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CHAPTER 13

General discussion and summary
This thesis aimed to evaluate and improve the diagnostic work-up of suspected acute pulmonary embolism (PE). Furthermore, this thesis aimed to assess the short- and long-term prognosis of patients diagnosed with acute PE and to investigate the possibility of outpatient treatment in selected low-risk patients. Finally, this thesis aimed to assess the clinical implications of incidentally diagnosed PE. Chapter 1 provides a general introduction of the diagnosis and management of PE and addresses the topics that require further research.

**PART I: DIAGNOSIS OF SYMPTOMATIC PULMONARY EMBOLISM**

Chapter 2 reviews the recent advances and remaining pitfalls in the diagnostic workup of patients with suspected acute PE. Establishing a prompt diagnosis of acute PE is challenging due to its non-specific signs and symptoms. To streamline the diagnostic workup, several clinical decision rules have been proposed in recent years. Of those, the Wells rule is the best validated and therefore most widely practised clinical decision rule. Combined with a normal D-dimer test result, a low pre-test clinical probability, as assessed with the Wells rule, safely rules out acute PE. For patients with a high pre-test probability or elevated D-dimer levels, contrast-enhanced computed tomographic pulmonary angiography (CTPA) is required to either establish or rule out acute PE. It has been postulated that D-dimer testing more frequently yields false negative results in patients with a delay in clinical presentation. Therefore, in chapter 3, we aimed to assess the impact of delay in clinical presentation on the safety of excluding PE on the basis of a low clinical probability score and a normal D-dimer test result. In addition we aimed to assess the impact of a delayed presentation on the clinical outcome of patients with PE. In a large cohort of 4044 consecutive patients with clinically suspected PE, delay in clinical presentation was found to be common: 19% of the patients presented with symptoms lasting more than seven days. As the diagnostic failure rate was 0.5% for patients both with and without a delay in presentation, we concluded that PE can still safely be excluded in patients with a delayed presentation on the basis of a clinical decision rule and a normal D-dimer test result. A delayed presentation was associated with a more central location of the PE, although this did not appear to affect the 3-month clinical outcome.

The main drawback of D-dimer testing is its low specificity at its conventional threshold of 500 μg/l, which is approximately 35-40% for high sensitivity assays. As D-dimer levels increase with age, regardless of the presence of PE, the clinical usefulness of D-dimer testing is particularly limited in elderly patients, leading to high numbers of CTPA examinations. In chapter 4, we aimed to prospectively validate the efficiency and safety of applying an age-adjusted D-dimer cut-off, defined as a patient’s age times 10
in patients aged 50 years or older with clinically suspected PE. For this purpose, a large multicenter, multinational, prospective management outcome study was performed. A total of 3346 patients with suspected PE were included. Among the 2898 patients with a low pre-test probability, 337 patients (11.6%) had a D-dimer between 500 µg/L and their age-adjusted cut-off (95% CI, 10.5%-12.9%). During three months of follow-up, the incidence of venous thromboembolism (VTE) was low: 0.3% (95% CI: 0.1%-1.7%). This study therefore confirms that applying this diagnostic strategy is effective and safe.

**PART II: MANAGEMENT AND PROGNOSIS OF SYMPTOMATIC PULMONARY EMBOLISM**

The widespread use of multi-detector CTPA, which allows better visualization of segmental and subsegmental pulmonary arteries, has led to an increased detection of small peripheral emboli confined to subsegmental branches of the pulmonary artery tree. It has been doubted whether isolated subsegmental PE (SSPE) is of clinical relevance and requires anticoagulant treatment. Therefore, in chapter 5, we compared the risk profile and clinical outcome of patients with SSPE compared to patients with more proximal PE and a reference group of patients in whom PE was suspected but ruled out. No differences were seen in the prevalence of VTE risk factors, the 3-month risk of recurrent VTE (3.6% vs 2.5%; P=0.42), and mortality (10.7% vs 6.5%; P= 0.17) between patients with SSPE and those with more proximal PE. When SSPE patients were compared to patients in whom clinically suspected PE was ruled out, age >60 years, recent surgery, estrogen use, and male gender were found to be independent predictors of SSPE, and patients with SSPE were at an increased risk of VTE during follow-up (hazard ratio: 3.8; 95% CI: 1.3-11.1). This study indicates that patients with SSPE mimic those with more proximally located PE and differ from patients without PE, with regard to their risk profile and clinical outcome.

In recent years, the possibility of treating patients with acute PE at home has emerged. Because the initial prognosis of acute PE can be complicated by serious, potentially life-threatening events, it is of vital importance that careful risk stratification takes place when considering outpatient treatment. For this purpose, several methods for risk stratification are available. In chapter 6, the Hestia criteria were compared to the simplified PE severity index (sPESI) for prediction of 30-day mortality. Results showed that both methods had an equally good performance in selecting patients with a low-risk of 30-day mortality. The negative predictive value was 99% for the Hestia rule versus 100% for the sPESI score. However, this study indicated that the Hestia criteria are able to identify a significant proportion of patients who were classified as high-risk with use of the sPESI, who could still be safely treated at home.
To assess whether NT-proBNP, a marker of myocardial stress, would provide additional safety to the Hestia criteria in selecting outpatient treatment candidates, we performed a multicentre randomized trial of which the results are reported in chapter 7. A total of 530 patients with acute PE who met the Hestia criteria were either assigned to NT-proBNP testing or to direct discharge. Patients assigned to NT-proBNP testing were initially admitted if NT-proBNP levels were > 500ng/L. The risk of adverse outcome was similar in patients assigned to the NT-proBNP group (0%; 95% CI: 0-1.3%) versus patients assigned to the direct discharge group (1.1%; 95% CI: 0.2-3.2%). None of the patients who experienced an adverse outcome had elevated NT-proBNP levels at baseline. We therefore concluded that selecting PE patients for outpatient treatment with use of the clinical Hestia criteria alone, appears to be as safe as performing additional prognostic assessment with NT-proBNP testing.

In chapter 8, we assessed the rate of thromboembolic resolution in patients diagnosed with and treated for acute PE. In this multicenter prospective study of 157 PE patients, we found that complete PE resolution occurred in 84.1% of the patients (95% CI: 77.4–89.4%) after six months of treatment. The presence of residual thromboembolic obstruction was not associated with recurrent VTE (adjusted hazard ratio: 0.92; 95% CI: 0.2–4.1). This study indicates that the incidence of residual thrombotic obstruction following treatment for PE is considerably lower than currently anticipated. Therefore, routine use of follow-up CT-imaging in patients treated for acute PE does not seem warranted.

PART III: DIAGNOSIS AND PROGNOSIS OF INCIDENTAL PULMONARY EMBOLISM

Since computed tomography (CT) imaging techniques have evolved significantly over the past few decades, PE is increasingly detected incidentally in patients in whom PE was not clinically suspected at the time of the CT examination. This is true for cancer patients in particular, who display an increased risk of PE and who frequently undergo CT-scanning for reasons such as tumor staging and treatment evaluation. To determine the clinical relevance of these incidental findings, data on the prognosis of cancer patients with incidental PE is of great importance. Chapter 9 provides an overview of the scope of this problem and summarizes recent studies addressing the clinical course and outcome of cancer patients with incidental PE. In chapter 10, we aimed to assess the accuracy of diagnosing incidental PE. The CT-scans of 62 cancer patients with incidental PE and 19 cancer patients without PE, were reassessed in a blinded fashion by two thoracic radiologists. The level of agreement between the two expert readers was high: they disagreed on the presence of PE in only two patients (3.2%), resulting in a Kappa
statistic of 0.93. Therefore, this study indicates that an incidental PE diagnosis is reliable and highly reproducible.

In chapter 11, we aimed to evaluate the current management of incidental PE by distributing a questionnaire to a large number of physicians worldwide. All of the 183 physicians that responded reported that they would treat a patient with central incidental PE with anticoagulants. In case of segmental PE, 98% would initiate treatment, regardless of the presence or absence of malignancy. When a patient with subsegmental PE (SSPE) was presented, 11% (95%CI: 6-15%) and 28% (95%CI: 21-35%) opted not to treat in the presence and the absence of malignancy respectively. This study reveals that most physicians would treat a patient with incidental PE. However, uncertainty exists about the need for anticoagulants in patients with incidental SSPE.

To assess the clinical implications of incidental PE in cancer patients, we compared 51 cancer patients with incidental PE and 144 with symptomatic PE in chapter 12. All patients included in this study received anticoagulant therapy. We did not find a difference in the one year cumulative risk of symptomatic recurrent VTE in the incidental PE group compared to the symptomatic PE patients (13.3% and 16.9% respectively, P = 0.77). In addition, we observed similar one-year mortality rates in incidental PE patients (52.9%) compared to symptomatic PE patients (53.3%; P = 0.7). These findings suggest that incidental PE mimics symptomatic PE with regard to the long-term clinical outcome, thereby justifying a similar management approach.

**FUTURE PERSPECTIVES**

Current diagnostic algorithms, combining clinical probability estimation with D-dimer testing and imaging tests, are very safe for excluding PE but require high numbers of CT-examinations. In view of cost- and time-saving as well as safety issues, future studies should attempt to reduce the number of required imaging tests without affecting the sensitivity of current diagnostic algorithms. At present, the YEARS study is being undertaken to investigate a simplified diagnostic algorithm, with a higher D-dimer cut-off for patients with a low pre-test probability. If this algorithm is found to be safe and is implemented in clinical practice, the need for CTPA will likely be reduced.

As for the management of acute PE, the most important development in recent years is the introduction of a new class of anticoagulant agents: the non-vitamin K-dependent oral anticoagulants (NOACs). These agents overcome several of the disadvantages of vitamin K antagonists (VKAs), including its slow onset and offset of action, many interactions with food and drugs, and the need for close monitoring and frequent dose adjustments. The efficacy and safety of NOACs have been evaluated in large, well-designed randomized clinical trials, which demonstrated that these agents are at least non-inferior
compared to VKAs. However, experience with these drugs in large patient populations is lacking, and real-world patient outcomes will need to be carefully monitored. Furthermore, prospective management studies are required to assess the potential of NOACs for outpatient treatment of low-risk PE. As NOACs do not require laboratory monitoring and continuous dose-adjustment, these agents may further facilitate the management of acute PE on an outpatient basis.