The diagnostic and therapeutic management of pulmonary embolism

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CHAPTER 1

General introduction and outline

Pulmonary embolism (PE) is defined as an obstruction of a pulmonary artery caused by a thrombotic embolus and was first described by Virchow in 1846 [1]. PE shares many characteristics of epidemiology and pathophysiology with deep vein thrombosis (DVT) and they are generally considered as two different presentations of the same disease called venous thromboembolism (VTE). With an annual rate of 1-2 per 1000 patients, PE is a relatively common disease [2-3]. A rapid diagnosis and accurate treatment is essential, since PE can be a fatal disease.

The diagnostic management of suspected acute PE is challenging due to the non-specific and highly variable signs and symptoms. As a consequence, the diagnosis has to be confirmed by a reliable objective test, which is nowadays computed tomography pulmonary angiography (CTPA) [4]. Many efforts have been made to exclude PE without the use of CTPA, since unrestricted use of CTPA is associated with several disadvantages, being radiation exposure, complications related to the administration of intravenous contrast and high health-care costs. An overview of the current diagnostic management strategies, as well as current therapeutic management strategies, is presented in **chapter 2**.

The first part of this thesis focuses on the diagnostic management of suspected acute PE. First, we thoroughly investigated the performance of the currently most commonly applied diagnostic management strategy. In **chapter 3**, a systematic review and patient-level meta-analysis is described that investigated the performance of the Wells clinical decision rule combined with a quantitative D-dimer test in order to exclude acute PE without CTPA, which is the most commonly used diagnostic strategy. The aim of **chapter 4** was to determine whether a normal CTPA alone is a safe criterion to rule out acute PE, particularly in patients with the highest clinical probability. Second, we evaluated two alternative diagnostic strategies in an attempt to further improve the efficiency, i.e. reducing the number of required CTPA, while maintaining the high safety of the diagnostic management. **Chapter 5** discusses the potential of applying an increased D-dimer threshold in patients with the lowest clinical probability. The results from the YEARS study, a prospective multicentre cohort study investigating a simplified and more efficient diagnostic management strategy are provided in **chapter 6**.

The topic of the second part of this thesis is the therapeutic management of acute VTE. One of the key developments of recent years is the introduction of the direct oral anticoagulants for the treatment of acute VTE. In **chapter 7**, a meta-analysis is provided on the effectiveness and the safety of these drugs compared to vitamin K antagonists. The safety of considering a limited duration of anticoagulant treatment in patients with a second VTE that occurred after a relatively long interval, as recommended in the Dutch guideline and only based on indirect evidence, was evaluated in **chapter 8**. In the following chapters, some issues on the management of cancer-associated VTE are addressed. In **chapter 9**, the current recommendations regarding treatment duration

for cancer-associated VTE are evaluated, particularly whether it is safe to stop anticoagulant treatment in patients cured from cancer. In **chapter 10**, the evidence from phase 3 studies on the efficacy and safety of the direct oral anticoagulants in patients with a cancer-associated VTE is summarized in a meta-analysis. The final chapter focusses on PE diagnosed on computed tomography scanning not performed for suspected PE, the so called incidental PE. Incidental PE is a growing challenge for clinicians, particularly in cancer patients. Although it is a relatively common diagnosis the evidence regarding the optimal management is scarce. In **chapter 11**, we combined results from 11 individual cohort studies in order to provide the best available evidence on the management of incidental PE in cancer patients.

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