Chapter 10

General discussion and summary

The aims of this thesis were to investigate the efficacy and safety of outpatient treatment of patients with pulmonary embolism (PE) and to identify the best method for selection of PE patients for outpatient treatment. Therefore, we performed the Hestia study and compared the selection of patients with the Hestia criteria to other methods for risk stratification, for example the simplified Pulmonary Embolism Severity Index and the method described in the European Society of Cardiology guidelines. **Chapter 1** provides a general introduction to the history of treatment of patients with PE and an overview of risk stratification methods.

A recent systematic review on outpatient treatment in PE patients concluded that outpatient treatment could not be implemented in clinical practice yet, because only a few small observational studies could be included. High quality evidence on the safety of outpatient PE treatment was lacking.[1] In recent years large studies have been published on the subject, including the Hestia study.[2-4] The results of the large, multicenter Hestia study are described in **chapter 2**. This study was performed in 12 Dutch hospitals from 2008 to 2010. Patients with acute and symptomatic PE were screened for eligibility for outpatient treatment with the Hestia criteria: 11 clinical criteria based on signs and symptoms. We concluded that outpatient treatment following the Hestia criteria is safe, because patients had a low incidence of recurrent venous thromboembolism (VTE) of 2.0% (95% confidence interval (CI) 0.8-4.3), a low incidence of major bleeding of 0.7% (95% CI 0.08-2.4) and a low incidence of all-cause mortality of 1.0% (95% CI 0.2-2.9). None of the patients treated at home died of fatal PE. These favorable clinical outcomes in patients treated as outpatients are contrasted by the more severe clinical outcomes in patients selected for hospital treatment by the Hestia criteria, as discussed in **chapter 3**. Patients treated in-hospital had marked higher incidences of recurrent VTE of 3.9%, major bleeding of 4.8% and all-cause mortality of 9.6%. Five patients treated as inpatients died of PE-related causes in contrast to none of the patients treated at home. Therefore, we concluded that the Hestia criteria can be used to discriminate PE patients with low risk for adverse clinical outcome from patients with high risk for adverse clinical outcome. Low-risk patients with PE can be safely treated at home.

Because a few large studies investigating outpatient treatment of patients with PE had been published recently, we performed a meta-analysis on this subject (**chapter 4)**. In this meta-analysis we pooled incidences of recurrent VTE, major bleeding and all-cause mortality of three groups of patients: patients treated as outpatients, patients admitted initially to the hospital, but discharged early within 3 days and patients treated in the hospital for 3 days or more. Patients treated as outpatients had equally low pooled incidences of recurrent VTE 1.7%, major bleeding 1.0% and all-cause mortality 1.9% as patients discharged early or treated as inpatients. We concluded that home treatment or early discharge of selected low-risk patients with acute PE is as safe as inpatient treatment.

Besides the Hestia criteria, other methods for risk stratification in outpatient PE treatment have been described: methods based on clinical signs and symptoms[5,6], laboratory values[7] and imaging modalities.[8] In **chapter 5** the performance of the Hestia criteria was compared to the performance of the simplified Pulmonary Embolism Severity Index (sPESI) for prediction of 30-day mortality.[9] Both methods had a good performance in selecting PE patients with low risk for 30-day mortality; the negative predictive value for the Hestia criteria was 99% and for the sPESI 100%. The advantages of the use of the Hestia criteria are that these criteria can be implemented in clinical practice without modifications, in contrast to the sPESI. With the Hestia criteria more than 50% of PE patients can be selected for outpatient treatment, which is high compared to the sPESI. Although both the Hestia criteria and the sPESI had good test characteristics in predicting 30-day mortality, according to the Hestia criteria 20-30% of patients with cancer, cardiopulmonary co-morbidity or elderly patients can be safely treated at home. These patients would have been excluded from outpatient treatment by the sPESI.

In **chapter 6** we compared the performance of the Hestia criteria to the selection method advised by the European Society of Cardiology (ESC). The ESC method combined hemodynamic status (blood pressure and heart frequency) with right ventricular (RV) function to assess whether patients were eligible for outpatient treatment. Adverse events occurred in 22 patients (4.5%) treated in the hospital versus none in the patients treated at home ($p<0.001$). Sensitivity and negative predictive value for adverse outcome were 100% for the Hestia criteria and 83% and 98% for the ESC criteria, respectively. Of the patients treated at home according to the Hestia criteria, 34% could not have been treated at home according to the ESC criteria because they had RV dysfunction. When this group of patients with RV dysfunction was treated at home in the Hestia study no adverse events happened. In conclusion clinical criteria, like the Hestia criteria, could be helpful in selecting patients, including those with RV dysfunction, who have low risk for adverse clinical outcome and could be candidates for outpatient treatment.

Elevated NT-proBNP is a known risk factor for adverse outcome after PE.[10] One study previously selected patients with a low NT-proBNP and treated them at home safely.[7] We hypothesized that repeated measurements of NT-proBNP could potentially select a larger proportion of patients with PE for early discharge from the hospital. The results are presented in **chapter 7**. We demonstrated that repeated NT-proBNP testing within 48 hours after presentation with PE can identify 20% extra patients with PE as low risk than when using a single measurement at day 1.

Patients with PE without a provoking risk factor have a higher risk for various types of adverse clinical outcome, including non-malignancy related mortality, newly diagnosed malignancies and recurrent VTE, than patients with provoked PE. Importantly, **chapter 8** demonstrated that the fraction of all patients without clinical adverse events 1 year after PE was only 70% and decreased to fewer than 60% after 2 years and fewer than 50% after 4 years, whereas this latter was 84% for the control patients without PE.

In **chapter 9** an additional risk factor for adverse outcome after PE is described. Patients admitted to university hospitals had higher risks on venous thromboembolic recurrence (3.3% vs. 2.6%; odds ratio (OR) 1.3, 95% CI 0.50-3.3) and mortality (9.0% vs. 6.9% OR 1.3, 95% CI 0.75-2.4) than patients in non-university hospitals. Furthermore, hemorrhagic complications occurred twice more often in patients from university hospitals (4.3% vs. 2.2% OR 2.0, 95% CI 0.77-5.1). These bleeding complications were strongly associated with the baseline presence of active malignancy (OR 3.4, 95% CI 1.5-7.9). Our data demonstrate that patients with acute PE presenting to university hospitals are different from patients presenting to non-university hospitals regarding baseline characteristics (gender, proportion of outpatients and malignancy) and clinical outcome. Physicians should be aware of these differences when interpreting results from large clinical trials and applying these to their everyday medical practice.

Future perspectives

Evidence on the safety of outpatient treatment of patients with PE is accumulating. The recent American College of Chest Physicians guidelines give a grade 2B recommendation on the safety of early discharge of selected PE patients.[11] Before outpatient treatment of patients with PE will be graded with an 1A recommendation, more high quality evidence is needed.

As suggested in this thesis, risk stratification of normotensive patients with PE can be based on clinical criteria, biomarkers or measurements of RV dysfunction. Current evidence from large multicenter studies, including the Hestia study, suggests that patients with a low risk for adverse events can be treated on outpatient basis. However, it is yet to be determined which method of risk stratification most safely selects patients for outpatient treatment. Therefore, trials have to be performed in which different selection methods for outpatient treatment will be compared, preferably in a randomized way.

Another important change in treatment of patients with PE will be the introduction of the new oral anticoagulants (NOACs), for example the factor Xa and thrombine inhibitors. Clinical trials on the efficacy and safety of these drugs in treatment of PE patients are ongoing. Introduction of NOACs will potentially simplify the outpatient treatment of patients with PE, because these medications do not need frequent laboratory monitoring. However, before NOACs can be used in the outpatient treatment of patients with PE, adequate care has to be guaranteed, especially in the first weeks. In the future, prospective trials have to be performed to prove the safety of using these drugs in outpatient PE treatment.

References

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