Chapter 1

General introduction and outline of the thesis

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GENERAL INTRODUCTION

A large and growing number of patients is evaluated at hospital emergency departments each year because of clinically suspected pulmonary embolism (PE). The disease can be fatal if left untreated. However, treatment with anticoagulants has its own risks, most notably the risk of bleeding (1,2). Therefore, adequate diagnosis is mandatory to prevent PE related morbidity and mortality on one hand, and unnecessary treatment on the other.

The diagnostic management of PE has been subject of medical research for decades. Over the last two decades, many new diagnostic methods and strategies have been introduced for the diagnostic workup of patients with suspected PE. Individual signs and symptoms have low sensitivity and specificity, meaning there is no single risk factor or clinical sign that can be used to confirm or refute the diagnosis (3). The available diagnostic tests also have several limitations, for they can be invasive, non-specific and costly. These limitations may contribute to over or undertreatment of PE, an occurrence that is not uncommon (4-6). To enforce an accurate diagnosis, concurrently reducing costs and invasiveness, diagnostic tests have now been integrated in diagnostic algorithms consisting of clinical pre-test probability, D-dimer testing followed by imaging. Because only 1 of 5 patients in whom the diagnosis is suspected actually has the disease, these diagnostic strategies focus on a safe and efficient exclusion of the diagnosis.

The first step in the approach to patients with suspected PE is a thorough clinical history and physical examination, in order to determine the clinical probability of PE. Although not sensitive nor specific when used alone, particular information regarding clinical signs and symptoms can be used to categorize patients in probability categories, by either using implicit judgment or validated clinical decision rules (7-11). Next to several available and well validated clinical decision rules (CDRs), two rules have recently been simplified to facilitate computing the score (12,13). These simplified scores need further validation and comparison to the already implemented scores.

The introduction of the D-dimer test, a laboratory assay that measures fibrin degradation products, and therefore indirectly measures blood coagulation activation, has been a major asset to the diagnostic workup of patients with suspected PE. A normal test, in combination with an unlikely clinical probability score safely excludes the diagnosis in a large proportion of patients, without the need for imaging testing. However, the D-dimer test has only moderate specificity. This results in a lower clinical utility of the CDR – D-dimer combination for certain subgroups of patients, for instance older patients, or patients with cancer. Also, because of this limited specificity and a very high, but not perfect sensitivity, it should not be used as a screening test.

If clinical probability of PE is “likely” or the D-dimer test is abnormal, further imaging is necessary to confirm or rule out the diagnosis. Introduced in 1992, computed tomography (CT) scanning has evolved to the main imaging test for the diagnosis of PE. Initially, physicians were skeptical about the accuracy of detecting emboli in segmental and subsegmental arteries with
early single-slice detector CT (14,15). However, with the introduction of multi-detector row CT (MDCT), sensitivity has greatly improved and even small subsegmental emboli can now be visualized (16,17). What remains a debate is whether a normal CT scan is also safe to exclude PE in the subgroup of patients with a high clinical pretest probability for PE and if the advent of newer generations (multi-)detector row CT scans with even higher sensitivity may perhaps result in over-diagnosis of PE. Furthermore, there is considerable radiation exposure with (repeated) CT-scanning, resulting in a significant risk of (breast) cancer, especially among young women.

Regarding the treatment and prognosis of pulmonary embolism, two important questions have surfaced. Although most hemodynamically stable patients with PE benefit from standard anticoagulant treatment, mortality rates are higher in a subgroup of patients with limited cardiopulmonary reserve. Currently, the definition of this group is uncertain, and risk stratification could help in identifying the patients who could benefit from more aggressive thrombolytic treatment with a faster lysis of pulmonary emboli and thereby the relieve of cardiac overload. On the other hand, the short-term clot resolution with standard anticoagulant treatment is insufficiently known.

**OUTLINE OF THE THESIS**

This thesis consists of three parts. The first part focuses on the diagnosis of pulmonary embolism. An overview of the current approach to patients with suspected PE is presented in **chapter 2**, along with background information on epidemiology and risk factors for PE. In **chapter 3**, one of the recently simplified scores, the simplified Wells rule is validated in an external cohort for its safety and clinical utility for the exclusion of PE, while in **chapter 4**, four recently introduced and widely used clinical decision rules are prospectively compared for the exclusion of PE, in combination with D-dimer testing. In **Chapters 5a and 5b**, the results are described of questionnaire based studies on the implementation of CDRs and D-dimer testing, and the influence of D-dimer knowledge on clinical probability assessment.

Next, in **chapter 6**, we studied whether an age-adjusted D-dimer cut-off could increase the clinical utility of the CDR – D-dimer combination for older patients, and in **chapter 7**, we examined the performance of the Wells CDR and the D-dimer for the exclusion of PE among patients with cancer. Furthermore, excluding the diagnosis outside the hospital, in primary care, would further optimize the diagnostic strategy for PE. A scenario-analysis for a diagnostic strategy consisting of a CDR combined with a point-of-care D-dimer test for the exclusion of PE is described in **chapter 8**.

Although a normal CT-scan safely excludes PE in patients with an unlikely clinical probability, **Chapter 9** focuses on the accuracy of the CT-scan in patients with a high probability. Furthermore, in **chapter 10**, a ‘low’-end CT scan and a ‘high’-end CT scan are compared for
differences in PE detection patterns. In chapter 11, an alternative diagnostic strategy is proposed and retrospectively evaluated, in which women younger than 50 years of age with suspected PE are investigated with a CDR, D-dimer test and the combination of a chest X-ray and perfusion scintigraphy, sequentially, in order to avoid CT-scanning and thereby, the radiation exposure.

Part II of this thesis focuses on the treatment and the prognosis of pulmonary embolism. In chapter 12, the literature is reviewed for the advantages and disadvantages of thrombolytic therapy. In chapter 13, the predictive value is studied of CT-measured right ventricular overload and biomarkers on the outcome of patients with PE, as possible risk stratification parameters. The result of conventional anticoagulant medication on the lysis of clots in the pulmonary arteries is assessed in chapter 14.

In the third part of this thesis, two studies are described on venous thromboembolism (VTE) and its complications in specific patient populations. From autopsy studies we know that the actual incidence of VTE is much higher than assumed, since many cases remain asymptomatic. Careful re-evaluation of CT scans may show asymptomatic VTE, especially among cancer patients (18). We assessed the prevalence of asymptomatic (incidental) VTE on staging CT scans of patients with cancer and the therapeutic implications of these thrombi in chapter 15. Similar to patients with malignancy, patients with Klippel-Trenaunay syndrome (KTS), a congenital malformation syndrome with vascular malformations, also have an increased risk of developing VTE. Continuous thrombus formation without treatment may result in long term sequelae such as chronic PE or chronic thromboembolic pulmonary hypertension (19). In chapter 16, the prevalence of chronic PE among KTS patients is assessed.

REFERENCE LIST