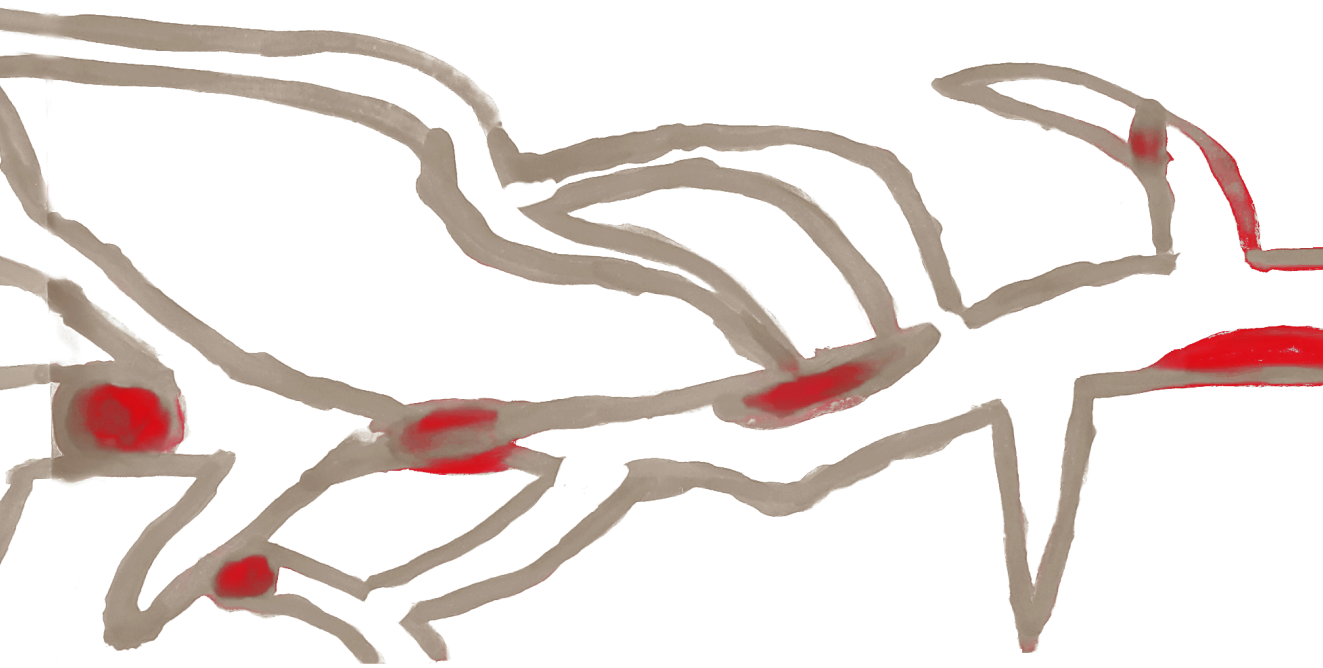
Chapter 9

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.