptomen van PTS. De 0-1 jaar cumulatieve incidentie van PTS was 21,8%. Na een gemiddelde follow-up duur van 8 jaar heeft nog eens 7% van de patiënten PTS ontwikkeld. Tijdens de follow-up periode verbeterden de symptomen van PTS in 69% van de patiënten en verslechterde dit in 7% van de patiënten. Relevante risicofactoren voor het ontwikkelen van PTS na 1 jaar follow-up waren het vrouwelijk geslacht, kortere lichaamslengte en obesitas. Na 1-8 jaar follow-up was alleen obesitas een revelante risicofactor voor het ontwikkelen van PTS. De resultaten van deze studie laten zien dat patiënten ook na lange tijd PTS kunnen ontwikkelen en dat de symptomen van PTS door de tijd heen vaak verbeteren.

TOEKOMST PERSPECTIEF

Beschikbare onderzoeksresultaten suggereren dat patiënten bij wie CTEPH werd vastgesteld een ander soort longembolie doormaakten dan patiënten die niet deze complicatie ontwikkeld hebben: in het algemeen ervaarden patiënten met CTEPH al lang klachten voordat de diagnose longembolie werd gesteld en waren er op de initiële CTPA scan gemaakt voor de diagnose longembolie al kenmerken van CTEPH aanwezig. Het is op

basis van deze gegevens waarschijnlijk dat de CTEPH al aanwezig was op het moment van de longemboliediagnose. Op basis van deze hypothese zou het mogelijk moeten zijn de diagnose CTEPH eerder te stellen. In de op dit moment lopende InShape 2 study (ClinicalTrials.gov identifier NCT02555137) wordt een nieuw screeningsalgoritme om de diagnose CTEPH eerder vast te stellen prospectief gevalideerd. Deze bestaat uit een klinische beslisregel en een set 'rule out' criteria. Dit screeningsalgoritme omvat geen uitgebreide beoordeling van de initiële CTPA scan behoudens het meten van de RV/LV diameter ratio. Voor een toekomstige studie zou het interessant zijn te evalueren of de combinatie van het algoritme van de InShape 2 studie met een uitgebreide beoordeling van de initiële CTPA scan nog verder kan bijdragen aan het eerder vaststellen van CTEPH. De beste studieopzet om deze vraag te beantwoorden is een gerandomiseerde klinische studie waarbij het screenen naar CTEPH volgens het algoritme van de InShape 2 studie vergeleken wordt met het algoritme van de InShape 2 studie in combinatie met een uitgebreide beoordeling van de initiële CTPA scan.

Opvallend genoeg is de toegevoegde waarde van het sneller vaststellen van CTEPH nog niet aangetoond. Om deze vraag definitief te beantwoorden is een vergelijkende studie noodzakelijk waarin patiënten met CTEPH na een longembolie uit centra die een screeningsstrategie toepast vergeleken worden met patiënten met CTEPH na longembolie uit vergelijkbaar centra waar geen screening wordt toegepast. Uitkomstmaten van deze studie zouden duur tot diagnose, operabiliteit, hartfunctie, functionele status (bijvoorbeeld de 6 minuten looptest), kwaliteit van leven ten tijde van de diagnose en na behandeling, en totale overleving kunnen zijn.

Patiënten met chronisch trombo-embolische ziekte (CTED) hebben na het doormaken van een longembolie persisterende obstructieve afwijkingen in de longslagaders, verminderde inspanningscapaciteit zonder PH in rust en ervaren een verminderde kwaliteit van leven. Deze patiënten kunnen PH hebben tijdens inspanning en/of dode ruimte ventilatie als voornaamste verklaring voor hun functionele beperkingen. Op dit moment zijn er geen aanbevolen behandel mogelijkheden voor patiënten met CTED. Het zou interessant zijn te onderzoeken of deze patiënten vroegtijdig behandeld kunnen worden met PEA of BPA. De meest optimale studie opzet hiervoor is een gerandomiseerde klinische studie waarbij patiënten met CTED gerandomiseerd worden tussen PEA, BPA of geen interventie, met als uitkomstmaten de functionele status van de patiënten, kwaliteit van leven en behandelcomplicaties na 6 maanden.

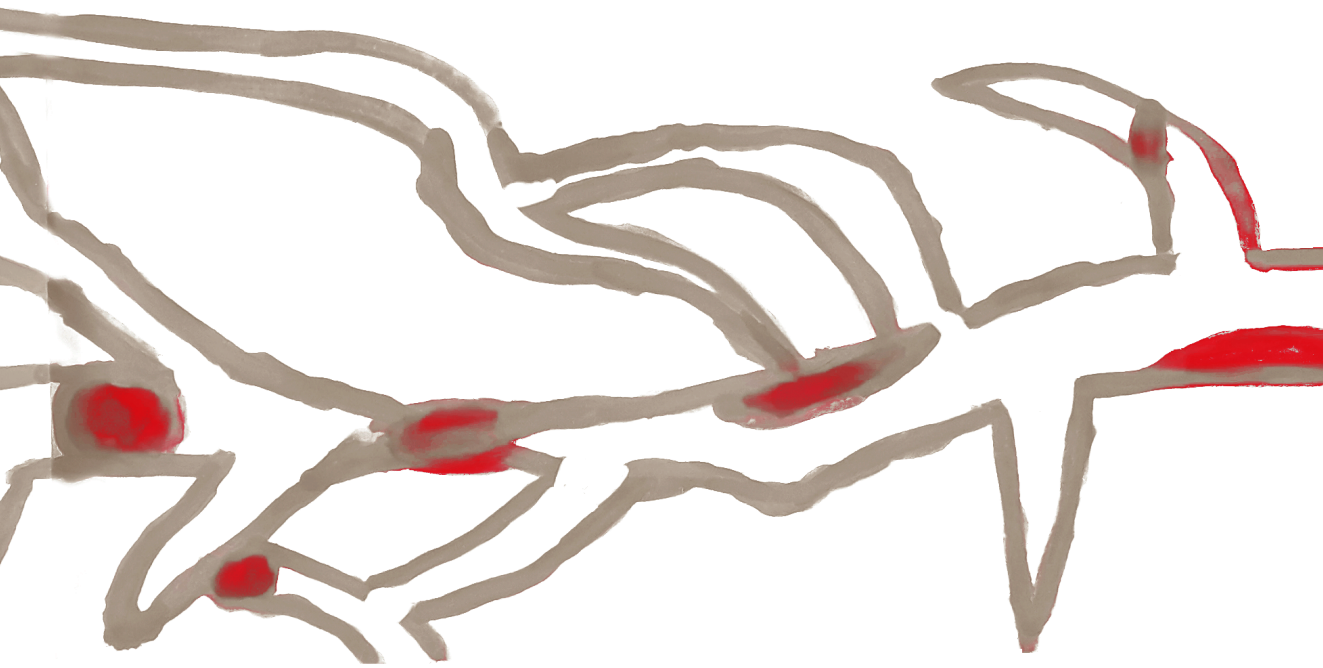
Op basis van de huidige richtlijnen over VTE behandeling wordt de meerderheid van de patiënten met een VTE diagnose op dit moment behandeld met directe orale anticoagulantia (DOAC) in plaats van met een vitamine K antagonist. Doordat er sprake is van een stabieler niveau van antistolling wordt er gesuggereerd dat behandeling van een DVT met een DOAC de incidentie van PTS zal verlagen. Een andere aanpassing in de huidige richtlijn is de aanbeveling om patiënten met een spontane VTE voor

onbepaalde duur met antistolling te behandelen om zo het risico op een recidief te voorkomen. Zoals in dit proefschrift staat beschreven en in de literatuur wordt gerapporteerd, zijn zowel het doormaken van een spontane VTE als het doormaken van een recidief VTE risicofactoren voor het krijgen van PTS/CTEPH. Hieruit kan gesteld worden dat 'moderne' antistollingsbehandeling de incidentie van PTS/CTEPH kan verlagen. Er is een grote nationale registratie studie nodig om de incidentie van PTS en CTEPH te kunnen beoordelen voor en na de introductie van de nieuwe richtlijn over de duur van antistolling en het gebruik van DOACs als het nieuwe middel van voorkeur voor de behandeling van VTE.

List of publications

Dankwoord

Curriculum vitae



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DANKWOORD

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CURRICULUM VITAE

Yvonne Maria Verhaar werd geboren op 20 september 1983 te Uithoorn. In 2002 behaalde zij haar Atheneum diploma aan het Amstelveen college te Amstelveen. In datzelfde jaar startte zij met de studie Geneeskunde aan de Vrije Universiteit in Amsterdam. In 2006 vingen haar coschappen aan en in december 2008 behaalde zij haar artsexamen. Aansluitend was zij werkzaam als arts assistent niet in opleiding in het Groene Hart ziekenhuis tot zij in 2010 kon beginnen met de opleiding tot internist in datzelfde ziekenhuis (opleiders dr. T. Koster en dr. H.G. Peltenburg). Sinds 2014 heeft zij haar opleiding tot internist voortgezet in het Leids Universitair Medisch Centrum (opleider prof. dr. J.W. de Fijter). In 2015 begon zij aan wetenschappelijk onderzoek op de afdeling Trombose en Hemostase van het Leids Universitair Medisch Centrum onder begeleiding van prof. dr. M.V. Huisman en dr. F.A. Klok, waarvan de resultaten zijn beschreven in dit proefschrift. Sinds 2018 is zij begonnen met het aandachtsgebied Vasculaire geneeskunde (opleider prof. Dr. M.V. Huisman). Zij is getrouwd met Peter Ende met wie zij 3 kinderen heeft, Laura (2012), Maaike (2015) en Matthijs (2018).