Prediction of long-term complications of venous thromboembolism

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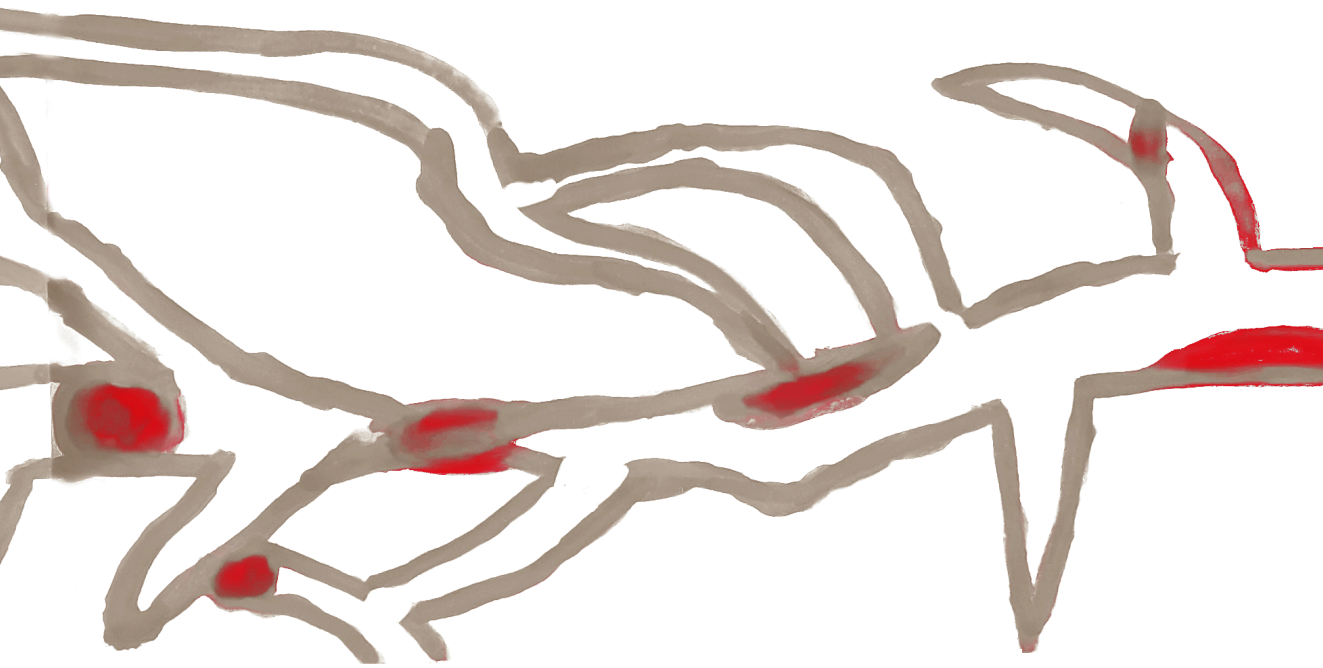
Chapter 1

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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