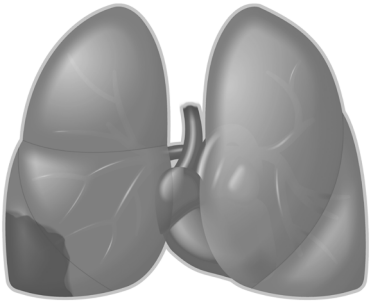
CHAPTER 10

General discussion and summary



In patients with a suspected pulmonary embolism (PE), multiple diagnostic strategies are available to confirm or exclude this diagnosis. The objectives of this thesis are to simplify, to validate and compare diagnostic strategies in patients with clinical suspicion of acute PE, with special focus on suspected recurrent PE. Subsequently, diagnostic outcomes of these strategies in patients with proven PE were studied and the possibility of home-treatment was evaluated. **Chapter 1** provides a general introduction to the diagnostic methodologies for patients with suspected acute PE and highlights some subjects for further related research.

PART I. DIAGNOSTICS IN ACUTE PULMONARY EMBOLISM

Chapter 2 provides a general overview of current diagnostic methods to confirm or rule out acute PE, focusing on different clinical decision rules, D-dimer tests and additional imaging techniques. In addition, diagnostic strategies will be evaluated that combine the preceding diagnostic tools.

In the available literature, several clinical decision rules are described. One of the best validated and widely used clinical decision rules is the Wells clinical decision rule. However, the merits of this rule are often debated, mainly because the rule includes one subjective item by which the physician must consider the possibility of an alternative diagnosis. A clinical decision rule as a well as a D-dimer test do not generate reliable clinical outcomes when executed as single tests, but an unlikely score of the decision rule combined with a normal D-dimer test result safely excludes a PE. In all other cases, additional imaging is necessary with CTPA as first choice modality.

In **chapter 3** the revised Geneva score was simplified and validated, which is a clinical decision rule with only objective variables. The revised Geneva score was simplified by attributing one point to each of the variables, which makes it easier to remember and helps to avoid miscalculations. In 1049 patients with suspected PE the proportion of patients classified as low clinical probability was 36% with a 7.7% prevalence of PE, this was comparable with the originally revised Geneva score. The area under the receiver operating characteristics curves (AUC of ROC) was similar, 0.74 (95% CI 0.70-0.77) versus 0.75 (95% CI 0.71-0.78), which shows that the diagnostic accuracy is not diminished by applying simplification. Furthermore, it appeared to be safe to withhold anticoagulation to patients with a low, intermediate (using a 3-part rule) or unlikely (in a 2-part rule) clinical probability on PE combined with a normal D-dimer test. During a 3-month follow-up period, none of these patients was diagnosed with VTE.

In addition to this simplification, prospective validation is described in **chapter 4**. Four clinical decision rules (the Wells rule, the revised Geneva score, the simplified Wells rule and the simplified revised Geneva score) were directly compared in excluding PE in

combination with D-dimer testing. Different variables of the four CDRs were collected and D-dimer test were performed in all 807 included patients. A computer program calculated all scores and indicated whether PE could be excluded (PE unlikely according to all four CDRs and a normal D-dimer test), or a CTPA should be performed (at least one CDR indicating PE likely or an elevated D-dimer level). Additionally, we evaluated the results of the individual CDRs for each patient. The number of patients categorized as "PE unlikely" ranged from 62% (simplified Wells) to 72% (Wells rule), the prevalence of PE in group of patients categorized as PE unlikely was similar (13-16%) for all CDRs. Combined with a normal D-dimer level, PE could be excluded in similar proportion of patients in 22 to 24% of the cases. The incidence of VTE during the 3-month follow-up period was comparable, 0.5-0.6% (upper limit 95% CI 2.9-3.1). Despite the discordant results in 30% of patients, PE was missed in none of these patients with a normal D-dimer level. It was concluded that the four CDRs in combination with a D-dimer test performed similarly in the exclusion of acute PE. In addition the prospective validation indicated that the simplified CDRs may be used in clinical practice.

A CTPA scan is currently the preferred imaging test to confirm or exclude PE. Nonetheless, the safety of withholding anticoagulant therapy in especially patients with a high clinical pretest probability and a negative CTPA is being debated. In **chapter 5**, a meta-analysis was performed to determine the safety of ruling out PE by normal CTPA in a specific group of patients with a strict indication for CTPA, i.e. likely or high clinical probability of PE, an elevated D-dimer level, or both. The pooled negative predictive value of CTPA as sole imaging test was 98.8% (95% CI 98.2-99.2), and the pooled NPV based on a normal CTPA followed by negative compression ultrasonography of the legs was 98.9% (95% CI 98.0-99.4). These numbers are comparable with those after a normal pulmonary angiography, historically the gold standard methodology for the diagnosis of PE. The 3-month risk of fatal PE after a negative CTPA was very small (0.6%), complementing this test with normal compression ultrasonography had no additional value (0.5%). In conclusion, it can be stated that a normal CTPA alone can safely exclude PE in all patients in whom CTPA is required to rule out VTE in these patients.

PART II. RECURRENT ACUTE PULMONARY EMBOLISM

Part II focuses on patients with suspected recurrent PE. In **chapter 6** the incidence of recurrent thrombosis in a well defined population, the Leiden region, was studied. The study estimated an overall annual incidence of recurrent VTE of 0.22 per 1000 inhabitants, the incidence of recurrent PE was 0.08 per 1000 inhabitants per year. The incidence of recurrent events was higher in male patients and the majority of recurrences occurred

in the first two years after the previous event. Malignancy was the most prevalent risk factor associated with recurrent VTE.

Chapter 7 describes the performance of a simple diagnostic strategy in patients with clinically suspected recurrent PE, using the Wells CDR, a D-dimer test and CTPA. 17% of the 516 included patients with suspected recurrent PE had a low clinical probability and normal D-dimer test result. A recurrent PE could be excluded safely, none of these patients had a recurrent VTE during the 3-month follow-up period. CTPA excluded recurrent PE in 253 patients, however, during follow-up seven patients had a recurrent VTE event (2.8%; 95% CI 1.2-5.5%), of which one was fatal (0.4%; 95% CI 0.02-1.9%). This analysis showed that the algorithm is effective in the management of patients with clinically suspected recurrent acute PE. CTPA provides reasonable safety in excluding acute recurrent PE in patients with high clinical probability for recurrent PE, with a low risk for fatal PE at follow-up.

PART III. CLINICAL OUTCOMES OF ACUTE PULMONARY EMBOLISM

The stratification of hemodynamically stable patients with proven PE, in a group with high and a group with low probability at adverse clinical outcome, can be important for diagnostic and therapeutic management. Right ventricular dysfunction predicts complicated outcome in patients with acute PE. Brain-type natriuretic peptide (BNP) is a hormone released in response to myocyte stretch and thereby a marker of ventricular dysfunction. It is synthesized as an inactive pro-hormone (pro-BNP) that is split into the active hormone BNP and the inactive N-terminal fragment (NT-pro-BNP) In **chapter 8** a meta analysis is described in which the role of (NT-pro-) BNP has been evaluated for the risk assessment for adverse clinical outcome for patients with proven acute PE. This study shows the ability to distinguish an increased risk with elevated (NT-pro-) BNP values for complications during the hospital stay (odds ratio 6.8%, 95% CI 4.4–10) and 30-day mortality (odds ratio 7.6, 95% CI 3.4 -17) and it is an indicator for right ventricular dysfunction in patients with acute PE. Whether a high (NT-pro-) BNP value by itself can stratify patients for more or less intensive treatment is yet to be proven.

In **chapter 9** patients with a proven PE and a low suspicion at complications according to predefined criteria were treated at home with the standard treatment of anticoagulants. In total 297 patients, 51% of screened patients, were treated at home. During a 3-month follow-up period, 6 patients developed a recurrent VTE (2.0%;95% CI: 0.8-4.3%); one patient a DVT and five patients PE. In total three patients died during the follow up period, one patient as a result of an intracranial bleeding, the two other patients as a

result of progressive malignancy. Besides the patient with an intracranial bleeding one other patient developed a major bleeding (total 0.7%;95% CI:0.1-2.4%). It is concluded that home treatment with anticoagulant seems effective and safe in patients with acute PE, when selected according to pre defined criteria.

FUTURE PERSPECTIVE

The goal of the diagnostic process at suspicion of PE is to develop a standardized, accurate and simple strategy that can be easily applied for the majority of patients with suspicion on PE. With the current diagnostic methodologies, consisting of clinical decision rules, D-dimer tests and imaging with CTPA as first choice, we have well validated, safe and efficient strategies for patients with suspected PE. Challenges remain to further optimize this strategy. In clinical practice, the clinical decision rules are not always applied in the correct and optimal manner. This can be improved by implementing the simplified decision rules, as described earlier, in clinical practice. Also further optimization can take place in several subgroups of patients. Research can hereby focus on elderly patients, D-dimer tests get less reliable with increasing age. A current study, the Adjust study, is focusing on a age adjusted D-dimer cut-off level. The D-dimer cut off level is defined as patient's age x 10 in patients above 50 years of age, potentially increasing the proportion of older patients in whom PE safely could be excluded. In patients with a decreasing kidney function the reduced usage of contrast is desirable and for women in the age of fertility reduction of radiation by CT scans is reason for further research. Finally, data are scarce for pregnant women, with increased risks of radiation exposure to the fetus. Magnetic resonance angiography (MRA) has potential to be an alternative to CTPE in these patients. The less nephrotoxic gadolinium contrast-enhanced acquisitions can be used for thrombus imaging with the advantage of avoiding ionizing radiation and iodinated contrast material. But accuracy is currently insufficient for implementation in routine clinical care. With further development of CTPA with higher resolutions, more and smaller emboli will be detected. Further research needs to be done to understand the clinical relevance of these smaller clots.

Specific algorithms or cutoff values can help to get a better prediction of the probability on PE for the individual patient, implementation in daily practice is however more difficult with the usage of different values in different patient groups. With electronic assistance a more individually generated risk stratification based on the unique features of the patient may become feasible.

According to the current guidelines, a patient with proven PE needs to be hospitalized. The Hestia study, described in this thesis, has shown however, that home treatment seems to be a good alternative for a carefully selected group of patients. Randomized

trials are necessary to further optimize this evidence. Finally, the added value of markers such as NT- pro BNP have to be evaluated, with the goal to optimally, clearly and simply select patients with a low risk for acute complications.