Risk stratification of outpatient management in acute venous thromboembolism

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General discussion

This thesis aimed to evaluate and improve the risk stratification of outpatient management in acute pulmonary embolism (PE) patients. In addition, this thesis aimed to establish current patterns of home treatment and to assess the safety of anticoagulant treatment in PE patients. Finally, this thesis aimed to provide an overview of outpatient treatment of venous thromboembolism (VTE) in cancer patients at high risk of adverse events. **Chapter 1** provides a general introduction of the diagnosis and risk management in PE and addresses the topics that require further research.

PART 1. RISK STRATIFICATION OF OUTPATIENT MANAGEMENT IN ACUTE PULMONARY EMBOLISM

Chapter 2 reviews the recent advances in home treatment of acute PE patients in the past decade and describes current risk stratification strategies for selecting patients for home treatment. Historically, because of the necessity of parenteral anticoagulation, patients with acute PE were hospitalized. Despite improvements in prognostic risk stratification and the introduction of the direct oral anticoagulants, home treatment is still not widely applied, even though it has been estimated that home treatment is feasible and safe in 30–55% of all acute PE patients. In this review, the great variety in length of hospital stay throughout Europe is described, demonstrating that the decision to choose for home treatment or hospitalization is not solely is based on patient characteristics and risk stratification, but also greatly depends on locoregional preferences. The main trials in outpatient management of PE are discussed and more insight in the optimal strategy to select patients with PE for home treatment are provided. In short, two validated risk stratification tools to select for home treatment are currently used. First, the Pulmonary Embolism Severity Index (PESI) score or its simplified version (sPESI), which predicts the 30-day mortality rate in hospitalized patients with acute PE. Second, the Hestia criteria, which directly selects patients who may be treated at home. Other scores like The BOVA and FAST risk scores suffer from a lack of external validation and evaluation in outcome studies, and can therefore not be applied.

In the two following chapters, the aim was to investigate whether risk assessment in patients at low risk of adverse events and eligible for home treatment may be improved. In **chapter 3**, we evaluated the added prognostic value of high-sensitive troponin T (hsTnT) measurement on top of the Hestia criteria in patients with acute PE treated at home. In a cohort of 347 normotensive patients with confirmed PE, hsTnT was elevated in 58 patients (17%). Adverse events within a 30-day period, defined as composite of haemodynamic instability, ICU admission and death related to either PE or major bleeding, occurred in one out of 58 (1.7%) PE patients with elevated levels of hsTnT versus two out of 289 (0.70%) with normal values. This difference was not significant due to a very low overall rate of adverse events and resultant wide confidence intervals. Although this was the main limitation in this cohort by strong preselection of the

Hestia criteria, it did confirm the strength of the Hestia clinical decision rule to select low-risk PE patients. Moreover, normal hsTnT levels did not exclude PE-associated adverse events in all PE patients. Lastly, we found that patients with elevated hsTnT did not have a higher risk for all-cause mortality: one patient with elevated hsTnT (1.7%) versus five patients with normal hsTnT (1.7%) died (OR 1.0; 95%CI 0.11-8.7). Hence, an incremental prognostic value of hsTnT on top of the Hestia criteria for the purpose of selecting PE patients for outpatient treatment could not be established.

Besides combining cardiac biomarkers with a clinical decision rule, imaging biomarkers may also be used for identifying low risk patients. In the next two chapters the explicit value of RV overload assessed on computed tomography pulmonary angiography as a tool in the risk stratification for PE severity was further addressed. In **Chapter 4** we aimed to investigate the incidence of CT-measured right ventricular (RV) dilatation and its impact on clinical outcome in acute PE patients treated at home based on absence of the Hestia criteria. For this purpose, a large patient-level post-hoc analysis of the combined prospective Hestia and Vesta study databases was performed. The study included 1474 patients, of whom 752 were treated at home. Of the latter, 225 patients (30%) had a RV/LV diameter ratio >1.0. The incidence of adverse events, i.e. recurrent VTE and mortality, was 2.7% in those with a RV/LV diameter ratio >1.0 treated at home compared to 2.3% in patients with normal RV/LV ratio, for an Odds Ratio of 1.2 (95%CI 0.44-3.2). Of those adverse events, five (2.2%) patients died in the group treated at home with a RV/LV diameter ratio >1.0 compared to five (0.9%) treated at home without signs of RV dilation. Importantly, taking a closer look at the patients who died during the 3-month follow up, four out of five patients with signs of RV dilatation had metastasized carcinoma and all deaths occurred beyond the first 14 days after diagnosis. Hence, this result implies that RV function assessment should not be obligatory to guide management in all low risk PE patients.

Of all the Hestia items, one is subjective, i.e. "medical or social reason for treatment in the hospital for more than 24 hours", allowing the treating physician to consider all patient-specific circumstances in the final management decision. In **chapter 5**, we evaluated reasons for hospitalization according to the Hestia criteria. We aimed specifically to explore the reasons for the application of the subjective Hestia criterion, and additionally set out to evaluate whether assessment of PE severity is relevant in awarding the subjective Hestia criterion as sole argument for hospitalization. Among 600 hospitalized patients, the most frequent reason for hospital admission was the need for oxygen therapy (45%), while a large group of 38% was admitted solely based on the subjective Hestia criterion. In the further exploration of the latter, 22% was judged to have too severe PE to consider home treatment: those 22% had a considerably higher RV/LV ratio (mean difference +0.30, 95%CI 0.19-0.41) as well as a higher heart rate (+18/min, 95%CI 10-25) compared to patients with RV dilatation (RV/LV ratio >1.0) treated at home. This observation suggests that the hemodynamic profile of a patient, i.e. the severity of RV overload and the resulting hemodynamic response rather than just an abnormal RV/LV ratio,

is intrinsically taken into account in the decision to treat patients at hospital or at home when applying the Hestia criteria.

PART II. CURRENT PATTERNS OF HOME TREATMENT AND THE SAFETY OF ANTICOAGULANT TREATMENT IN PE

Over the last decade, there has been a trend towards treating PE patients at low-risk of early adverse events at home. It has been suggested that up to 55% of patients with acute PE could be eligible for outpatient management, but these percentages were reported in prospective outcome studies focusing on home treatment. Therefore, in **Chapter 6**, we evaluated current practice patterns and the outcome of home treatment of patients with confirmed PE in 12 Dutch Hospitals. In this post-hoc analysis of the YEARS study, a total of 456 patients were diagnosed with acute PE in this prospective, multicenter, diagnostic management study. We observed that 46% of all PE patients were treated at home. The remaining 54% were treated in hospital with a median duration of admission of 3.0 days (interquartile range 2.0-5.0). Interestingly, relevant inter hospital differences were observed for home treatment with percentages ranging from 13% to 83% of all patients. The incidence of adverse outcome for those treated at home was low (3.8%), consisting of two recurrent VTE, three major bleedings and two non-PE related deaths. Furthermore, the rate of PE-associated unscheduled readmissions were not different between patients treated at home or in hospital (crude hazard ratio (HR) of 1.1 (95%CI 0.57-2.1)). These findings supports the widespread trend to treat PE patients at home.

In current literature, the evidence for treating patients with cancer and VTE at home is very scarce, as outpatient management studies included only a small minority of patients with cancer-associated VTE. According to the simplified PE severity index, all patients with cancer are categorized as high-risk for adverse events and death, implicating that those should be treated initially in a hospital based setting. In **Chapter 7** we aimed to provide an overview of Dutch clinical practice of home treatment in patients with cancer-associated VTE and its adverse events. Among 183 outpatients diagnosed with cancer-associated VTE, 114 had PE (± DVT) and 69 had DVT. Home treatment was initiated in 83% of patients with cancer-associated DVT and in 55% of patients with cancer-associated PE. VTE-related mortality within a 3-months follow-up period occurred in 2 patients treated at home (1.7%) and in 5 patients initially treated in hospital (7.9%; crude HR 0.32; 95% CI 0.06-1.6). Four patients (3.3%) experienced symptomatic recurrent VTE during follow-up in the group treated at home versus 6 initially hospitalized patients (9.5%; crude HR 0.33; 95%CI 0.09-1.2). The most frequent adverse events for patients treated at home were however major bleeding events (n=10, 8.6%), occurring beyond the first 14 days after diagnosis. The majority of these bleeds occurred at the cancer site without evidence of supratherapeutic anticoagulant treatment. Moreover, most bleedings

evolved long after duration of hospitalization of the admitted patients. Therefore, it is unlikely that these bleedings could have been prevented by initial hospitalization. Taking everything into consideration, rates of adverse events were high, but independent of initial in hospital or home treatment. This study showed that home treatment could be a good option for selected patients with cancer-associated DVT and/or PE.

Chapter 8 was aimed to investigate the safety of apixaban in a practice based setting in patients who were mostly treated at home. Among 671 consecutive VTE patients treated with apixaban, 371 were diagnosed with acute PE and 300 patients had DVT. During a three months follow-up period, two patients (0.3%) had recurrent VTE, 12 patients (1.8%) experienced major bleeding and 11 patients (1.6%) died. Of the latter, seven patients (64%) had active malignancy. All 7 died after initiation of palliative care at home or hospice because of metastasized end-stage cancer. The most notable difference of this analysis compared to the phase 3 Amplify-study was the incidence of major bleeding: 1.8% during 3-month period compared to 0.6% during a 6-month follow-up, respectively. Both efficacy and bleeding rates may be underestimated in phase 3 trials because patients at higher risk of bleeding are usually excluded. This study therefore confirmed the importance of daily practice evaluation and the fact that results from phase III clinical studies cannot be directly extrapolated towards daily practice.

In **chapter 9**, we assessed the economic impact of home treatment. Cost reduction is a frequent mentioned argument in favor of home treatment, but an accurate estimation of cost saving per patient is currently still lacking. In this analysis, using detailed patient level data of the YEARS study, a €1.483 reduction was estimated per acute normotensive PE patient if they were treated at home, instead of initial hospitalization. The decrease in total costs was mainly driven by the reduction in costs for hospital admission. With the safety and feasibility of home treatment already been proven in carefully selected patients with PE, this difference underlines the advantage of triage-based home treatment of these patients.

FUTURE PERSPECTIVES

The risk stratification in patients with acute PE who could be eligible for home treatment has greatly evolved over the last decades. The introduction of clinical decision rules has created the opportunity of reproducibly selecting patients for home treatment and (imaging) biomarkers have been recommended to further optimize this risk stratification. The introduction of DOACs, with its more practical use, has likely further lowered the threshold for the treating physician to treat a PE patient at home. With the more widespread and increased use of DOACs, home treatment will probably be more initiated in the near future. This will be also very relevant for those with cancer-associated VTE as recent large phase III trials, HOKUSAI-VTE CANCER trial and CARAVAGGIO trial, have emerged the possibility of DOAC use in this specific subgroup.

It is likely that DOACs will become first line therapy in the near future for those with cancer-associated VTE.

The optimal identification strategy for patients who are able to be treated at home is further elucidated with the publication of the HOME-PE study, which aimed to compare two sets of clinical criteria, sPESI and the Hestia rule, to identify candidates for early discharge. While more patients in the sPESI group than in the HESTIA group got their home treatment triage assessment overruled by the physician-in-charge, more than a third of patients were treated at home with a low incidence of complications. Similar safety and effectiveness was found for the strategy based on the Hestia rule and the strategy based on sPESI, also lending support for elderly patients and those with active cancer not to be a priori excluded for home treatment.

Further prospective research regarding to the additional role of cardiac biomarkers and imaging biomarkers on top of clinical decision rules is warranted. In general, the addition of cardiac biomarkers and/or the assessment of right ventricle dysfunction to clinical criteria will likely increase sensitivity of risk stratification at cost of lower specificity, i.e. leading to lower risk patients selected for home treatment but also an increase in the proportion of patients hospitalized. To answer the ongoing debate on the relevance of right ventricle dysfunction selection of patients for home treatment, a randomized trial should be initiated focussing on patients at low risk for adverse events, i.e. patients without any Hestia criteria, but a RV/LV ratio >1.0. The study should be designed as a non-inferiority trial with a primary endpoint focusing on early adverse events, e.g. symptomatic recurrent VTE or PE-related death within one month, hemodynamic instability, ICU admission and the number of readmissions due to VTE.

In addition to identifying the optimal selection for patients eligible for home treatment, the treatment of some aspects of PE can be improved. In this thesis we showed that 9.7% of all PE patients treated at home are readmitted due to PE-related problems, with thoracic pain as the most frequent reason. In contrast, no clear guidelines are currently available for the optimal pharmacological treatment of thoracic pain in PE patients, which is probably caused by pleurisy. A prospective trial evaluating pain management, comparing non-steroidal agents versus opiates could be helpful to aid in this issue. Better knowledge on the prevention and optimal treatment of persistent chest pain likely leads to higher patient satisfaction and lower healthcare costs, the latter due to less readmittances.

Lastly, with the emerging options in eHealth, it is to be expected that better monitoring of patients treated at home will be introduced. In the first days after PE diagnosis, it would be interesting to see if smartphone-enabled health monitoring devices could aid in the detection of early adverse events but also in improving patient treatment compliance and preventing PE-related unscheduled readmissions.