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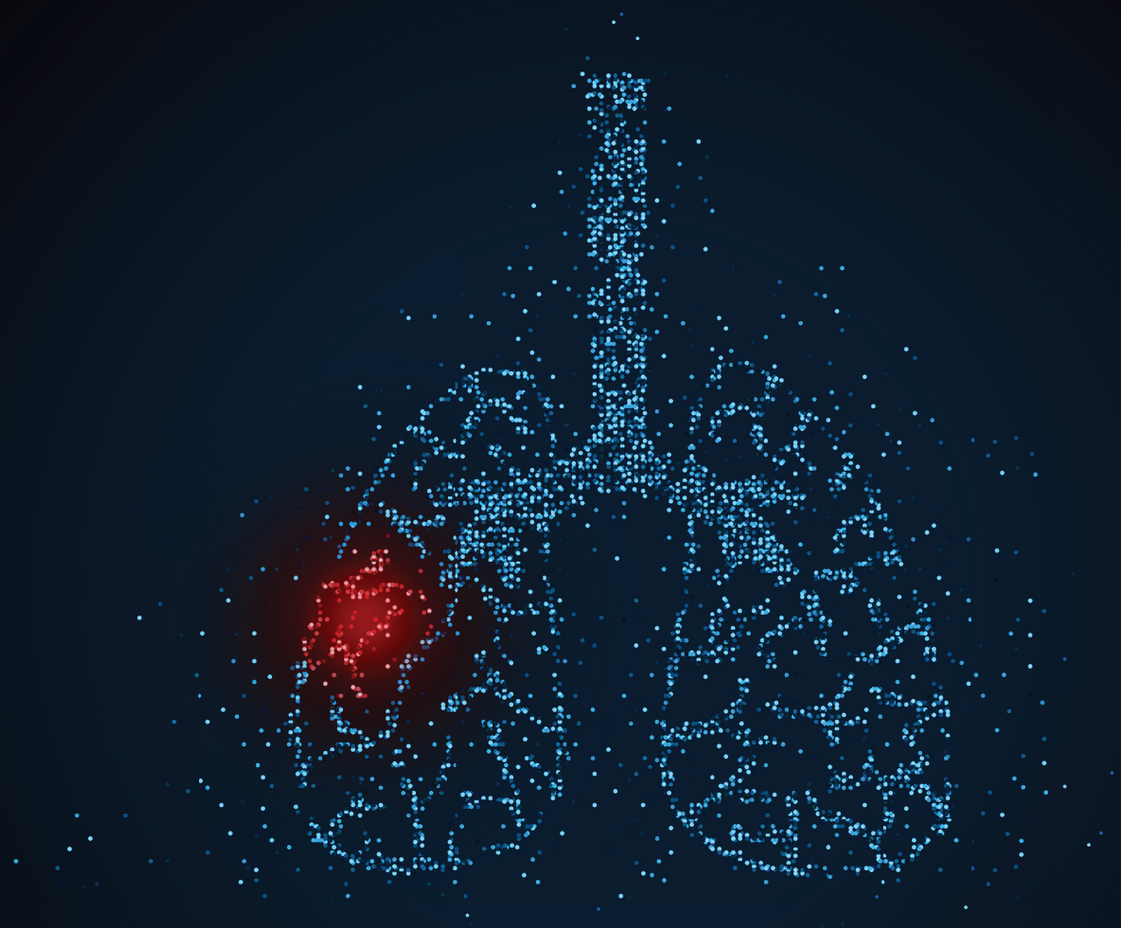

STEPHAN VINCENT HENDRIKS

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Stephan Vincent Hendriks

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Prof dr. M.V. Huisman

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Prof. dr. F.A. Klok

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Prof. dr. S.C. Cannegieter

Prof. dr. A. Vonk Noordegraaf (Amsterdam UMC, VU medisch centrum, Amsterdam)

Prof. dr. P.W.B. Nanayakkara (Amsterdam UMC, VU medisch centrum, Amsterdam)

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CONTENTS

1

General introduction and outline

Thrombosis is the formation of a blood clot that obstructs the blood flow through the circulatory system. Rudolf Virchow described this process in the 19th century. Factors in his triad predisposing for the formation of venous thrombosis include: blood stasis, changes in the vessel wall and hypercoagulability. Venous thromboembolism (VTE), mainly consisting of acute pulmonary embolism (PE) and deep-vein thrombosis (DVT), refers to a blood clot in the pulmonary arteries and to the veins of the lower and upper extremities. The burden of VTE constitutes a major global health issue and it represents the third leading cause of vascular disease with nearly 10 million annual cases worldwide.[1] In the past two decades the incidence of VTE has been increased due to a number of reasons. First, because of increasing numbers of patients longer surviving severe diseases such as cancer. Second due to the more advancing age of the overall population and last due to earlier diagnosis due to the availability of more accurate diagnostic imaging modalities.[1,2]

The treatment of patients with thromboembolic disease, and especially acute PE, was historically exclusively provided in a hospital based setting, mainly because of the necessity of parenteral anticoagulation. However, with the introduction of low-molecular-weight heparins (LMWHs) and, more recently, direct oral anticoagulants (DOACs), the option of early hospital discharge or even complete home treatment has emerged. Home treatment or outpatient management has become widely accepted and practiced for the diagnosis DVT in the 90ties of last century.[3,4] Meanwhile, although there has been a trend toward treating more patients with low-risk PE at home in the last decade, the majority of PE patients are still being hospitalized for the initiation of anticoagulant treatment.[5-11]

The first part of this thesis focuses on the outpatient management of acute VTE and especially on optimizing the risk stratification of patients with acute PE. This latter is crucial for selecting patients who can be treated safely at home. An overview of current risk stratification strategies for this purpose is presented in **Chapter 2**. Moreover, the great variety of admission duration throughout Europe is described, demonstrating that the decision to choose for home treatment or hospitalization is not solely based on patient characteristics and risk stratification, but also greatly depends on locoregional preferences as well as the organization of outpatient care by general practitioners and/or outpatient clinics.

In several large trials, the safety and feasibility of home treatment in selected patients with PE has been shown. However, the optimal method for selecting relevant patients for home treatment is still being debated. According to the European Society of Cardiology guidelines (ESC guidelines), this identification process should start with calculating the Pulmonary Embolism Severity Index (PESI) score or its simplified version (sPESI).[12] Both have been shown to appropriately predict the 30-day rate of adverse events in patients with acute PE. However, the decision for home treatment is not only confined to risk of 30-day outcome measures. An alternative risk stratification tool are the Hestia criteria. These latter contain eleven pragmatic parameters of both risk of mortality and bleeding, but also of hypoxemia and pain requiring intravenous analgesia. It has been suggested that risk stratification could be further improved

by combining clinical decision scores such as sPESI and Hestia with cardiac biomarkers.[13-16] In **Chapter 3**, a post-hoc analysis of the Vesta study is described in which the added prognostic value of high-sensitive troponin T measurements on top of the Hestia criteria is investigated.

Besides combining biomarkers and risk stratification tools, imaging biomarkers may also be used for identifying patients with a good prognosis. For instance, CT parameters such as a higher degree of embolus load, higher RV/LV diameter ratio and presence of contrast reflux to the inferior vena cava have been associated with more severe PE. The precise role of measures of RV overload in normotensive PE patients as a tool to identify low-risk patients eligible for home treatment is however debated. According to the current ESC guidelines, all PE patients with signs of RV overload are to be hospitalized.[17] According to the Hestia criteria, formal assessment of RV function is not required to select candidates for home treatment. This contrast in both strategies regarding the explicit value of RV overload in the risk stratification is addressed in the next two chapters. In **Chapter 4**, the incidence of RV dilatation and centrally located PE is described in patients treated at home based on the application of the Hestia clinical decision rule alone. In this way we aimed to investigate the additional prognostic value of RV dilatation on clinical outcome of patients treated at home after application of the Hestia criteria. In **Chapter 5** we aimed to evaluate reasons for hospitalization according to the Hestia criteria, and specifically to explore the reasons for the application of the subjective Hestia criterion. Application of this latter criterion could indeed involve measures of the RV function. To do so, we scrutinized medical charts of PE patients who were hospitalized to identify the exact reasons for hospitalization, and particularly, the impact of hemodynamic parameters and RV/LV diameter ratio on that decision.

The second part of this thesis focuses on current patterns of home treatment and the safety of anticoagulant treatment of PE. Results of outpatient management in the Netherlands are described in **Chapter 6**. In this chapter, we also compare PE-related readmissions between patients treated at home and in hospital. For certain patient populations, the decision to treat patients at home is complicated. One of those settings is cancer-associated PE, where patients have a particular high risk of recurrent VTE but also of major bleeding. According to the simplified PE severity index, all patients with cancer are categorized as high-risk for adverse events and death, implicating that all should be initially hospitalized. However, initial hospitalization of cancer patients with PE will likely not prevent cancer-associated mortality. Moreover, the psychosocial advantages and quality-of life considerations of home treatment in those patients are particularly relevant. In **Chapter 7** we aimed to provide an overview of Dutch clinical practice of home treatment in patients with cancer-associated VTE, and report its outcomes.

In **Chapter 8** the effectiveness and safety of apixaban in practice-based conditions is evaluated in patients with acute PE who were mostly treated at home. Large Phase 3 trials have already shown comparable efficacy of DOACs and vitamin K antagonists in patients with VTE, with less major bleeding events in patients with DOAC treatment. As phase 3 trials have strict in- and exclusion criteria both efficacy and bleeding rates may be underestimated. Evaluation of

the DOACs using practice based data sources in those treated at home is needed to provide a better insight into their effectiveness and safety. Lastly, the aim of **Chapter 9** was to quantify the economic impact of home treatment. It has been suggested that home treatment of PE is associated with significant cost savings which would be a further advantage on top of higher patient satisfaction and the prevention of hospital overcrowding. In this chapter an accurate estimation of cost savings per patient treated at home is described.

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Home treatment of acute pulmonary embolism: state of the art in 2018.

van der Wall SJ*, Hendriks SV*, Huisman MV and Klok FA

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*Both authors have contributed equally to this paper

ABSTRACT

Purpose of review: Historically, because of the necessity of parenteral anticoagulation, patients with acute pulmonary embolism (PE) are hospitalized until stable oral anticoagulation is achieved. Despite improvements in prognostic risk stratification and the introduction of the direct oral anticoagulants, home treatment is still not widely applied. Main advantages of home treatment involve improvement of quality of life and significant healthcare cost reduction. In this review, we summarized recent published data on home treatment of patients with acute PE.

Recent findings: Although a significant decrease in mean duration of hospital admission for PE has been demonstrated over the last decade in Europe, most PE patients are currently hospitalized while they might be treated in an outpatient setting. In recent years, five major studies have been performed, in which the decision to initiate home treatment was based on the Hestia criteria in most patients. Over 98% of patients treated at home had an uncomplicated course.

Summary: Home treatment of acute PE is suggested to be feasible and safe in 30% to 55% of all patients. Results of ongoing trials will provide more insight in the optimal strategy to select patients with PE who are eligible for home treatment and likely will result in more widespread application of this practice.

INTRODUCTION

Pulmonary embolism (PE) is a common and serious condition that often leads to hospitalization because of a potential risk of early adverse events and historical indication for parenteral anticoagulation. These adverse events particularly include thromboembolic recurrence or major bleeding potentially leading to death.[1,2] However, this risk of adverse events differs among patients, depending on the presence of a variety of clinical characteristics during diagnosis, including -and most importantly- hemodynamic status.[3,4]

Over the last decade, there has been trend towards identifying PE patients at low-risk of early adverse events who may be treated in an outpatient setting instead of initial hospitalization. This is partially due to introduction of low-molecular weight heparins (LMWH), fondaparinux and more recently, direct oral anticoagulants (DOACs) since these agents do not require laboratory monitoring and can be administered according to either weight based doses (for LMWH) or fixed doses (for DOACs). 'Home' or 'outpatient' treatment has many advantages, such as improvement of quality of life compared to hospitalisation, prevention of hospital overcrowding and significant reduction in healthcare costs.[5-7] It has been estimated that 30% to 55% of acute PE patients could be selected for home treatment which could lead to a decrease in yearly US health care costs of $1 billion.[8,9] However, despite improvements in prognostic risk stratification, home treatment is still not widely applied.[10] The aim of this review is to summarise recent published data on home treatment of patients with acute PE.

CURRENT DURATION OF HOSPITAL ADMISSION FOR ACUTE PE IN EUROPE

The median duration of hospital admission for acute PE has decreased over the past decade in Europe. According to a recent large study comprising mainly European hospitals, the mean duration of admission was 13.6 days (standard deviation (SD) 4.7) in 2001 and 9.3 (SD 0.9) days in 2013[10]**. Data for individual European countries show large regional differences (**Table 1**). A nationwide population-based cohort study in Spain of 165.229 patients found a mean hospitalization length of 14 (SD 13) days between 2001 and 2010 [11], and a nationwide retrospective study in France including 34,179 PE patients reported this length to be 10 days (SD 7.7) in 2010.

Length of hospital stay strongly depends on clinical characteristics and PE-related findings of the study population, e.g. age, blood pressure, heart rate, oxygen supplementation and comorbidities. Several clinical prediction rules have been developed that contain a mixture of these characteristics and can help to identify patients with low risk of adverse outcome[12-16]. In addition to the risk of recurrent PE and bleeding, obvious criteria such as hypoxaemia requiring supplemental oxygen, pain requiring intravenous analgesia and home circumstances that ensures adequate therapy compliance in an outpatient setting also influence the length of hospitalization.

The decision to choose for home treatment thus greatly depends on local case mix as well as the organization of outpatient care by general practitioners and/or in the outpatient clinics.

Table 1. Current hospital stay after PE in Europe.

Article	Country, centres	Design	N	Hospital stay (days)
Guijarro et al. (2016) (11)	Spain, nationwide	Prospective registry	165,229	Mean 14 ± 13
Balahura et al. (2017) (25)	Romania, 1	Retrospective cohort	221	Mean 10 ± 5
Paczynska et al. (2016) (26)	Poland, 1	Prospective cohort	215	Median 7 (range 2-22)
Motte et al. (2016) (27)	Belgium, 10	Retrospective cohort	621	Mean 10 ± 6
Zanova et al. (2015) (28)	Czech Republic, 1	Retrospective cohort	188	Median 7*
Werth et al. (2015) (29)	Germany, 1	Retrospective cohort	439	Median 9 (IQR 2-16)
Olie et al. (2013) (30)	France, nationwide	Retrospective cohort	34,179	Mean 10*
Casazza et al. (2012) (31)	Italy, 47	Prospective cohort	1716	Mean 10 ± 7
Sharma et al. (2009) (32)	Croatia, 1	Retrospective cohort	165	Mean 15 ± 9

*No range could be retrieved from report.

WHAT IS HOME TREATMENT OF ACUTE PE?

In the literature, outpatient management of acute PE has been referred to as 'home treatment', 'early discharge' and 'outpatient treatment', although a clear definition is lacking. In recent years, five major prospective studies on home treatment of acute PE were performed; three RCTs and two prospective cohorts (**Table 2**). Two RCTs compared either discharge within 24 hours or within three days with 'full' hospitalization, whereas one RCT and two large prospective cohorts only evaluated patients who were discharged within 24 hours. While some patients in these studies were discharged from the emergency room, others were admitted on an observational unit or even to the hospital within this timeframe. Based on these definitions, home treatment does not only apply to patients who are not admitted at all, but comprises a more heterogeneous group of patients who are managed outside the hospital after a short period of hospitalization during which they are monitored and evaluated for the risks for adverse events before discharge. Notably, even when the broadest definition (discharge within 3 days after diagnosis) would be applied, this duration of admission is still much shorter that current European practice.

HOW TO IDENTIFY PATIENTS WHO ARE ELIGIBLE FOR HOME TREATMENT?

When considering home treatment of patients with acute PE, the first challenge is to identify patients who are at low risk for adverse events. This identification process can be facilitated by using validated risk stratification tools. The recommended approach by the ESC guidelines refers

to the Pulmonary Embolism Severity Index (PESI) score or its simplified version (sPESI).[12,17] The sPESI comprises six variables that are listed in **Table 3.** More recently, the BOVA and modified FAST risk scores have been derived.[13,14] The BOVA and FAST risk scores include various clinical features and biochemical markers, such as NT-proBNP, Troponin, D-dimer or a heart-type fatty acid binding protein (H-FABP), but suffer from a lack of external validation and evaluation in outcome studies.

Table 2. Definition and outcomes of five large studies.

Study	Design	Definition of home treatment	Selection method for outpatients	Treatment	Number of patients enrolled	% home treatment	3-month outcome incidences
Aujeski et al. (2011) (12)	RCT	Within 24 hours	sPESI score	LMWH followed by VKA	344	50	*Outpatient:* VTE: 0.6% Major Bleeding: 1.8% Mortality: 0.6% *Hospitalized:* VTE: 0% Major Bleeding: 0% Mortality: 0.6%
Zondag et al. (2011) (16)	Cohort	Within 24 hours	Hestia rule	LMWH followed by VKA	297	100	VTE: 2% Major bleeding: 0.7% Mortality: 1%
Agterof et al. (2010) (18)	Cohort	Within 24 hours	NT-proBNP	LMWH followed by VKA	152	100	VTE recurrence: 0% Major Bleeding: 0% Mortality: 0%
Den Exter et al. (2016) (19)	RCT	Within 24 hours	Hestia rule	LMWH followed by VKA	550	94	VTE: 1% Major bleeding: 0.8% Mortality: 1.3%
Otero et al. (2010) (20)	RCT	Within five days	Uresandi score	LMWH followed by VKA on day 10	132	55	*Outpatient:* VTE: 2.8% Major Bleeding: 5.5% Mortality: 4.2% *Hospitalized:* VTE: 3.3% Major Bleeding: 5.0% Mortality: 8.3%

LMWH=Low-Molecular-Weight Heparin, VKA=Vitamin K Antagonist VTE=Venous Thromboembolism

Table 3. Uresandi score (15)

Clinical variable	Score
Recent major bleeding episode	4 points
Cancer with metastasis	4 points
Creatinine levels of over 2 mg/dL	3 points
Cancer without metastasis	2 points
Immobility due to a recent medical condition	2 points
Absence of surgery in the past 2 months	1 point
Age of over 60 years	1 point

Risk of complications:
Low: ≤2
High: 2

PESI and sPESI have been shown to appropriately predict the 30-day rate of adverse events in patients with acute PE. However, the decision for home treatment is not only confined to risk of 30-day outcome measures. The 'Hestia' clinical decision rule contains pragmatic parameters of both risk of mortality and bleeding, but also of hypoxemia, pain requiring analgesia and bleeding risk (**Table 4**).[16] Currently, the Hestia rule is the best-validated clinical decision tool in the English literature for selecting PE patients eligible for home treatment, while prospective studies evaluating clinical outcome of home treatment based on the sPESI, BOVA or modified FAST score are not available.

Table 4. sPESI score (12)

Criteria	Score
Age>80	1
Cancer	1
Chronic cardiopulmonary disease	1
Pulse > 110 bpm	1
SBP <100mmHg	1
Arterial blood oxygen saturation <90%	1

Mortality risk:
Low: 0
High: ≥1

HOME TREATMENT VERSUS HOSPITALIZATION

The five largest prospective studies published to date are listed in **Table 2.**[12,16,18-20] These studies are not easily comparable because of heterogeneous selection criteria and various definitions of home treatment. In all studies, patients were initially treated with LMWH with overlapping vitamin-K antagonist (VKA) therapy, with most of studies using a minimum of five days LMWH treatment until the international normalized ratio was in the therapeutic range of 2.0–3.0. Two

studies also included patients with active malignancies who received monotherapy with LMWH treatment.[16,19]

The first randomized controlled trial by Otero *et al.* [20] compared the 3-month rate of VTE recurrences and bleeding events of discharge within three days versus standard hospitalization in 132 low-risk PE patients. Low-risk patients were identified according to the (non-validated) Uresandi clinical score **(Table 3).**[15] This study found no significant differences between the rates of recurrent VTE (2.8%, 95% confidence interval (CI) 1.1-6.6, versus (vs.) 3.3%, 95%CI 1.3-8) and bleeding (1.4% vs. 1.6%) between home treatment and hospitalization respectively. The study became suspended after the first 132 patient were enrolled, due to an unexpected high mortality rate in both arms of the study (4.2%, 95%CI 0.5-8.9, early discharge vs. 8.3%, 95%CI 1.1-15, hospitalization; relative risk (RR): 0.5, 95%CI 0.12-2.01). Inherent to early termination of the trial, the confidence intervals of this mortality rate were wide.

In the second trial [12], 1557 acute PE patients were assessed for eligibility, of whom only 344 low-risk PE patients were randomized to discharge from the emergency department within 24 hours or hospitalization. After initial screening based on ad hoc criteria necessitating hospitalisation, the Pulmonary Embolism Severity Index (PESI) score was used to identify patients with low mortality risk (categories I and II; **Table 4**). Non-inferiority was shown in the incidence of recurrent VTE (0.6% vs. 0%, 95% upper confidence limit (UCL) of difference 2.7) and death (0.6% vs. 0.6%, 95% UCL 2.1) at 90 days for home treatment and hospitalization, respectively. Although the major bleeding incidence at 90 days exceeded the non-inferiority threshold in the home treatment group (1.8% vs. 0%, 95% UCL 4.5), the authors concluded that outpatient was non-inferior to inpatient treatment in terms of efficacy and safety.

The third study included 152 hemodynamically stable PE patients with normal N-terminal pro–brain natriuretic peptide (NT-proBNP) levels (18). Patients were discharged immediately from the emergency room or within a maximum of 24 hours after admission. The study reported no recurrent VTE, major bleeding or death occurrences during the 3-month follow-up period. It was therefore concluded that home treatment was safe in low-risk PE patients.

The Hestia study evaluated the efficacy and safety of home treatment in 297 PE patients using the Hestia criteria to identify eligibility for home treatment (**Table 5**).[16] Home treatment was started immediately or within 24 hours after PE diagnosis. Half of the patients diagnosed with PE were deemed eligible for home treatment. Of these patients, 2% (95%CI 0.8-4.3) suffered recurrent VTE, 0.7% (95%CI 0.08-2.4) experienced a major bleeding events and 1% (95%CI 0.2-2.9) died during the 3-month follow up period. The authors concluded that home treatment in patients with PE and none of the Hestia criteria is safe.

The safety of home treatment was further established by a third and largest RCT.[19]** This study compared the safety of the Hestia criteria alone with the Hestia criteria combined with NT-proBNP testing in 550 patients diagnosed with PE. Low incidences of VTE recurrence (1.1%, 95%CI 0.2-3.2), major bleeding (1.1%, 95%CI 0.2-3.2) and mortality (1.1%) were observed in patients selected for home treatment by the Hestia clinical decision rule alone. In the group

randomized to NT-proBNP testing, only 34 of the 257 patients (12.4%) had an elevated NT-proBNP level and thus were treated as inpatients. Adverse outcomes did not differ significantly between both groups. The most likely explanation for the low number of patients with elevated NTproBNP is that the Hestia rule preselects patients with normal NT-proBNP levels. This further strengthens the results of previous studies that applied the Hestia criteria. The authors concluded that the decision for home treatment can be safely based on these criteria alone.

Table 5. Hestia criteria (16)

Is the patient hemodynamically unstable? [a]	Yes/No
Is thrombolysis or embolectomy necessary?	Yes/No
Active bleeding or high risk of bleeding? [b]	Yes/No
More than 24 hour of oxygen supply to maintain oxygen saturation > 90%?	Yes/No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes/No
Severe pain needing intravenous pain medication for more than 24 h?	Yes/No
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?	Yes/No
Does the patient have a creatinine clearance of < 30 ml/min? [c]	Yes/No
Does the patient have severe liver impairment? [d]	Yes/No
Is the patient pregnant?	Yes/No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes/No
If the answer to one of the questions is 'yes', the patient cannot be treated at home	

[a] Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure <100mmHg with heart rate >100 beats per minute; condition requiring admission to an intensive care unit.

[b] Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 9 109/L), uncontrolled hypertension (systolic blood pressure > 180mm Hg or diastolic blood pressure > 110mm Hg).

[c] Calculated creatinine clearance according to the Cockroft-Gault formula.

[d] Left to the discretion of the physician.

Two meta-analyses have summarized these five studies and confirmed the safety of home treatment in selected PE patients.[9,21] The meta-analysis by Zondag *et al.* included 1657 PE patients who were treated at home and found low pooled incidences of recurrent VTE (1.7%, 95%CI 0.92-3.1), major bleeding (0.97%, 95%CI 0.58-1.59) and mortality (1.9%, 95%CI 0.79-4.8) which did not differ relevantly from these rates in hospitalized patients.[9] The meta-analysis of Piran *et al.* included 1258 patients and found these pooled incidences to be 1.47% (95%CI 0.47-3), 0.81% (95%CI 0.37-1.42) and 1.58 (95%CI 0.71-2.8), respectively (37). Consequently, since 2014, international guidelines indicate that home treatment for selected PE patients with adequate home circumstances should be considered (Grade 2B evidence).[22,23]

Only two studies addressed patient satisfaction of home treatment.[12,18] In the study performed by Aujeski *et al.* [12], a similar number of patients treated at home (92%) and hospitalized patients (95%) reported to be satisfied with their treatment. Agterof *et al.* [18] reported satisfac-

tion (PSQ-18) and anxiety (HADS-A) scores among the study patients. The HADS-A anxiety score did not change significantly between inclusion and after 10 days, whereas the PSQ-18 showed a high score for satisfaction with home treatment. However, evidence of improved patient satisfaction with home treatment is still limited and more research is required to evaluate patient experience of both in- and outpatient care.

DOACS

Anticoagulation is recommended in patients with acute PE to prevent both early death and recurrent symptomatic or fatal VTE.[22,23] In the last decades, the treatment of choice was LMWH with overlapping VKA until a stable therapeutic anticoagulant level was reached. The introduction of direct oral anticoagulants (DOACs) that specifically inhibit factor Xa or thrombin offer the advantage of oral treatment without overlapping treatment with parenteral anticoagulants, and monitoring of the anticoagulant effect is not necessary. Importantly, dabigatran and edoxaban need to be preceded with a short course of LWMH, while rivaroxaban and apixaban can be started at diagnosis. Because DOACs have been shown to be associated with less major, intracranial and fatal bleeding [24], international guidelines do now favour use of DOACs over VKA plus LMWH for the initial and long-term treatment of VTE.[22,23]

The availability of DOACs has further lowered the bar for treating patients with acute PE at home, although management studies applying DOACs in PE patients treated in the outpatient setting are currently not (yet) available.

FUTURE OUTLOOK

Four ongoing trials are currently enrolling patients. The HOME-PE study is a phase III, multicentre, non-inferiority study, which is randomizing 1975 normotensive PE patients to either using the Hestia rule or sPESI score to triage patients for home treatment (Clinicaltrials.gov identifier: NCT02811237). The main objective will be to demonstrate that a strategy based on the HESTIA rule compared to a strategy based on the sPESI score is at least as safe with regard to the 30-day rate of recurrent VTE, major bleeding and death. An important secondary objective is to demonstrate the superiority of Hestia with regard to the proportion of patients who are discharged within 24 hours after inclusion.

The three other trials aim to evaluate the use of DOACs in the setting of home treatment of PE. The Home Treatment of Pulmonary Embolism (HoT-PE) study will determine the feasibility, effectivity, and safety of rivaroxaban (EudraCT Nr. 2013–001657–28). This is a phase III, multicentre study with a planned sample size of 1050 patients with PE and none of the Hestia criteria. Moreover, patients can only enter the study if CT or echocardiographic assessed right

ventricular function is normal. The primary outcome is recurrent VTE or PE-related death within three months of enrolment. The third study is a multicentre prospective observational study to investigate the effectiveness of apixaban in a planned enrolment of 850 PE patients treated at home, who have none of the Hestia criteria or at discretion of the clinician in combination with an sPESI score of 0. Primary outcome will be the number of re-hospitalizations for VTE recurrence or bleeding within the first 30 days (Clinicaltrials.gov identifier: NCT03404635). Lastly, the MERCURY PE study is currently randomizing low-risk PE patients, as selected by the Hestia criteria, to home treatment or hospitalization, to compare the 30-day rates of recurrent VTE and major bleeding (ClinicalTrials.gov Identifier: NCT02584660). All patients randomized to home treatment are treated with rivaroxaban, while the initial hospitalization group will receive standard-of-care as per local protocol and defined by the medical team caring for the participant.

These ongoing studies will provide more insight on PE management and the optimal identification strategy for patients who are able to be treated at home and likely results in more wide application of this practice.

CONCLUSION

Home treatment is feasible and safe in selected PE patients due to the low incidence of adverse events. Although most PE patients in Europe are currently hospitalized for almost two weeks, the availability of DOACS and the change in guideline recommendations will likely lead to a further decrease in the mean duration of hospitalization and an increase in the number of patients discharged within 24 or 48 hours of diagnosis. Results from ongoing trials are expected to further strengthen the current guideline recommendations on home therapy for acute PE.

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3

Uncertain Value of High-sensitive Troponin T for Selecting Patients With Acute Pulmonary Embolism for Outpatient Treatment by Hestia Criteria

Stephan V. Hendriks, Mareike Lankeit, Paul L. den Exter, Wendy Zondag, Rolf Brouwer, Michiel Eijsvogel, Marco J. Grootenboers, Laura M. Faber, Roxanne Heller-Baan, Herman M.A. Hofstee, Antonio Iglesias del Sol, Albert T.A. Mairuhu, Christian F. Melissant, Henny G. Peltenburg, Marcel A. van de Ree, Erik H. Serné, Stavros Konstantinides, Frederikus A. Klok and Menno V. Huisman, *on behalf of the Vesta investigators*

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ABSTRACT

Background: In a randomized trial, the incremental prognostic value of normal NT-proBNP to the Hestia criteria for selecting patients with pulmonary embolism (PE) for outpatient treatment could not be established, due to low prevalence of elevated NT-proBNP. The potential role of highly sensitive troponin T (hsTnT) for this purpose has not been studied.

Aim: To investigate the added prognostic value of hsTnT measurement to the Hestia criteria in patients with acute PE treated at home, and to assess whether hospitalization because of elevated hsTnT would have prevented adverse events.

Methods: In this post-hoc analysis of the Vesta study, we assessed a 30-day adverse outcome in normotensive patients with confirmed PE managed according to the Hestia criteria with normal versus elevated hsTnT levels.

Results: Of all 550 patients included in the original Vesta study, hsTnT was measured in 347 (63%) and elevated in 58 patients (17%). The adverse 30-day composite adverse outcome occurred in 1/58 patients (1.7%) with elevated hsTnT versus 2/289 patients (0.70%) with normal hsTnT (OR 2.5, 95%CI 0.22-28). One patient (1.7%) with elevated hsTnT died compared to five with low hsTnT (1.7%; OR 1.0; 95%CI 0.11-8.7), including the only PE-related death (on day 15).

Conclusion: Although we observed a trend for elevated hsTnT towards a 2.5- fold higher 30-day adverse outcome, we could not establish an incremental value of hsTnT to the Hestia criteria due a very low overall rate of adverse events resulting in wide confidence intervals. Moreover, normal hsTnT levels did not exclude PE-associated adverse events.

INTRODUCTION

Current guidelines emphasize the importance of early risk stratification of patients with acute pulmonary embolism (PE) to facilitate assessment of the prognosis and guide therapeutic decision-making.[1,2] The Hestia criteria have been shown to select patients with PE at low risk of adverse events, who can be managed safely at home.[3-5] It has been suggested that by combining cardiac biomarkers with clinical risk stratification rules, the risk stratification could be further improved.[1,6-8] Specifically, patients with no Hestia criteria and normal cardiac biomarker levels might have an even lower risk of adverse events than patients with no Hestia criteria but an abnormal biomarker indicating right ventricular dysfunction or myocardial injury.[9,10] In a randomized controlled study, the additional incremental value of N-terminal pro brain natriuretic peptide (NT-proBNP) testing to the assessment of the Hestia criteria could not be established due, among others to a lower than expected number of Hestia criteria negative patients with elevated NT-proBNP.[4]

Several other biomarkers have been suggested to aid in the risk stratification for management of acute PE, e.g. elevated circulating levels of cardiac troponin (troponin I or T, by "conventional" or highly sensitive assays). Of those, low troponin T values have been associated with a high sensitivity and negative predictive value (NPV) in predicting an adverse 30-day outcome.[10] Also, it has been shown that troponin T values measured with a highly sensitive assay (hsTnT) provide superior prognostic information compared to the "conventional" fourth generation assay in normotensive patients with acute PE. In a subsequent multicentre observational study, these findings could be confirmed in 526 normotensive patients with acute PE.[10] None of the 127 patients (24.1%) with both hsTnT <14 pg/ml and simplified Pulmonary Embolism Severity Index (sPESI) of 0 points had an adverse outcome (NPV and sensitivity 100% each).[8]

Whether a combination of the Hestia criteria and hsTnT might provide an additional prognostic information in acute PE has not been investigated. We therefore set out to evaluate whether hsTnT measured on admission could provide additional prognostic information on top of the absence of any Hestia criteria for safe(r) outpatient management. Furthermore, we aimed to evaluate whether hospitalization of patients selected for outpatient treatment based on elevated hsTnT levels could have prevented adverse events.

METHODS

Design and patients

This is a post-hoc analysis of the Vesta study. The Vesta study was a multicentre, randomised, interventional study investigating whether outpatient treatment based on the Hestia criteria alone is as safe as a strategy based on the Hestia criteria combined with NT-proBNP measurement in patients with acute symptomatic PE.[4] This study included consecutive normotensive

patients with confirmed PE from two academic and 15 non-academic Dutch hospitals.[4] Patients were eligible for randomization if none of the items of the Hestia criteria were present, with the main exclusion criteria of a life expectancy less than 3 months or an expected inability to attend the required 3-month follow-up. Patients were followed for three months to assess the occurrence of recurrent venous thromboembolism (VTE), major bleeding, all-cause mortality and for 30-day adverse outcome, i.e. a composite of haemodynamic instability, intensive care unit (ICU) admission and death related to PE or major bleeding.

As part of the Vesta study, venous plasma and serum samples were obtained, processed following standard operating procedures and immediately stored at -80 °C. For the present analysis, these stored samples were used to measure concentrations of hsTnT after a single thaw. Main exclusion criterion for the current analysis was the absence of available blood samples for post-hoc hsTnT measurement, which was performed with the use of a quantitative electrochemiluminescence immunoassay (Elecsys/E170; Roche Diagnostics). The assay is specific for troponin T without relevant interferences and has an analytic range from 3 to 10,000 pg/ml. A concentration of 14 pg/ml has been identified as the 99th percentile of a healthy reference population with a coefficient of variation of less than 10%, and therefore served as the predefined threshold for an abnormal test result.

Study objective

The primary aim of this study was to compare the incidence of a composite 30-day adverse outcome in PE patients with no Hestia criteria present with a normal versus elevated hsTnT. This adverse outcome included a composite of haemodynamic instability, ICU admission and death related to either PE or major bleeding. Furthermore, we aimed to evaluate the PE-related adverse events that occurred in patients treated at home with normal versus elevated hsTnT. For this latter study aim, we only considered patients whose management was based on the Hestia criteria alone, i.e. patients who were not subjected to NT-proBNP testing in the original Vesta study.

Secondary objectives of this study were occurrence of recurrent VTE, major bleeding and all-cause mortality during the 3-month follow-up period in patients treated at home with normal versus elevated hsTnT.

Study definitions

Recurrent VTE was defined as a new intraluminal filling defect on computed tomographic pulmonary angiography (CTPA) or confirmation of a new PE at autopsy. Recurrent lower extremity DVT was defined as new non-compressibility by ultrasonography or as an increase in vein diameter under maximal compression, as measured in the abnormal venous segment, indicating an increase in thrombus diameter (≥ 4 mm).[11]

Major bleeding was defined according to the ISTH criteria and included: any bleeding resulting in death; symptomatic bleeding in a critical organ (intracranial, intra spinal, intraocular, retro-

peritoneal, intra articular and pericardial bleeding and muscle bleeding resulting in compartment syndrome) or symptomatic bleeding resulting in a decrease in the haemoglobin concentration of at least 2 g/dl or resulting in the transfusion of at least two packs of red blood cells.[12]

The cause of death among patients who died within the study period was evaluated by autopsy or based on a clinical report indicating the likely cause of death. An independent adjudication committee evaluated all relevant suspected adverse events.

Statistical analysis

Descriptive statistics tables were provided for all relevant demographic characteristics, comorbidities, risk factors for VTE, clinical findings and symptoms on admission, diagnostics procedures and biomarker measurements. Continuous variables were summarised (number, mean, standard deviation). Frequency and percentage of subjects within each category were provided for categorical data.

In order to describe differences with regard to the primary and secondary outcomes of patients with hsTnT <14 pg/ml compared to patients with hsTnT ≥14 pg/ml, Odds Ratios were provided with corresponding 95% confidence intervals (95%CI). Kaplan Meier analyses of patients stratified according to the hsTnT cut-off value of 14 pg/ml with regard to the primary outcomes were performed. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

A total of 550 patients were included in the original Vesta study, of whom 347 patients (63%) had stored blood samples for hsTnT measurement. **Table 1** summarizes the baseline characteristics of these 347 study patients.

Table 1: Baseline characteristics of study patients

	all study patients (n=347)	hsTnT <14 pg/ml (n=289)	hsTnT ≥14 pg/ml (n=58)	OR (95%CI)
Demographics				
Male, n (%)	183 (52.7%)	146 (50.5%)	37 (63.8%)	1.7 (0.96-3.1)
Female, n (%)	164 (47.3%)	143 (49.5%)	21 (36.2%)	
Age (years), mean (SD)	54.5 (15.3)	51.9 (15.6)	60.3 (13.0)	
Age >60 years, n (%)	136 (39.2%)	99 (34.3%)	37 (63.8%)	3.4 (1.9-6.1)
BMI, kg/m², mean (SD)	27.5 (4.9)	27.4 (4.8)	28.1 (5.0)	
Risk factors for VTE				
Immobilization or recent surgery, n (%)	46 (13.5%)	40 (14.1%)	6 (10.3%)	
Previous VTE, n (%)	84 (24.6%)	67 (23.6%)	17 (29.3%)	

Table 1: Baseline characteristics of study patients (continued)

	all study patients (n=347)	hsTnT <14 pg/ml (n=289)	hsTnT ≥14 pg/ml (n=58)	OR (95%CI)
Active malignancy, n (%)	23 (6.7%)	19 (6.7%)	4 (6.9%)	
Estrogen use, n (%)	54 (15.8%)	48 (16.9%)	6 (10.3%)	
Comorbidities				
Chronic heart failure, n (%)	3 (0.9%)	2 (0.7%)	1 (1.7%)	
COPD, n (%)	15 (4.4%)	12 (4.2%)	3 (5.2%)	
Clinical status and symptoms on admission				
Systolic blood pressure (mmHg), mean (SD)	138 (18.3)	137 (17.8)	140 (20.7)	
Heart rate (bpm), mean (SD)	82 (15.7)	81 (15.5)	87 (16.1)	
Oxygen saturation (%), mean (SD)	97.0 (1.9)	97.3 (1.9)	96.2 (2.2)	

Abbreviation: hsTnT, highly sensitive troponin T; OR, Odds Ratio; SD, standard deviation; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; bpm, beats per minute

Results of troponin testing

HsTnT levels were elevated in 58 of 347 patients (17%). Patients with elevated hsTnT were older than those with normal values (mean difference 10.7%; 95%CI 6.5 – 14.8%) and more male (64%) than female patients (36%; OR 1.7, 95%CI 0.96-3.1) had elevated hsTnT levels.

Primary outcome

The adverse 30-day composite outcome occurred in one of 58 patients (1.7%) with elevated hsTnT levels compared to two of 289 patients (0.70%) with normal hsTnT; associated with an OR of 2.5 (95%CI 0.22-28; **Table 2**).

The adverse 30-day composite outcome in the elevated hsTnT group consisted of an ICU admission because of respiratory insufficiency due to pneumonia in the right lower lobe which was temporarily treated with mechanical ventilation on day 2 after inclusion, whereas the adverse events in patients with normal hsTnT consisted of one ICU admission on day 12 because of respiratory insufficiency secondary to pneumonia, and one PE-related death on day 15. Of note, all three adverse events occurred in the direct discharge group not subjected to initial NT-proBNP testing.

Secondary outcome

All-cause death occurred in one patient with elevated hsTnT (1.7%) versus five patients with normal hsTnT (1.7%; OR 1.0; 95%CI 0.11-8.7; **Table 2**). The cumulative 3-month incidence of recurrent VTE was 1.7% (95%CI 0.0-9.2) in patients with elevated hsTnT versus 1.0% in the normal hsTnT group (95%CI 0.2-3.0) associated with an OR of 1.7 (95%CI 0.17-16; **Table 2**).

During the study period, major bleeding was observed in two patients with elevated hsTnT (3.4%) at baseline versus one with normal hsTnT (0.35%, OR 10.3; 95%CI 0.91-115).

Table 2: Outcomes of study patients stratified according to post-hoc assessed hsTnT level.

	all study patients (n=347)	hsTnT <14 pg/ml (n=289)	hsTnT ≥14 pg/ml (n=58)	OR	95% CI
30-day adverse outcome	N=3 (0.9%)	N=2 (0.7%)	N=1 (1.7%)	2.5	(0.22-28)
-PE-related mortality	N=1 (0.29%)	N=1 (0.3%)			
-ICU admission	N=2 (0.58%)	N=1 (0.3%)	N=1 (1.7%)		
3-month all-cause death	N=6 (1.7%)	N=5 (1.7%)	N=1 (1.7%)	1.0	(0.11-8.7)
Recurrent VTE at 3 months	N=4 (1.2%)	N=3 (1.0%)	N=1 (1.7%)	1.7	(0.17-16)
- DVT	N=2 (0.58%)	N=1 (0.3%)	N=1 (1.7%)		
- PE	N=2 (0.58%)	N=2 (0.7%)			
Major bleeding at 3 months	N=3 (0.9%)	N=1 (0.3%)	N=2 (3.4%)	10.3	(0.91-115)

Abbreviation: hsTnT, highly sensitive troponin T; OR, Odds Ratio; CI confidence interval; PE, pulmonary embolism; ICU, intensive care unit; VTE, venous thromboembolism;

DISCUSSION

In this analysis, in patients with PE treated at home based on Hestia criteria, we observed a 2.5 fold higher incidence of 30-day adverse outcome in those with elevated hs-TnT, with wide confidence intervals due to overall low rate of adverse events. Of note, only one of 58 patients in the elevated hsTnT group had an adverse outcome which consisted of a pneumonia necessitating mechanical ventilation at the ICU. These low adverse event rates were also observed in the original Vesta study for patients with abnormal NT-proBNP levels, because of which we were unable to draw definite conclusions on the incremental value of NT-proBNP testing in patients with PE and none of the Hestia criteria. We assume that the Hestia rule preselects patients with normal NT-proBNP and hsTnT levels, and thus low rates of PE-associated adverse events.

For optimal selection of haemodynamically stable patients with acute PE who qualify for outpatient management, proper and simple risk stratification is of utmost importance. Currently two different approaches have been applied for risk stratification: the sPESI, which predicts the 30-day mortality rate in hospitalized patients with acute PE and the Hestia criteria, which directly selects patients who may be treated at home.

In a recent systematic review of the literature, a higher all-cause mortality rate (3.8%) was observed in low-risk PE patients (according to the PESI, sPESI or Hestia criteria) with abnormal levels of cardiac troponin I or T compared to those with normal troponin levels (0.5%; OR 6.3,

95% CI 2.0–20). Furthermore, in this same analysis, PE patients with BNP/NT-proBNP values above the cut-off value had an increased risk of early PE-related adverse outcomes (OR 3.6; 95% CI 1.7–7.8), despite being "low-risk" according to clinical criteria. The authors concluded that the prognostic value of abnormal cardiac biomarkers appeared to be comparable to that of signs of right ventricular dysfunction on imaging.[6] These results, if validated by prospective management studies, are of importance for clinical decision making. Of note, most of the studies selected for this meta-analysis were observational and the results were retrospectively collected, i.e. a predefined algorithm to select patients for home treatment was not applied. Because of that, they may not be representative of the clinical setting where management decisions are taken based on one or sequential prognostic tests.

In our cohort, we found that patients with elevated hsTnT indeed had a higher incidence of 30-day adverse outcome, but not of all-cause mortality. Moreover, the rate of adverse events was generally low, and the very only adverse event that occurred in patients randomized to direct outpatient treatment but with elevated hsTnT levels was non-PE related (respiratory insufficiency due to pneumonia). Notably, the incidence of adverse events in patients with normal hsTnT was not zero. Hence, as for NT-proBNP in the original study, we could not establish an incremental prognostic value of hsTnT to the Hestia criteria for the purpose of selecting PE patients for outpatient treatment.

In general, the addition of biomarkers and/or the assessment of right ventricle dysfunction to clinical criteria will likely increase sensitivity of risk stratification in acute PE at cost of lower specificity, i.e. more patients would need to be hospitalized. The main question to be answered is which incidence as well as type of adverse events would be considered acceptable to consider outpatient management of PE 'safe'. Importantly, the decision to treat PE patients at home depends not only on PE-specific circumstances or the presence of comorbidities, but also on the healthcare system and the infrastructure in a given country as well as on local culture and patient preferences. Thus, international guidelines cannot mandate that patients with certain characteristics be treated at home, but only indicate what patient categories could be treated at home at a certain risk. The acceptability of that risk level is not necessarily the same in each different situation. In this light, although it has been established that cardiac biomarker measurements and assessment of right ventricular function improve risk stratification in patients with a sPESI of 0 points, our data do not appear to support the same conclusion for the Hestia criteria, which well may be the result of the strong preselection of low-risk PE patients by applying the Hestia criteria.

Strong points of this post-hoc analysis include the use of predefined and adjudicated outcomes of a large randomized controlled trial. The main limitation of this study is the low proportion of patients with elevated hsTnT levels, probably due to preselection by the Hestia criteria, which has led to limited statistical power for the performed analyses. Furthermore, the absence of hsTnT measurements in some study patients may cause selection bias, although samples were missing at random.

In conclusion, our data suggest that elevated hsTnT levels are associated with a 2,5 fold higher incidence of 30-day adverse outcome in patients with none of the Hestia criteria, although confidence intervals were wide and the rate of adverse events was overall low. While PE-associated death occurred in patients with normal hsTnT levels, adverse events in patients with elevated hsTnT levels were not PE-related. Hence, we could not establish an incremental value of hsTnT measurement on top of assessment of the Hestia criteria for selecting PE patients for outpatient treatment.

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4

Right Ventricle-to-Left Ventricle Diameter Ratio Measurement Seems to Have No Role in Low-Risk Patients with Pulmonary Embolism Treated at Home Triaged by Hestia Criteria

Stephan V. Hendriks, Frederikus A. Klok, Wendy Zondag, Paul L. den Exter, Rolf Brouwer, Michiel Eijsvogel Marco J. Grootenboers, Laura M. Faber, Roxanne Heller-Baan, Herman M.A. Hofstee, Antonio Iglesias del Sol, Lucia J.M. Kroft, Marieke J.H.A. Kruip, Albert T.A. Mairuhu, Christian F. Melissant, Henny G. Peltenburg, Marcel A. van de Ree, Erik H. Serné and Menno V. Huisman *on behalf of the Hestia/Vesta investigators*

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ABSTRACT

Background: There is a continuing debate on the relevance of right ventricular (RV) dilatation in normotensive pulmonary embolism (PE) patients as a tool to identify low-risk patients eligible for outpatient treatment. Formal assessment of RV function is not part of the Hestia clinical decision rule, which has been shown to safely select patients for home treatment.

Aim: To assess the incidence of CT-measured RV dilatation and centrally located PE in patients treated at home based on the application of the Hestia clinical decision rule, and its impact on clinical outcome.

Methods: Patient-level post-hoc analysis of two multicenter prospective outcome studies evaluating the safety of outpatient treatment for PE based on the Hestia criteria. Primary outcome was the combined 3-month incidence of recurrent VTE, major bleeding and mortality in patients with CT measured RV/LV ratio >1 versus those with RV/LV <1.0.

Results: Of 1627 consecutive patients eligible for the two studies, 752 were treated at home (46%); 225/752 (30%) had a RV/LV diameter ratio >1.0 (range 0.74-2.4). The incidence of adverse events was 3.1% in patients with an RV/LV ratio of >1.0 and 3.0% in those with an RV/LV ratio ≤1.0, for an Odds Ratio of 1.1 (95%CI0.44-2.7).

Conclusions: In this study, RV/LV ratio >1 alone as measured on CT does not add to the Hestia criteria to predict poor outcome in patients selected for outpatient treatment. This challenges the concept that CT measured RV function should always be used to guide or change management decisions in these low risk patients.

INTRODUCTION

Current guidelines emphasize the importance of early risk stratification of patients with acute pulmonary embolism (PE) to facilitate assessment of prognosis and guide therapeutic decision-making.[1-3] There is a continuous debate on the relevance of measuring right ventricular (RV) dysfunction in normotensive PE patients as a tool to identify low-risk patients eligible for home treatment. To date, three studies have demonstrated that patients with acute PE can be safely selected for outpatient treatment on a clinical basis alone, with either use of the PESI score or Hestia clinical decision rule.[4-6] In contrast, the 2019 ESC guidelines recommend objective assessment of RV dysfunction in combination with clinical risk assessment based on either the Pulmonary Embolism Severity Index (PESI) score or its simplified sPESI version, to select patients suitable for home treatment.

In a relatively small sample size of 95 patients as part of a post-hoc analysis of the Hestia study, it was shown that patients treated as outpatients based on the Hestia criteria but with (retrospectively assessed) right ventricular dysfunction had an uncomplicated clinical course.[7] However, a recent systematic review of the literature showed a different point of view demonstrating a higher all-cause mortality in low-risk PE patients with RV dysfunction than in those with a normal RV.[8]

Several methods to determine RV dysfunction on computed tomographic pulmonary angiography (CTPA) have been proposed and validated; abnormal position of the interventricular septum, backflow of contrast in the vena cava, enlargement of the pulmonary truncus and right to left ventricle volumes. According to the latest ESC guideline the right ventricle to left ventricle (LV) diameter ratio >1.0 may be the most appropriate to indicate poor prognosis on CTPA.[3-9] This measurement has also been shown to be reproducible, even for (non-radiologist) clinicians.[10]

Notably, besides RV/LV ratio, additional CT parameters such as a higher degree of embolus load have been proposed as predictors of PE severity, although these have never been evaluated in the setting of selecting patients for home treatment, and guidelines do not consider these in initial risk assessment.[11-13]

Considering the above, it remains challenging for the clinician to determine which patients may qualify for outpatient treatment. In an attempt to solve the issue on relevance of CT parameters of RV function and thrombus location for selection of candidates for home treatment, we assessed the incidence of CT-measured RV dilatation and central PE localization in patients treated at home solely selected on the application of the Hestia criteria, and their impact on clinical outcome.

METHODS

Design

This is a patient-level post-hoc analysis of the combined Hestia and Vesta studies, both multicenter prospective outcome studies evaluating the safety of outpatient treatment for PE based on the Hestia criteria.[4,5] These two studies included consecutive normotensive patients with confirmed PE from 3 academic and 11 non-academic Dutch hospitals.

The Hestia Study was a multicenter prospective cohort study in patients with acute PE who were selected to start anticoagulant treatment at home according to the Hestia criteria, which are 11 simple and readily available clinical selection criteria (**Table 1**). If none of the criteria were present, the patient was treated at home, i.e. discharged within 24 hours after diagnosis of PE. The efficacy and safety of this practice was assessed during a 3-month follow-up period.[4]

Table 1: Hestia Criteria

Is the patient hemodynamically unstable? [a]	Yes/No
Is thrombolysis or embolectomy necessary?	Yes/No
Active bleeding or high risk of bleeding? [b]	Yes/No
More than 24 hour of oxygen supply to maintain oxygen saturation > 90%?	Yes/No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes/No
Severe pain needing intravenous pain medication for more than 24 h?	Yes/No
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?	Yes/No
Does the patient have a creatinine clearance of < 30 ml/min? [c]	Yes/No
Does the patient have severe liver impairment? [d]	Yes/No
Is the patient pregnant?	Yes/No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes/No
If the answer to one of the questions is 'yes', the patient cannot be treated at home	

[a] *Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure <100mmHg with heart rate >100 beats per minute; condition requiring admission to an intensive care unit.*

[b] *Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 9 109/L), uncontrolled hypertension (systolic blood pressure > 180mm Hg or diastolic blood pressure > 110mm Hg).*

[c] *Calculated creatinine clearance according to the Cockroft-Gault formula.*

[d] *Left to the discretion of the physician.*

The Vesta study was a multicentre, randomised, interventional study investigating whether outpatient treatment based on the Hestia criteria alone is as safe as a strategy based on the Hestia criteria combined with N-terminal pro brain natriuretic peptide (NT-proBNP) measurement in patients with acute symptomatic PE.[5] Patients were eligible for randomization if none of the items of the Hestia criteria were present, with the main exclusion criteria of a life expectancy less than 3 months or an expected inability to attend the required 3-month follow-up. Patients were followed for three months to assess the occurrence of a composite outcome

of haemodynamic instability, intensive care unit (ICU) admission and death related to PE or major bleeding. In addition, occurrence of recurrent venous thromboembolism (VTE), major bleeding and all-cause mortality were monitored.

For the present analysis, all patients diagnosed with acute PE at baseline and treated at home were eligible for inclusion. The main exclusion criteria was the inability to measure the RV/LV ratio due to either the use of ventilation-perfusion scan for initial diagnosis or insufficient quality of CT images for valid post-hoc RV/LV ratio measurement. Furthermore, all patients with routinely assessed NT-proBNP as part of the intervention arm of the Vesta study were excluded irrespective of the NT-proBNP level, as they had been managed based on the outcome of the NT-proBNP.

Hypothesis

In this cohort of acute PE patients managed according to risk stratification by the Hestia criteria, we hypothesized that patients with RV dilatation and/or centrally located PE selected by the treating physician for outpatient treatment, did not have a higher incidence of PE-associated adverse outcomes than those selected for outpatient treatment with normal RV function and/or more peripheral PE localization.

Study objectives

The primary aim of this study was to assess the incidence of CT-measured RV dilatation in patients treated at home based on the application of the Hestia criteria, and its impact on clinical outcome. Additionally, we set out to assess the prevalence of centrally located PE and its association with clinical outcome.

The primary outcomes were 1) the proportion of patients treated at home with a RV/LV ratio >1.0, and 2) the combined 3-month incidence of recurrent VTE, major bleeding and mortality ('adverse events') in patients with versus those without RV dilatation. The secondary outcomes of this study were the combined 3-month adverse events in 1) patients with versus those without severe RV dilatation and 2) patients with centrally located PE versus those with peripheral PE.

Study definitions

Home treatment was defined as discharge from the hospital within 24 hours after diagnosis. The definition of acute PE was an intraluminal filling defect of the subsegmental or more proximal pulmonary arteries confirmed by computed tomography pulmonary angiography. Right ventricular dilatation was defined as a RV/LV diameter ratio greater than 1.0 with ventricular diameters measured in the transverse plane at the widest points between the inner surface of the free wall and the surface of the interventricular septum.[14] Severe right ventricular dilatation was defined as a RV/LV ratio greater than 1.5.[7,15] Centrally located PE was defined as a clot involving the main pulmonary artery, the left or right pulmonary arteries or the interlobar

arteries. Clot location was scored by the most proximal embolus. Peripheral located PE was defined as a clot involving the segmental or subsegmental arteries.

Recurrent VTE was defined as a new intraluminal filling defect on CTPA or confirmation of a new PE at autopsy. Recurrent lower extremity DVT was defined as new non-compressibility in a previously affected segment by ultrasonography or as an increase in vein diameter under maximal compression, as measured in the abnormal venous segment, indicating an increase in thrombus diameter (≥ 4 mm).[16]

Major bleeding was defined in accordance to the ISTH criteria.[17] The cause of death among patients who died within the study period was evaluated by autopsy or based on a clinical report indicating the most likely cause of death. An independent adjudication committee evaluated relevant suspected adverse events as part of the original Hestia and Vesta studies.

Statistical analysis

Descriptive statistics were provided for all relevant demographic characteristics, comorbidities, risk factors for VTE, clinical findings and symptoms on admission. Continuous variables were summarised (number, mean, standard deviation). Frequency and percentage of subjects within each category were provided for categorical data.

In order to describe differences with regard to the primary and secondary outcomes, odds ratios (OR) were provided with corresponding 95% confidence intervals (95%CI). The proportion of patients treated at home with an RV/LV ratio >1.0 was provided as frequency with corresponding 95%CI. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

Of 1627 consecutive patients eligible for the Hestia and Vesta studies, RV/LV ratio were available for 1474 patients, of whom 752 were treated at home (51%). The baseline characteristics of these 752 study patients are summarized in **Table 2**. Their mean age was 54 years (standard deviation (SD) 15), 44% was female and 9% had active malignancy at time of diagnosis. In this cohort 4.8% suffered from chronic obstructive pulmonary disease, while heart failure was present in 0.8% of all patients.

Primary outcome

Of the 752 patients diagnosed with acute PE and treated at home, 225 (30%) had a RV/LV diameter ratio >1.0 (range 0.74-2.4). A larger proportion of male than female patients treated at home was diagnosed with RV dilatation (OR 1.9, 95%CI 1.5-2.5). The mean age was also higher in patients treated at home who had RV dilatation, and the proportion of patients aged >60

years was higher (OR 2.6, 95%CI 1.9-3.6). At baseline no relevant differences were found in vital parameters in patients with versus those without RV dilatation.

Table 2: Baseline characteristics of PE patients treated at home

	RV/LV ratio > 1.0 (n=224)	RV/LV ratio ≤ 1.0 (n=527)
Demographics		
Male, n (%)	161 (71.6)	263 (49.9)
Female, n (%)	64 (28.4)	264 (50.1)
Age (years), mean (SD)	60.4 (13.2)	51.3 (14.8)
Age >60 years, n (%)	117 (52)	154 (29.2)
Length (cm), mean (SD)	178 (10)	175 (13)
Weight (kg), mean (SD)	88 (18)	85 (18)
BMI, kg/m², mean (SD)	27.6 (5.0)	27.1 (5.0)
Risk factors for VTE		
Immobilization or recent surgery, n (%)	21 (9.3%)	69 (13.1%)
Previous VTE, n (%)	68 (30.2%)	126 (23.9%)
Active malignancy, n (%)	26 (11.6%)	40 (7.6%)
Estrogen use, n (%)	13 (5.8%)	105 (19.9%)
Comorbidities		
Chronic heart failure, n (%)	4 (1.8%)	2 (0.4%)
COPD, n (%)	7 (3.1%)	29 (5,5%)
Clinical status and symptoms on admission		
Systolic blood pressure (mmHg), mean (SD)	140 (18)	139 (19)
Heart rate (bpm), mean (SD)	84 (17)	84 (15)
Oxygen saturation (%), mean (SD)	97 (2)	97 (2)

Abbreviation: PE, pulmonary embolism; RV, right ventricular; LV, left ventricular; OR, Odds ratio; SD, standard deviation; BMI, body mass index; VTE, venous thromboembolism; COPD, chronic obstructive lung disease;

The incidence of adverse events was seven of 225 patients (3.1%) with a RV/LV diameter ratio >1.0 treated at home compared to 15 of 527 (3.0%) patients with a normal RV/LV ratio treated at home, for an Odds Ratio of 1.1 (95% CI 0.44-2.7; **Table 3**). In the group treated at home with a RV/LV diameter ratio >1.0 the following adverse events were observed: four out of five patients died during the 3-month follow up in the presence of metastasized carcinoma with all deaths occurring beyond the first 14 days after diagnosis (**Figure 1**); one major bleeding occurred on day 14, consisting of a large hematoma in the abdominal muscle sheath with a drop in hemoglobin of 2,5 mmol/l; and lastly, one event was adjudicated as recurrent VTE, consisting of an episode of chest pain on day 8 in the presence of unstable INR levels, diagnosed clinically without objective testing.

Table 3 Adverse outcomes in patients with acute pulmonary embolism treated out-of-hospital stratified by RV/LV ratio

	RV/LV ratio > 1.0 (n=224)	RV/LV ratio ≤ 1.0 (n=527)	OR	95% CI
1. All-cause mortality within 3 months	5 (2.2%)	5 (0.9%)	2.4	(0.7-8.3)
2. Major bleeding within 3 months	1 (0.45%)	3 (0.6%)	0.78	(0.1-7.6)
3. Recurrent VTE within 3 months	1 (0.45%)	7 (1.3%)	0.33	(0.0-2.7)
4. Total adverse events	7 (3.1%)	15 (3.0%)	1.1	(0.4 -2.7)

Abbreviation: RV, right ventricular; LV, left ventricular; OR, Odds ratio; VTE, venous thromboembolism;

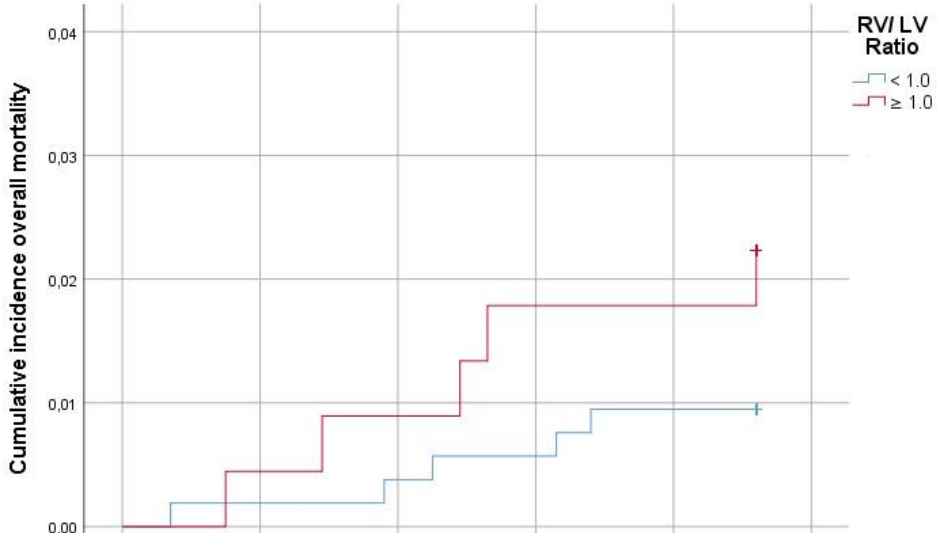

Figure 1 Cumulative incidence of overall mortality in time in patients with acute pulmonary embolism treated out-of-hospital stratified by RV/LV ratio

Secondary outcome

RV dilatation with a RV/LV diameter ratio >1.5, was present in 19 patients treated at home (2.5%). No adverse events occurred in these patients. The location of the PE involved a central pulmonary artery in 250 patients (34%). The remaining patients had segmental (n=268, 50%) or subsegmental (n=115, 16%) PE. The incidence of adverse events was 4.1% in patients with central PE and 2.3% in those with peripheral PE on CTPA (OR 1.8; 95%CI 0.75 -4.3; **Table 4**).

Table 4: Adverse outcomes in patients with acute pulmonary embolism treated out-of-hospital stratified by embolic burden

	Central PE (n=246)	Peripheral PE (n=477)	OR	95% CI
1. All-cause mortality within 3 months	3 (1.2%)	6 (1.2%)	1.0	(0.3-4.2)
2. Major bleeding within 3 months	3 (1.2%)	1 (0.2%)	2.6	(0.3-0.8)
3. Recurrent VTE within 3 months	4 (1.6%)	4 (0.8%)	1.3	(0.7-2.6)
4. Total adverse events	10 (4.1%)	11 (2.3%)	1.8	(0.8-4.3)

Abbreviation: RV, right ventricular; LV, left ventricular; OR, Odds ratio; VTE, venous thromboembolism; PE, pulmonary embolism

DISCUSSION

In this study in patients with acute PE treated at home based on absence of all Hestia criteria, our most important finding was that there was no difference in the incidence of adverse events in those with RV/LV diameter ratio >1 on CTPA compared to those without a RV/LV diameter ratio <1. Importantly, and in line with our earlier observations, RV/LV ratio >1 was present in 30% of patients treated at home.[7] Overall, the number of adverse events in patients treated at home were low, independent of RV/LV ratio and independent of the location of the PE, as was observed in the original Hestia and Vesta studies.[4,5]

In the 2019 ESC guideline, the selection of low-risk PE patients, who qualify for home treatment, is based on the PESI score or its simplified version (sPESI) combined with the mandatory absence of RV dysfunction on transthoracic echocardiography or CTPA.[3] Of the latter, the presence of RV enlargement, i.e. RV/LV ratios of > 0.9 or >1.0 measured in the transverse or four-chamber view, was used as indicator of RV dysfunction. If no other reason for hospitalization is present, patients are eligible for early discharge or home treatment. This recommendation is largely based on a recent systematic review of the literature, in which a higher early all-cause mortality was shown in low risk PE patients with abnormal cardiac biomarkers levels or signs of RV dysfunction, on CTPA or transthoracic echocardiography, compared to those with normal biomarker levels or with normal RV function.[8] These results indeed do imply that assessment of RV dysfunction by imaging methods should be considered, even in the presence of a low PESI or a negative sPESI score. However and importantly, the vast majority of studies included in this meta-analysis were observational studies with results collected post-hoc or retrospectively. No management decisions were made based on the (s)PESI. Moreover, all but one study were studies in hospitalised patients with unclear selection criteria. This implies that hospitalization in these patients was unable to prevent the mortality occurring more frequently in those with elevated RV/LV ratio. Finally, the authors could not indicate which percentage of patients had fatal PE among all-cause mortality, leaving it unclear whether there was a true association between RV dysfunction and PE-related mortality in low-risk patients.

In the current analysis, using the Hestia criteria as clinical decision rule for the selection of home treatment, we did not observe a significantly higher all-cause mortality or incidence of adverse events in patients with a RV/LV diameter ratio >1.0 on CTPA. Notably, four out of five patients with signs of RV dilatation who died during the 3-month follow up had metastasized carcinoma and all deaths occurred beyond the first 14 days after diagnosis (**Figure 1**). It is unlikely that these adverse events likely could have been prevented by initial hospital admission, given a mean hospital duration of 3.9 days in the inpatient arm of OTPE study. [6]

In our view and based on the published literature, several risk assessment methods can be used to select for home treatment: 1) the strategy recommend by the ESC, 2) the Hestia criteria, 3) the PESI score and 4) the combination of a clinical decision rule, with the majority of the exclusion criteria correspond to the items of the Hestia criteria, and the mandatory absence of signs of RV dysfunction on echocardiography or CTPA as applied in the HOT-PE trial.[3,4,6,18,19] Because all have been studied in prospective studies and shown safe, and comparative studies are lacking, none of these four strategies can be considered superior. However, efficiency and medical health care costs should also be considered when selecting the optimal approach for selecting outpatient treatment candidates. It is therefore of relevance that our analyses show that RV assessment would have excluded a large proportion of 30% of our cohort from outpatient treatment without affecting their prognosis, making the Hestia model not only less efficient but also more cost-consuming.

The results of the HOME-PE study (Clinicaltrials.gov identifier: NCT02811237), comparing safety of outpatient management in normotensive PE patients stratified by the HESTIA rule or the simplified PESI score without mandatory assessment of RV dysfunction, will shed more light on this issue.

Strengths of this analysis include the use of predefined and adjudicated outcomes of both large prospective studies and also the completeness of follow-up. The main limitation of this study is its post-hoc design. Further, of 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.[4] It is likely that this item preselects the patients at low risk of adverse events, even when signs of RV dysfunction are present. Furthermore, likely due to this preselection by the Hestia criteria, the rate of PE-associated adverse events was low leading to wide confidence intervals of our outcomes.

In conclusion, in this study, neither RV/LV ratio >1.0 nor RV/LV ratio >1.5 on CTPA and centrally located PE were associated with less favorable outcome in patients selected for outpatient treatment by the Hestia criteria, challenging the concept that RV function assessment should be used routinely to guide management in all low risk PE patients.

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5

Reasons for Hospitalization of Patients with Acute Pulmonary Embolism Based on the Hestia Decision Rule

Stephan V. Hendriks, Paul L. den Exter, Wendy Zondag, Rolf Brouwer, Michiel Eijsvogel, Marco J. Grootenboers, Laura M. Faber, Roxanne Heller-Baan, Herman M.A. Hofstee, Antonio Iglesias del Sol, Marieke J.H.A. Kruip, Albert T.A. Mairuhu, Christian F. Melissant, Henny G. Peltenburg, Marcel A. van de Ree, Erik H. Serné, Menno V. Huisman and Frederikus A. Klok, *on behalf of the Hestia/Vesta investigators*

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ABSTRACT

Background: The Hestia criteria can be used to select pulmonary embolism (PE) patients for outpatient treatment. The subjective Hestia criterion "medical/social reason for admission" allows the treating physician to consider any patient-specific circumstances in the final management decision. It is unknown how often and why this criterion is scored.

Method: This is a patient-level post-hoc analysis of the combined Hestia and Vesta studies. The main outcomes were the frequency of all scored Hestia items in hospitalized patients and the explicit reason for scoring the subjective criterion. Hemodynamic parameters and CT-assessed RV/LV ratio of those only awarded with the subjective criterion were compared with patients treated at home.

Results: From the 1166 patients screened, data were available for all 600 who were hospitalized. Most were hospitalized to receive oxygen therapy (45%); 227 (38%) were only awarded with the subjective criterion, of whom 51 because of 'intermediate to intermediate-high risk PE'. Compared to patients with intermediate risk PE (RV/LV ratio >1.0) treated at home (179/566, 32%), hospitalized patients with only the subjective criterion had a higher mean RV/LV ratio (mean difference +0.30, 95%CI 0.19-0.41) and a higher heart rate (+18/min, 95%CI 10-25). No relevant differences were observed for other hemodynamic parameters.

Conclusion: The most frequent reason for hospital admission was oxygen therapy. In the decision to award the subjective criterion as sole argument for admission, the severity of the RV overload and resulting hemodynamic response of the patient was taken into account rather than just abnormal RV/LV ratio.

INTRODUCTION

The majority of patients diagnosed with acute pulmonary embolism (PE) are hospitalized during the initiation of anticoagulant treatment.[1-7] The main benefit of hospitalization of patients with acute PE is close monitoring for early detection and treatment of adverse events. It may however also expose patients to a higher risk of iatrogenic complications, especially in the elderly, and is associated with higher healthcare costs than home treatment.

According to the 2019 ESC guidelines, all high or intermediate risk PE patients are advised to start initial treatment in hospital.[8] Intermediate risk is defined as normotensive PE patients with either a PESI class III–V, a sPESI ≥1 or those with signs of right ventricular (RV) dysfunction. Notably and in contrast, the Hestia rule is the most widely validated clinical decision tool in the literature for selecting PE patients eligible for home treatment.[6] These pragmatic criteria contain among others objective parameters of risk of mortality such as shock or hypoxaemia, but not explicit parameters of RV function (**Table 1**). Of all 11 score items, one however 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, including RV function.[9] It is unknown how often and why this subjective criterion of the Hestia criteria is scored and used as the main argument to hospitalize the patient.

Table 1: Hestia Criteria

Is the patient hemodynamically unstable? [a]	Yes/No
Is thrombolysis or embolectomy necessary?	Yes/No
Active bleeding or high risk of bleeding? [b]	Yes/No
More than 24h of oxygen supply to maintain oxygen saturation > 90%?	Yes/No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes/No
Severe pain needing intravenous pain medication for more than 24h?	Yes/No
Medical or social reason for treatment in the hospital for more than 24h?	Yes/No
Does the patient have a creatinine clearance of < 30 ml/min? [c]	Yes/No
Does the patient have severe liver impairment? [d]	Yes/No
Is the patient pregnant?	Yes/No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes/No
If the answer to one of the questions is 'yes', the patient cannot be treated at home in the Hestia study	

a) Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure <100mmHg with heart rate >100 beats per minute; condition requiring admission to an intensive care unit.

b) Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count <75* 10^9/L), uncontrolled hypertension (systolic blood pressure > 180mm Hg or diastolic blood pressure > 110mm Hg).

c) Calculated creatinine clearance according to the Cockcroft-Gault formula.

d) Left to the discretion of the physician.

We therefore aimed to evaluate reasons for hospitalization according to the Hestia criteria. We aimed specifically to explore the reasons for the application of the subjective Hestia criterion "medical/social reason for admission", and additionally set out to evaluate whether assessment of PE severity is relevant in awarding the subjective Hestia criterion as sole argument for hospitalization in daily clinical practice in the Netherlands.

METHODS

Design

This is a patient-level post-hoc analysis of the combined Hestia and Vesta studies.[9,10] The Hestia Study was a multicenter prospective cohort study aimed to evaluate the efficacy and safety of outpatient treatment in PE patients in the absence of all Hestia criteria (**Table 1**). Patients were selected to start anticoagulant treatment at home (discharge within 24 hours after diagnosis) if none of the Hestia criteria were present. The remainder of screened patients was hospitalized.

The Vesta study was a multicentre, randomised, interventional study investigating whether outpatient treatment based on the Hestia criteria alone is as safe as a strategy based on the Hestia criteria combined with N-terminal pro brain natriuretic peptide (NT-proBNP) measurement in patients with acute symptomatic PE.[10] Patients were eligible for randomization if none of the items of the Hestia criteria were present. Patients were hospitalized in the presence of at least one Hestia criterion or an abnormal NT-proBNP test (if randomized to the NT-proBNP arm).

For the present analysis, all patients screened for either of the studies hospitalized because of the presence of one or more Hestia criteria were included. Patients randomized to the intervention arm of the Vesta study were excluded because cardiac function was routinely assessed at baseline. Further exclusion criteria were the inability to measure the right ventricular to left ventricular diameter ratio (RV/LV ratio) on CT images post-hoc due to 1) the use of ventilation-perfusion scan for the initial diagnosis or 2) insufficient quality of CT images for valid assessment.

Study objectives and outcomes

The primary aims of this study were to evaluate reasons for hospitalization and specifically, the reasons for the application of the subjective Hestia criterion "medical/social reason for admission". We additionally aimed to evaluate whether PE severity, i.e. RV/LV ratio, centrally located PE and/or hemodynamic status of the patient, were relevant in awarding this subjective Hestia criterion. Our hypothesis was that the hemodynamic impact of the PE is intrinsically weighted in the decision to award the subjective Hestia criterion and treat the patient at home or in hospital. We therefore expected a higher prevalence of RV overload, more severe RV overload, higher prevalence of centrally located PE and less favorable hemodynamic profile (e.g. higher

heart rate and lower blood pressure) in patients admitted solely because of the subjective Hestia criterion than in patients discharged within 24 hours after diagnosis.

The primary outcomes of this analysis were the frequency of all scored Hestia items in hospitalized patients, and the explicit reason for scoring the subjective Hestia criterion as noted in the patient chart. Our secondary outcomes were the proportion of 1) post-hoc assessed RV/LV ratio >1.0 and 2) centrally located PE in patients admitted to the hospital solely because of the subjective Hestia criterion and in those treated at home. Also, we evaluated the mean RV/LV ratio and clinical hemodynamic parameters, e.g. blood pressure and heart rate, in patients with RV/LV ratio >1.0 admitted because of the subjective Hestia criterion awarded due to 'intermediate or intermediate-high risk PE' versus those with RV/LV ratio >1.0 treated at home.

Study definitions

The definition of acute PE was an intraluminal filling defect of the subsegmental or more proximal pulmonary arteries confirmed by computed tomographic pulmonary angiography.[11] RV/LV ratio was measured in the transverse plane at the widest points between the inner surface of the free wall and the surface of the interventricular septum.[12,13] Centrally located pulmonary emboli were defined as clots involving the pulmonary truncus, right or left main pulmonary or lobar arteries.

Reasons for awarding the subjective Hestia criterion 'social or medical reason for admission' were scored as noted in the patient chart and classified in the following categories: concomitant infection, malignancy related admission, concomitant other acute condition (e.g. electrolyte disorders), intermediate to intermediate-high risk PE (including syncope as presenting symptom and/or cardiac arrhythmias), outpatient treatment not feasible because of comorbidities or social reasons, need for non-intravenous pain medication, contrast allergy, or other. For example, concomitant infection was scored if the patient was treated with intravenous antibiotics because of a proven or suspected infection, 'Outpatient treatment not feasible because of comorbidities or social reasons' was scored when the patient needed treatment for acute delirium and 'malignancy related admission' was for example noted if duration of admission was extended for administration of chemotherapy. Importantly, intermediate to intermediate-high risk PE was scored when extensiveness of clot burden, severity of RV overload and/or the presence of abnormal cardiac biomarkers was explicitly noted as reason for admission in the patient chart.

For assessment of the hemodynamic profile of the patients, we extracted the first registered measurement of blood pressure, heart rate and oxygen saturation of the presentation that lead to the PE diagnosis from the electronic patient charts.

Statistical analysis

Descriptive statistics were provided for all relevant demographic characteristics, comorbidities, risk factors for VTE, clinical findings and symptoms on admission. Categorical data are presented as percentages and continuous variables as means ± standard deviation (SD).

For the primary outcome frequencies and percentages for every reason for scoring the subjective Hestia were provided. For the secondary outcomes, the proportion of patients with a RV/LV ratio >1.0 and with embolus localization in the central arteries in those admitted because of the subjective Hestia criterion and those treated at home were compared by crude odds ratios with corresponding 95% confidence intervals (95%CI). In the same two groups but limited to those patients with RV/LV ratio >1.0 and when admitted because of the subjective Hestia criterion limited to those with signs of 'intermediate to intermediate-high risk PE', we calculated the absolute difference with corresponding 95%CI for the mean RV/LV ratio and for relevant hemodynamic parameters. Lastly, frequencies and percentages were provided for all scored Hestia criteria in hospitalized patients. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

Of 1166 consecutive PE patients eligible for either of the two studies without routinely assessed cardiac function, complete data were available for all 600 initially hospitalized patients. The remaining 566 patients were treated initially at home. **Table 2** summarizes the relevant baseline characteristics of the study patients. Their mean age was 64 years (SD 16), 17% had active malignancy, 4.8% had a history of heart failure and 8.5% suffered from chronic obstructive pulmonary disease. Centrally located PE was present in 57% of the admitted PE patients, while 55% had RV/LV ratio >1.0.

Table 2: Baseline characteristics of hospitalized patients with acute PE

	Total N=600
Age, mean (SD)	64 (16)
Male sex, no (%)	309 (50)
Weight in kg, mean (SD)	85 (19)
Body Mass Index, mean (SD)	27.9 (5.6)
Comorbidities	
COPD (%)	51 (8.5)
Heart failure (%)	29 (4.8)
VTE Risk factors	
Previous VTE — no. (%)	166 (27)

Table 2: Baseline characteristics of hospitalized patients with acute PE (continued)

	Total N=600
DVT	65 (11)
PE +/- DVT	96 (16)
Estrogen Use (%)	30 (5.0)
Active malignancy no. (%)	99 (17)
Immobilisation no. (%)	121 (20)
Clinical symptoms	
Systolic blood pressure in mmHg (mean, SD)	135 (45)
Proportion SBP < 100 mmHg (%)	36 (6.0)
Heart rate (mean, SD)	93 (22)
Proportion Heart rate > 110/min (%)	128 (21)
Median time from symptom onset (mean, SD)	6.5 (14)
Admission details	
Mean time of admission in days (SD)	6.5 (14)
Central located PE* (%)	344 (57)
RV/LV ratio >1 (%)	329 (55)

Abbreviations: PE, pulmonary embolism; SD, standard deviation; COPD, chronic obstructive pulmonary embolism; VTE, venous thromboembolism; DVT, deep venous thrombosis; SBP, systolic blood pressure; RV, right ventricle; LV, left ventricle
*Central located PE: clots involving the following arteries: the pulmonary truncus, right or left main pulmonary or lobar arteries

Primary outcome

The overall most frequent reason for admission according to the Hestia criteria was the need for oxygen supply (45%). Sixty out of six-hundred (10%) of the admitted patients were hemodynamically instable (i.e. high-risk PE), of whom 26 received reperfusion therapy. The need for intravenous pain medication was present in 6.3% whereas 4.7% had a high bleeding risk or were bleeding actively. Less frequently observed reasons for hospital admission were renal insufficiency (0.50%), severe liver impairment (0.16%), pregnancy (0.50%) and a history of heparin induced thrombocytopenia (0.33%). **Table 3** summarizes the number and percentages of the individual Hestia criteria.

Of all 600 study patients, 227 (38%; **Table 3**) were admitted solely because the subjective Hestia criterion was awarded. Of those, the criterion was awarded because of 'intermediate or intermediate-high risk PE' in 51 patients (8.5% of total population; **Table 4**). Other reasons for awarding the subjective Hestia criterion as explicitly noted in the chart were concomitant infection (6.5% of total population) and the need for inpatient treatment due to extensive comorbidities or social reasons (13% of total population).

Secondary outcome

The proportion of right ventricular dysfunction (RV/LV ratio >1.0) in patients only awarded with the subjective Hestia criterion because of 'intermediate to intermediate-risk PE was 57%

(29/51) versus 32% (179/565) in those without any Hestia criteria who were treated at home (OR 2.8, 95%CI 1.6-5.1). Centrally located PE was found in 73% (37/51) compared to 32% (176/546) in those treated at home (OR 5.6, 95%CI 2.9-11).

Table 3: Reasons for hospitalization according to the Hestia criteria (N=600)

Reasons for hospital admission	Frequency	Proportion
1. Hemodynamically unstable	60	10%
2. Need for thrombolysis of embolectomy	26	4.3%
3. Active bleeding or high bleeding risk	28	4.7%
4. > 24 hours oxygen supply	272	45%
5. Need for intravenous pain medication > 24 hours	38	6.3%
6. Subjective Hestia criterion: medical or social reasons	227	38%
7. Renal insufficiency (< 30 ml/min)	3	0.5%
8. Severe liver impairment	1	0.16%
9. Pregnancy	3	0.5%
10. Heparin induced thrombocytopenia	2	0.33%

Abbreviations: hr, Hour

Table 4: Reasons for awarding the subjective Hestia criterion 'social or medical reason for admission'

Reasons for hospital admission	Frequency n=227	Proportion 100 %
1. Concomitant infection	39	17%
2. Malignancy	9	4.0%
3. Concomitant acute condition, e.g. electrolyte disorders	32	14%
4. Intermediate to intermediate-high risk PE	51	22%
5. Outpatient treatment not feasible because of comorbidities or social reasons	76	34%
6. Need for pain medication (not i.v.)	13	5.7%
7. Contrast allergy	4	1.8%
8. Other	3	1.3%

Abbreviations: PE. Pulmonary embolism; i.v., intravenously

Of all patients with signs of RV dysfunction, the mean RV/LV ratio in patients admitted due to the subjective Hestia criterion because of `intermediate to intermediate-high risk PE' was 1.5 (SD 0.52) versus 1.2 (SD 0.21) in those treated at home, for a mean difference of +0.30 (95% CI 0.19-0.41). Also, a notable higher mean heart rate was observed in patients with RV/LV ratio >1.0 admitted due to the subjective Hestia criteria because of `intermediate to intermediate-high risk PE' than those treated at home with RV/LV ratio >1.0: 103/minute versus 85/minute, with a mean difference of +18 (95% CI 10-25). No relevant differences were observed for other hemodynamic parameters (**Table 5**).

Table 5: Differences in hemodynamic parameters in patients awarded with only the subjective criterion because of intermediate to intermediate-high risk PE and those threated at home with RV/LV ratio >1.0.

Clinical findings	Only subjective criterion because of intermediate-risk PE n=29	Treated at home with RV/LV ratio >1.0 n=179	Mean difference (95% CI)
Mean RV/LV ratio (SD)	1.50 (0.52)	1.20 (0.22)	0.3 (0.2-0.4)
Heart rate (SD)	103 (21)	86 (19)	18 (10-25)
Systolic blood pressure (SD)	133 (20)	140 (19)	-7.0 (-14 to 0.7)
Diastolic blood pressure (SD)	83 (15)	85 (14)	-1.6 (-7.4 to 4.2)
Oxygen saturation (SD)	95 (7.5)	97 (2.0)	-2.0 (-3.3 to -0.6)

Abbreviations: RV: right ventricular; CI: confidence interval; SD: standard deviation, LV: left ventricular

DISCUSSION

In this study, the overall most frequent reason for hospital admission according to the Hestia criteria was the need for oxygen supply (45%), while 10% of all PE patients had high-risk PE. Interestingly, a large group of 38% was admitted solely based on the subjective Hestia criterion. In the further exploration of the reason for awarding PE patients solely with the subjective Hestia criterion, 22% (8.5% of the overall population) were judged to have too severe PE to consider home treatment even despite the fact that by definition they were hemodynamically stable and did not require oxygen therapy. The main reasons for in hospital treatment of these patients awarded with only the subjective Hestia criterion however were concomitant infection and the need for inpatient treatment due to extensive comorbidities or social reasons requiring hospitalization.

The majority of patients with acute PE are treated in hospital.[1-7] Notably, over the last decades, due to the increased diagnostic sensitivity and frequency of computed tomographic pulmonary angiography testing, the incidence of PE and hospitalization rates have increased.[14-16] Partly because of this, overall outcomes for hospitalized PE patients have improved, with a decrease in average hospital admission from 8 to 4 days and a decreased inpatient mortality from 7.1% to 3.2% even despite an increasing age and prevalence of comorbidities in hospitalized patients with PE.[14-17] The threshold for treating patients at home has been lowered after the introduction of DOACs, which are more safe than conventional treatment with vitamin-k antagonists and have practical advantages.[18] Consequently, patient characteristics of inpatients with PE will very likely continue to change over the next years, as patients are not required to start with parenteral anticoagulants in hospital. As a proportion of low-risk PE patients will be discharged early or even treated at home, the population that requires hospitalisation will likely have more severe PE and/or comorbidities than those admitted in the past years, and thus is at higher risk of adverse events. This has important consequences for daily clinical practice, i.e.

health care utilization for the individual patient, and therefore is highly relevant for guideline and policy makers.

It remains challenging to select patients for initial in-hospital treatment or treatment at home. According to the 2019 ESC guidelines, hospitalization is recommended for all patients with intermediate risk PE.[8] In the Hestia and Vesta studies, RV function evaluation (which is critical to the risk stratification as recommended by the ESC) was not part of standard baseline assessment. As a consequence, 32% of all patients treated at home had a RV/LV diameter ratio >1.0, without a higher incidence of adverse outcome.[19] Our current study provides important insight in the ongoing debate on the relevance of RV dilatation in normotensive PE patients: we found relevant differences between patients with RV overload that were treated at home or were hospitalized. Those latter patients had a considerably higher RV/LV ratio as well as (and consequently) a higher heart rate. 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. Furthermore, and of interest, we also observed a larger proportion of patients with centrally located PE in hospitalized patients than those treated at home. Thrombus location is not part of standard risk assessment according to either the Hestia criteria or the 2019 ESC guidelines, whereas for the clinician, it seems to be important in clinical decision making when selecting the initial therapy.

Strengths of this analysis include the novelty and completeness of our data and the use of data of two large high-quality prospective studies. All baseline characteristics, vital parameters and Hestia criteria were collected prospectively. The main limitation of this study is its post-hoc design. Therefore, reasons for scoring the subjective Hestia criterion were collected retrospectively. Also, we could not adjust the hemodynamic parameters for initial fluid resuscitation or oxygen therapy.

In conclusion, after diagnosing PE the most frequent reason for hospital admission was oxygen therapy. The subjective Hestia criterion is used in 38% as sole reason to hospitalize patients and mostly involves patients with comorbidities or social circumstances precluding immediate discharge, or patients with concomitant infections. Based on our observations, management decisions were made based on the severity of RV overload and resulting hemodynamic profile of the patients rather than solely on assessment of the RV/LV ratio. This observation provides an explanation for the good prognosis of patients with dilated RV selected to be treated at home.

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6

Current practice patterns of outpatient management of acute pulmonary embolism: a post-hoc analysis of the YEARS study

Stephan V. Hendriks, Roisin Bavalia, Thomas van Bemmel, Ingrid M. Bistervels Michiel Eijsvogel, Laura M. Faber, Jaap Fogteloo, Herman M.A. Hofstee, Tom van der Hulle, Antonio Iglesias del Sol, Marieke J.H.A. Kruip, Albert T.A. Mairuhu, Saskia Middeldorp, Mathilde Nijkeuter, Menno V. Huisman and Frederikus A. Klok, *for the YEARS investigators*

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ABSTRACT

Background: Studies have shown the safety of home treatment of patients with pulmonary embolism (PE) at low risk of adverse events. Management studies focusing on home treatment have suggested that 30% to 55% of acute PE patients could be treated at home, based on the HESTIA criteria, but data from day-to-day clinical practice are largely unavailable.

Aim: To determine current practice patterns of home treatment of acute PE in the Netherlands.

Method: We performed a post-hoc analysis of the YEARS study. The main outcomes were the proportion of patients who were discharged <24 hours and reasons for admission if treated in hospital. Further, we compared the 3-month incidence of PE-related unscheduled readmissions between patients treated at home and in hospital.

Results: Of the 404 outpatients with PE included in this post-hoc analysis of the YEARS study, 184 (46%) were treated at home. The median duration of admission of the hospitalized patients was 3.0 days. The rate of PE-related readmissions of patients treated at home was 9.7% versus 8.6% for hospitalized patients (crude hazard ratio 1.1 (95%CI 0.57-2.1)). The 3-month incidence of any adverse event was 3.8% in those treated at home (2 recurrent VTE, 3 major bleedings and two deaths) compared to 10% in the hospitalized patients (3 recurrent VTE, 6 major bleedings and fourteen deaths).

Conclusions: In the YEARS study, 46% of patients with PE was treated at home with low incidence of adverse events. PE-related readmission rates were not different between patients treated at home or in hospital.

INTRODUCTION

Over the last decade, there has been a trend towards treating patients with pulmonary embolism (PE) at low-risk of early adverse events at home. The safety and feasibility of home treatment in selected patients with PE has already been shown in several large trials, although the optimal method for selecting relevant patients is still debated. [1-10] The severity of the PE and risk of adverse outcomes largely determine clinical decision making with regard to initial home treatment. Other factors such as locoregional cultural and patient preferences, the (financing of the) healthcare system and corresponding infrastructure also play a role. These latter greatly differ between countries, as was recently demonstrated in a post-hoc analysis of the Hokusai VTE study: the vast majority of Canadian patients was treated at home in contrast to only a quarter of the patients from the United States. [11] Same differences were observed between countries in Europe, as more than half of all patients were treated at home in Germany and the United Kingdom, whereas the majority of patients in Spain or France were initially hospitalized.

It has been suggested that as much as 30% to 55% of patients with acute PE could be selected for home treatment.[10,12,13] These numbers were found in prospective outcome studies focusing on home treatment, but detailed data from day-to-day clinical practice is currently largely unavailable. We therefore aimed to evaluate current practice patterns and outcome of home treatment of patients with confirmed PE in Dutch Hospitals.

METHODS

Design

The current study was a post-hoc analysis of the YEARS study. The YEARS study was a prospective, multicenter, diagnostic management study conducted in 12 university or community hospitals in the Netherlands between October 2013 and July 2015 in patients with suspected acute PE. The YEARS study aimed to validated the diagnostic YEARS algorithm, consisting of three Wells criteria (clinical signs of deep vein thrombosis, haemoptysis, and assessment whether PE is the most likely diagnosis) with simultaneous assessment of the D-dimer concentrations. [14] According to the algorithm, PE is excluded in patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL. Patients were eligible for inclusion if they were aged 18 years or older, with the main exclusion criteria of initiated therapeutic doses of anticoagulants 24 hours or more before eligibility assessment. Furthermore, a life expectancy less than 3 months, an expected inability to achieve the required 3-month follow-up, pregnancy and allergy to intravenous contrast agent were exclusion criteria. Patients were followed for three months to assess the occurrence of symptomatic venous thromboembolism (VTE).

For the present analysis, all outpatients who were diagnosed with acute PE at baseline were eligible for inclusion. Eleven of 12 hospitals were able to provide additional data. In the participating hospitals, decision for hospitalization or home treatment was mainly based on the Hestia criteria. However this was not part of the study protocol and was left to the discretion of the treating physician. The Hestia rule contains eleven pragmatic parameters to select PE patients who do not require in-hospital care (**Appendix**). [10]

Study objectives

The primary aim of this study was to determine current patterns of home treatment in patients with confirmed acute PE in the Netherlands, i.e. the proportion of patients with symptomatic PE who were treated at home, defined as discharged from the hospital within 24 hours after diagnosis. Furthermore, reasons for admission if treated in hospital were evaluated.

The secondary aims were 1) to evaluate the 3-month incidence of unscheduled PE-related readmissions in both home treated or hospitalized patients and 2) to evaluate the duration of hospitalization if treatment started initially in hospital, i.e. the median duration of admission; and 3) to compare the clinical outcome of PE patients treated at home or in hospital. This latter endpoint includes all-cause mortality, recurrent VTE and major bleeding during a 3-month follow-up period.

Study definitions

Acute PE was defined as an intraluminal filling defects of the subsegmental or more proximal pulmonary arteries confirmed by computed tomographic pulmonary angiography (CTPA). Recurrent VTE was defined as a new intraluminal filling defect on CTPA or confirmation of a new PE at autopsy. Recurrent lower extremity DVT was defined as new non-compressibility by ultrasonography or as an increase in vein diameter under maximal compression, as measured in the abnormal venous segment, indicating an increase in thrombus diameter (≥ 4 mm) or by a positive signal on magnetic resonance direct thrombus imaging (MRDTI) indicative of fresh thrombus in the proximal veins of the leg. [15]

Major bleeding was defined as any bleeding resulting in death; symptomatic bleeding in a critical organ (intracranial, intra spinal, intraocular, retroperitoneal, intra articular and pericardial bleeding and muscle bleeding resulting in compartment syndrome) or symptomatic bleeding resulting in a decrease in the hemoglobin concentration of at least 2g/dL or resulting in the transfusion of at least two packs of red blood cells, following the ISTH criteria. [16]

In case of death, information was obtained from the hospital records. Deaths were classified as caused by PE when confirmed by autopsy, shown by objective testing shortly before death, or if it could not be confidently excluded as a cause of death.

PE-related readmission was defined as any unscheduled visit to the outpatient clinic, emergency room or readmission in hospital due to PE-related complications, such as thoracic pain, dyspnea, major bleeding, clinically relevant non-major bleeding or (suspected) recurrent VTE.

An independent adjudication committee assessed and adjudicated all (suspected) adverse events occurring during follow-up.

Statistical analysis

Categorical data are presented as percentages and continuous variables as means ± standard deviation. The proportion of patients who were discharged within 24 hours after diagnosis and reasons for admission are provided as frequencies with corresponding 95% confidence intervals (95%CI). Also, frequencies with corresponding 95%CI will be provided to assess the 3-month incidence of PE-related unscheduled readmissions.

In order to describe the natural course of PE in patients treated at home or hospitalized (secondary outcomes), crude Odds Ratios are provided with corresponding 95%CI which allows for providing the relevant perspective. Because patients treated at home or hospitalised are inherently different (hospitalized patients have a different risk profile for adverse outcome), we did not perform multivariate analysis to formally compare the outcomes of the two patient cohorts. The cumulative incidence of PE-related unscheduled readmission according to initial treatment management were compared with a hazard ratio. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

A total of 456 patients were diagnosed with acute PE in the YEARS study. Of these, 52 were excluded for this current analysis because PE was diagnosed during hospitalization or patients were included in the one hospital that could not provide additional data for this sub study. The baseline characteristics of the 404 remaining study patients are summarized in **Table 1**. Their mean age was 59 years (standard deviation (SD) 16), 52% was female and 13% had active malignancy at time of diagnosis. Patients initially treated at home were younger with a mean age of 56 years compared to 62 of those initially hospitalized (mean difference 6.1 years (95%CI 2.9-9.3)) and had less renal insufficiency, 13 % vs 23% (OR 0.49 (95%CI 0.29-0.85). In this cohort, the majority of patients was treated with vitamin K antagonists while only 4.2% were treated with a direct oral anticoagulants (DOAC).

Table 1: Baseline characteristics of outpatients with acute pulmonary embolism of the YEARS study

	Home treatment (n=184)	Initial hospitalization (n=220)	Total (n=404)
Age, mean (SD)	56 (16)	62 (16)	59 (16)
Male sex, no (%)	92 (50)	100 (47)	195 (48)
Weight in kg, mean (SD)	85 (17)	86 (19)	86 (18)

Table 1: Baseline characteristics of outpatients with acute pulmonary embolism of the YEARS study (continued)

	Home treatment (n=184)	Initial hospitalization (n=220)	Total (n=404)
Body Mass Index, mean (SD)	28 (5.4)	28 (5.8)	28.1 (5.6)
Creatinine clearance < 60 ml/min* — no. (%)	23 (13)	48 (23)	73 (18)
COPD (%)	7 (3.8)	14 (6.6)	21 (5.2)
Heart failure (%)	2 (1.1)	8 (3.8)	11 (2.7)
Mean duration of symptoms in days (SD)	8.6 (17)	8.2 (18)	8.3 (17)
Previous VTE — no. (%)	51 (28)	44 (21)	95 (24)
DVT	21 (11)	14 (6.6)	35 (8.7)
PE +/- DVT	26 (14)	30 (14)	57 (14)
Estrogen Use (%)	25 (14)	19 (8.9)	44 (11)
Active malignancy no. (%)	21 (11)	31 (15)	53 (13)

Abbreviations: PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism; DVT, Deep vein thrombosis; COPD, chronic obstructive pulmonary disease

** estimated GFR* calculated *by the abbreviated* MDRD *equation*

Primary outcome

Of the 404 patients, 184 (46%, 95%CI 41-50) were treated at home whereas the remaining 220 patients (54%) were treated in hospital. The median duration of admission of those initially hospitalized was 3.0 days (interquartile range 2.0-5.0). In 1.7% of patients, the duration of admission could not be retrieved. Reasons for hospitalization are shown in **Table 2** and consisted mainly of need for oxygen administration (37%) and "medical or social reasons" (47%; **Table 3**). Of note, relevant inter hospital differences were observed in the proportion of patients treated initially at home treatment with percentages ranging from 13% to 83% (**Figure 1**).

Table 2: Reasons for hospitalization after diagnosis PE*

Reasons for hospital admission	Frequency n= 261	Proportion
1. Hemodynamically unstable	15	7.0%
2. Need for thrombolysis or embolectomy	1	0.5%
3. Active bleeding or high bleeding risk	10	4.7%
4. > 24 hour oxygen supply	78	37%
5. Need for intravenous pain medication > 24 hr	21	9.9%
6. Medical or social reasons	100	47%
7. Renal insufficiency (< 30 ml/min)	5	2.3%
8. Severe liver impairment	2	1.0%
9. New PE during anticoagulant treatment	3	1.4%
10 No risk stratification scheme such as Hestia applied	26	12%

** Multiple Hestia criteria for admission could be scored in one patient*

Abbreviations: PE, pulmonary embolism

Table 3: Reasons for awarding the subjective Hestia criterion 'social or medical reason for admission'

Reasons for hospital admission	Frequency n=100	Proportion
1. Concomitant infection	16	16 %
2. Malignancy	9	9 %
3. Concomitant acute condition, e.g. electrolyte disorders	14	14 %
4. Extensive PE	13	13 %
5. PE related cardiac problems	5	5 %
6. Outpatient treatment not feasible because of comorbidities or social reasons	16	16 %
7. Need for pain medication (not i.v.)	5	5 %
8. Contrast allergy	1	1 %
9. Other	21	21 %

Abbreviations: PE. Pulmonary embolism; i.v., intravenously, Extensive PE: saddle embolus, large thrombus load, RV dilatation; PE related cardiac problems: rhythm alterations, syncope

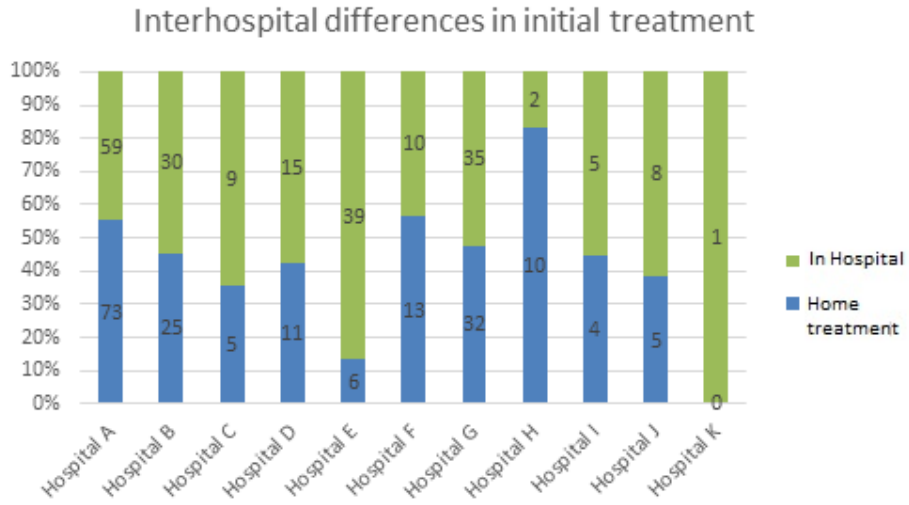

Figure 1: Inter hospital differences in initial treatment policy

Secondary outcome

The 3-month cumulative incidence of any adverse event was 3.8% (95% confidence interval (CI) 1.5% - 7.7%) in those treated at home (2 recurrent VTE, 3 major bleedings and two deaths) versus 10% (95% CI 6.7% - 15.3%) in the initially hospitalized patients (3 recurrent VTE, 6 major bleedings and fourteen deaths). Specifications of the adverse events of patients with PE treated at home are described in **Table 4**. In those patients treated at home, none of the major bleeding or recurrent VTE events were fatal. The two deaths were adjudicated not to be associated to VTE: one occurred in the setting of progressive non-small cell lung carcinoma and the other

patient died of progressive non-specified interstitial pneumonia requiring increasing amounts of oxygen suppletion.

Table 4: Details of adjudicated adverse events in all outpatient treated at home.

Patient	Sex	Age	Adverse event	Specification
No. 1	M	50	Major bleeding	Subdural bleeding during anticoagulant therapy with low-molecular weight heparin.
No. 2	F	51	Major bleeding	Spontaneous liver bleeding: subcapsular haematoma with multiple active bleeding foci treated with a coiling procedure. An inferior vena cava filter was placed and removed two months later; anticoagulation with vitamin K antagonist was stopped and switched to LMWH
No. 3	F	95	Major bleeding	Decrease in hemoglobin concentration > 2g/dL due to severe spontaneous m. rectus sheath hematoma, treated with transfusion of 2 packs red blood cells. Anticoagulation was stopped indefinitely and replaced by aspirin.
No. 4	F	43	Recurrent VTE and Death	Recurrent VTE during LMWH treatment with new thrombus load in superior vena cava in patient with advanced non-small cell lung carcinoma. Patient died thirteen days later due to progressive vena cava superior syndrome.
No. 5	M	42	Death	Death not adjudicated to PE. History of severe non-specific interstitial pneumoniae with increasing oxygen requirement.
No. 6	F	50	Recurrent VTE	New symptomatic DVT after initial diagnosis of PE during VKA treatment. LMWH was temporarily added on top of the VKA.

Abbreviations: SD, standard deviation; PE, pulmonary embolism; VTE, venous thromboembolism; VKA, vitamin K antagonists; LMWH, low-molecular weight heparin

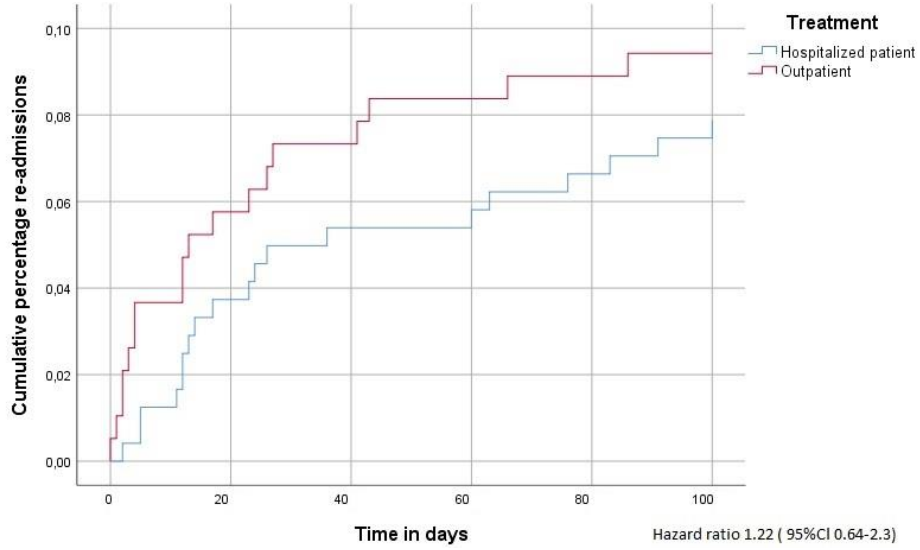

Figure 2: Cumulative incidence of PE-related unscheduled readmissions to the hospital.

The rate of PE-associated unscheduled readmissions in patients treated at home was 9.7% versus 8.6% for initially hospitalized patients, for a crude hazard ratio of 1.1 (95%CI 0.57-2.1; **Figure 2**). The main reason for readmission was thoracic pain (n=16, 43%). Specification of all reasons for an unscheduled readmission are provided in **Table 5**. The PE-associated unscheduled readmissions of patients initially hospitalized consisted of nine admissions, eight emergency room visits and two unscheduled visits to the outpatient clinic, whereas unscheduled PE-associated readmissions of patients treated at home consisted of nine admissions and nine emergency room visits.

Table 5: Reasons for readmission

	Home treatment n (%)	Initial Hospitalization n (%)	Median Time until readmission in days n (IQR)
1. Thoracic pain	8 (4.3)	8 (3.6)	9 (2-34)
2. Dyspnea (without any other explanation than PE)	2 (1.0)	3 (1.4)	7 (7-68)
3. Major bleeding	2 (1.0)	3 (1.4)	12 (8-39)
4. Clinically relevant non-major bleeding	3 (1.6)	4 (1.8)	25 (23-62)
5. Recurrent VTE	2 (1.0)	1 (0.5)	26 (14-34)
6. Total	18 (9.7)	19 (8.6)	29 (13-84)

Abbreviations: IQR interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism

DISCUSSION

This post-hoc analysis of the YEARS study showed that 46% of all outpatients with confirmed PE were treated at home in Dutch daily clinical practice. The incidence of adverse outcome for those treated at home was low and PE-associated unscheduled readmission rates were not different between patients treated at home or initially managed in hospital.

Although we observed relevant inter hospital differences regarding the proportion of home treatment with percentages ranging from 13% to 83%, the overall proportion of patients treated at home in this analysis is very much in line with numbers suggested in prospective outcome studies focusing on home treatment. In the Hestia study 297 (51%) of the initially screened 581 patients were treated at home, while this was 152/351 (43%) and 516/1102 (47%) in two other studies. [3,6,10] Limited data are available from practice based studies in other countries. Published literature from three countries showed lower rates of home treatment, with numbers variating from 10 to 33%. [13,17-19] This 33% was observed in a large Italian prospective cohort comparing different risk stratification scores. [13] In that study, the Hestia criteria identified a higher proportion (42%) of PE patients eligible for early discharge (within 48 hours) than the PESI (24%) and sPESI (18%) scores.

Where the introduction of DOACs has likely lowered the threshold for treating a PE patient at home, it may also lead to a decrease in the mean duration of hospitalization. The

median duration of admission in the hospitalized patients in our cohort was 3.0 days, with the vast majority of all patients in this cohort treated with low-molecular weight heparin followed by vitamin K antagonists. Notably, this was shorter than found in a large study comprising mainly European hospitals showing a mean duration of 13.6 days in 2001 and 9.3 days in 2013.[7,20] This decrease in length of stay was also observed in recent published data from the United States showing a decrease to 6 days of hospitalization in 2015.[21] Notably, the mean duration of admission in the current study may thus decrease even further with more extensive use of DOACs than the observed proportion of 4.2%. The main reasons for in-hospital care were oxygen administration (37%) and "medical or social reasons" (47%); these frequencies are very comparable to those shown in dedicated outpatient management studies. [6,10]

The incidence of adverse events in the patients treated at home was low. These low adverse event rates were very much comparable to those observed in the Vesta and Hestia studies, in which patients were treated at home in the absence of any Hestia criteria. [6,10] This low rate of events was also found in the HoT-PE trial, in which patients were selected by the majority of the exclusion criteria correspond to the items of the Hestia criteria in combination with the mandatory absence of right ventricular dysfunction.[22] In current literature, data regarding unscheduled readmissions in PE patients after initial home treatment is only sparsely available. To our surprise, we could not demonstrate a difference between patients treated at home or in hospital. Notably, the proportion of patients with a readmission or prolonged initial hospitalization in the HoT-PE study was 10% as well. Slightly higher readmission rates (+/-15%) were reported in a large retrospective cohort study in the United States using international classification of diseases (ICD) codes for the identification of PE. [21,22]

Strong points of this study include the novelty of our data, the completeness of follow-up, the multicentric design and the practice based setting. Main limitation of this study is the post-hoc design. Data concerning major bleeding and the Hestia criteria was not prospectively collected in the YEARS study, but were extracted from the medical charts. Also, as the YEARS study was a management study, underrepresentation of high-risk subgroups is possible, including but not limited to pregnant patients or hemodynamically instable patients. Even so, as the YEARS algorithm was implemented as standard diagnostic strategy in all participating hospitals, the vast majority of all potential PE patients participated in the original study, underlying the validity of our conclusions.

In conclusion, forty-six percent of all outpatients with acute PE participating in the YEARS study were treated at home. Rates of adverse events were low and PE-related unscheduled readmission rates were not different between patients treated at home or in hospital. This supports the widespread trend to treat PE patients more often at home.

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Appendix Hestia Criteria

Is the patient hemodynamically unstable? [a]	Yes/No
Is thrombolysis or embolectomy necessary?	Yes/No
Active bleeding or high risk of bleeding? [b]	Yes/No
More than 24 hour of oxygen supply to maintain oxygen saturation > 90%?	Yes/No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes/No
Severe pain needing intravenous pain medication for more than 24 h?	Yes/No
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?	Yes/No
Does the patient have a creatinine clearance of < 30 ml/min? [c]	Yes/No
Does the patient have severe liver impairment? [d]	Yes/No
Is the patient pregnant?	Yes/No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes/No
If the answer to one of the questions is 'yes', the patient cannot be treated at home	

[a] Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure <100mmHg with heart rate >100 beats per minute; condition requiring admission to an intensive care unit.

[b] Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 9 109/L), uncontrolled hypertension (systolic blood pressure > 180mm Hg or diastolic blood pressure > 110mm Hg).

[c] Calculated creatinine clearance according to the Cockroft-Gault formula.

[d] Left to the discretion of the physician.

7

Home treatment of patients with cancer-associated venous thromboembolism - An evaluation of daily practice

Stephan V. Hendriks, Menno V. Huisman, Jeroen C.J. Eikenboom, Jaap Fogteloo, Hans Gelderblom, Felix J.M. van der Meer, Wilhelmina J.E. Stenger, Arie J. Verschoor, Henri H. Versteeg and Frederikus A. Klok

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ABSTRACT

Background: Home treatment of cancer-associated venous thromboembolism (VTE) is challenging due to the high risk of adverse events. While home treatment is quite agreeable to cancer patients, studies evaluating the safety of VTE home treatment in this setting are largely unavailable.

Methods: This was an observational study in patients with cancer-associated VTE. The main outcomes were the proportion of patients treated at home (hospital discharge <24 hours after diagnosis) and the 3-month incidence of VTE-related adverse events (major bleeding, recurrent VTE and/or suspected VTE-related mortality) in patients managed in hospital versus at home.

Results: A total of 183 outpatients were diagnosed with cancer-associated VTE: 69 had deep vein thrombosis (DVT) and 114 had pulmonary embolism (PE ± DVT). Of those, 120 (66%) were treated at home; this was 83% for patients with DVT and 55% for patients with PE (± DVT). The 3-month incidence of any VTE-related adverse event was 13% in those treated at home versus 19% in the hospitalized patients (HR 0.48; 95%CI 0.22-1.1), independent of initial presentation as PE or DVT. All-cause 3-month mortality occurred in 33 patients treated as inpatient (54%) compared to 29 patients treated at home (24%; crude HR 3.1 95%CI 1.9-5.0).

Conclusions: Two-third of patients with cancer-associated VTE -including PE- were selected to start anticoagulant treatment at home. Cancer-associated VTE is associated with high rates of VTE-related adverse events independent of initial in hospital or home treatment. However, home treatment may be a good option for selected patients with cancer-associated DVT or PE.

INTRODUCTION

Several large trials have shown that home treatment of selected patients with venous thromboembolism (VTE) is feasible and safe due to a low incidence of adverse events.[1-10] In these outpatient management studies, only a small minority of patients with cancer-associated VTE were included. One of the reasons that studies in cancer-associated acute pulmonary embolism (PE) are lacking may be that the current European Society of Cardiology (ESC) algorithm for PE risk stratification -including criteria for home treatment- are based on the simplified PE severity index (sPESI) which categorizes all patients with cancer as 'high risk', implicating that those are considered to be 'non-suitable' for home treatment. [11]

In current literature, hardly any study has been performed for home treatment in cancer-associated VTE and those that have been published mainly involved incidentally detected PE.[12] Notably, this subgroup of cancer-associated VTE is very relevant for clinical practice. First, up to one in four patients with VTE has cancer. Second, due to the higher risk of recurrent thrombosis, major bleeding and all-cause mortality than in those without malignancy, management of patients with cancer-associated venous thromboembolism is particularly challenging.[13] Third, the psychosocial advantages and quality-of life (QOL) considerations of home treatment are particularly relevant for cancer patients. Studies in patients with advanced oncological disease for instance showed significant decline in QOL during hospitalization, especially with longer duration of hospitalization. [14,15]

Hence, knowledge of the frequency and outcome of home treatment of patients with cancer associated VTE is highly relevant for guiding clinical practice. We therefore aimed to evaluate current practice patterns and outcome of in hospital and home treatment of patients with cancer-associated VTE in a Dutch University Hospital.

METHODS

Design and patients

In this retrospective study, all consecutive patients diagnosed with cancer-associated VTE in a Dutch academic medical center (Leiden University Medical Center, Leiden, the Netherlands) between December 2015 and July 2018 were identified via the hospitals' administrative system. Active cancer was defined as a diagnosis of cancer that occurred within 6 months before the diagnosis of index VTE (excluding basal-cell or squamous-cell carcinoma of the skin), or any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer.[16,17] Patients were eligible for inclusion if they were 18 years or older and had established acute symptomatic or incidental PE involving subsegmental or more proximal pulmonary arteries confirmed by CTPA, or symptomatic or incidental deep vein thrombosis (DVT) of the upper or lower extremities, involving the popliteal, femoral, iliac, subclavian, axillary or brachial vein

or the inferior vena cava, diagnosed by compression ultrasound or CT venography.[18] The only exclusion criterion for this study was age below 18 years. The need for informed consent was waived by the institutional review board of the Leiden University Medical Center due to the retrospective study design. All patients were treated in our hospital for the cancer and the incident VTE. Hence, detailed follow-up data was available until patients died, were considered in remission or were referred back to the general practitioner for end-of-life care.

Study objectives

No specific decision tools for selecting patient with DVT for home treatment exist, and current guidelines do not make notion of a different policy on this issue between patients with cancer-associated DVT and other DVT. Patients with PE were routinely selected for home management according to the Hestia criteria, as described in the hospitals protocol for VTE management. According to the Hestia criteria, and in contrast to the ESC guidelines, patients with cancer-associated PE could be eligible for home treatment.[11] Our hypothesis therefore was that most patients with DVT were treated at home and that risk stratification by the Hestia criteria would allow for home treatment of a relevant number of PE patients as well. The primary objectives of the this study were to assess i) the proportion of outpatients diagnosed with VTE who were treated at home and ii) the 3-month incidence of a composite of VTE-related adverse events (major bleeding, recurrent VTE and/or suspected VTE-related mortality) in patients managed in hospital versus at home. The latter was to evaluate the natural course after initial therapy management, but not to compare in- and outpatient management of cancer-associated VTE.

We planned subgroup analyses for cancer-associated PE and DVT separately, and for incidental VTE. Secondary outcomes were i) the number and timing of PE-related re-admissions during a 3-month follow-up period after the index VTE diagnosis and ii) overall 3-month mortality.

Study definitions

Home management was defined as hospital discharge <24 hours after diagnosis of VTE. Major bleeding was defined as any bleeding resulting in death, symptomatic bleeding in a critical organ (intracranial, intra spinal, intraocular, retroperitoneal, intra articular and pericardial bleeding and muscle bleeding resulting in compartment syndrome) or symptomatic bleeding resulting in a decrease in the hemoglobin concentration of at least 2g/dL or resulting in the transfusion of at least two packs of red blood cells.[19] Recurrent VTE was defined as a new intraluminal filling defect on computed tomographic pulmonary angiography, confirmation of a new PE at autopsy or a new intraluminal filling defect on computed tomographic angiography in other venous beds. Recurrent lower extremity DVT was defined as new non-compressibility by ultrasonography or as an increase in vein diameter under maximal compression, as measured in the abnormal venous segment, indicating an increase in thrombus diameter (≥ 4 mm), or by a positive signal on magnetic resonance direct thrombus imaging (DTI) indicative of fresh thrombus in the proximal veins of the leg.[18,20,21] VTE-related mortality was defined as death within 7 days of PE

diagnosis, PE confirmed as cause of death during autopsy, or sudden unexpected death with no other explanation. VTE-related readmission was defined as any unscheduled outpatient visit, emergency room visit or readmission in hospital due to VTE-related problems, i.e. thoracic pain, dyspnea (without other explanation than PE), major bleeding, clinically relevant non-major bleeding or due to recurrent VTE within a 3 month follow-up. All events were adjudicated by 2 independent experts who were unaware of the initial management decision (in hospital or home treatment).

Statistical analysis

For the presentation of the baseline characteristics, categorical data are presented as percentages or as proportion and continuous variables as means with standard deviation (SD). The main outcomes of the study are expressed by frequency with corresponding 95% confidence interval (95%CI) or cumulative incidence calculated from Kaplan Meier analysis. Crude Cox regression analysis was used to compare the rate of adverse events between patients treated at home and those admitted to the hospital. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

Between December 2015 and July 2018, 706 consecutive patients were diagnosed with VTE in our hospital, of whom 228 were diagnosed with cancer-associated VTE (32%). In this group with cancer-associated VTE, 183 patients were diagnosed as outpatient: 114 patients with PE (± DVT) and 69 with DVT. Of the PE diagnoses, 30 were incidental (26%) versus none of the DVT diagnoses. **Table 1** summarizes the baseline characteristics of the study patients. Their mean age was 62 years (SD 13) and 63 years (SD 14) for patients treated at home or in-hospital, respectively. Slightly more patients who were hospitalized (77%) than those treated at home (63%) had recurrent or metastatic cancer. The vast majority was treated with LMWH (n=128; 70%), while 23 (13%) patients were treated primarily with vitamin K antagonists (after a short course of LMWH) and 30 (16%) with direct oral anticoagulants.

Table 1: Baseline characteristics at diagnosis of cancer-associated VTE

	Home treatment (n=120)	Initially hospitalized (n=63)
Age, mean (SD)	62 (13)	63.2 (14)
Male sex, no (%)	66 (55)	30 (49)
Previous venous thromboembolism — no. (%)	23 (19)	12 (20)
Weight in kg, mean (SD)	81 (17)	80 (20)
Body Mass Index, mean (SD)	26 (5.0)	26 (4.9)

Table 1: Baseline characteristics at diagnosis of cancer-associated VTE (continued)

	Home treatment (n=120)	Initially hospitalized (n=63)
Creatinine clearance < 60 ml/min — no. (%)	18 (15)	10 (16)
Platelet count below 100,000 per µl — no. (%)	10 (8.3)	4 (6.6)
Qualifying diagnosis of VTE — no. (%)		
PE with or without DVT	63 (53)	49 (80)
DVT only	57 (48)	12 (20)
Incidental PE no. (%)	21 (18)	8 (13)
Most proximal location of PE - no. (%)		
Central PE	21 (18)	26 (43)
Segmental PE	33 (28)	17 (28)
Subsegmental PE*	10 (8.3)	6 (9.8)
Primary site of malignancy no. — no. (%)		
Breast	7 (5.8)	3 (4.9)
Upper gastrointestinal	20 (17)	7 (12)
Lower gastrointestinal	6 (5.0)	2 (3.3)
Lung	5 (4.2)	11 (18)
Genitourinary tract	35 (29)	16 (26)
Brain	7 (5.8)	7 (12)
Heamatological	11 (9.2)	5 (8.2)
Skin (excl squamous/basal)	12 (10)	5 (8.2)
Other	13 (11)	5 (8.2)
Recurrent or metastatic cancer — no. (%)	76 (63)	47 (77)
Receiving systemic anti-cancer therapy †	63 (53)	30 (49)

Abbreviation: SD, standard deviation; VTE, venous thromboembolism; DVT, Deep vein thrombosis; PE, pulmonary embolism
* Eight cases of isolated subsegmental pulmonary embolism were included
† Systemic chemotherapy, immunotherapy or hormonal therapy

Primary outcome

Of all 183 outpatients with cancer-associated VTE 120 (66%) were treated at home; this was 83% for patients with DVT and 55% for patients with PE with or without DVT. For the patients treated as inpatients, the mean admission duration was 8.2 days (±7.9 days). Reasons for admission are shown in **Table 2**.

Table 2: Reasons for hospitalization according to Hestia criteria (n=61)

Reasons for hospital admission	Frequency	Proportion
1. Hemodynamically unstable	12	19.7%
2. Active bleeding or high bleeding risk	1	1.6%
3. > 24 hr Oxygen supply	22	36.1%
4. Diagnosis during anticoagulant treatment	5	8.2%
5. Need for intravenous pain medication > 24 hr	2	3.3%

Table 2: Reasons for hospitalization according to Hestia criteria (n=61) (continued)

Reasons for hospital admission	Frequency	Proportion
6. Renal failure (clearance < 30 ml/min)	4	1.7%
7. Severe liver impairment	1	1.6%
8. Heparin induced thrombocytopenia	1	1.6%
9. Medical or social reasons	27	44.3%
Concomitant infection	6	
Need for further diagnostic tests	4	
Social reasons	10	
(Oncological) surgery	3	
Need for non-intravenous pain medication	2	
Unknown	2	

VTE-related mortality within 3-months occurred in 2 patients treated at home (1.7%) and in 5 patients initially treated in hospital (7.9%; crude hazard ratio [HR] 0.32; 95% confidence interval [CI] 0.06-1.6; **Table 3a**). 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 details of diagnosis and management of the VTE recurrences are provided in **Table 4**. None of the recurrent VTE events were fatal, six were incidental findings and five occurred within the first month after the index VTE was diagnosed.

Table 3a: VTE-related adverse events in cancer-associated VTE

	Home treatment (n=120)	Initially hospitalized (n=63)	HR	95% CI
1. Suspected VTE-related mortality	N=2	N=5	0.32	(0.1-1.6)
2. Major bleeding	N=10	N=1	5.2	(0.7-41)
3. Recurrent VTE	N=4	N=6	0.33	(0.1-1.2)
4. Composite outcome	N=16	N=12	0.48	(0.2-1.1)

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism; HR, Hazard ratio; CI confidence interval

Table 3b: Subgroup analysis: VTE-related adverse events with cancer-associated PE as initial diagnosis

	Home treatment (n=63)	Initially hospitalized (n=51)	HR	95% CI
1. Suspected VTE-related mortality	N=1	N=5	0.27	(0.0-2.3)
2. Major bleeding	N=3	N=0	Not applicable	Not applicable
3. Recurrent VTE	N=2	N=3	0.52	(0.1-3.1)
4. Composite outcome	N=6	N=8	0.38	(0.1-1.1)

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism; HR, Hazard ratio; CI confidence interval

Table 3c: Subgroup analysis: VTE-related adverse events with cancer-associated DVT as initial diagnosis

	Home treatment (n=57)	Initially hospitalized (n=12)	HR	95% CI
1. Suspected VTE-related mortality	N=1	N=0	Not applicable	Not applicable
2. Major bleeding	N=7	N=1	1.5	(0.2-12)
3. Recurrent VTE	N=2	N=3	0.13	(0.0-0.8)
4. Composite outcome	N=10	N=4	0.42	(0.1-1.6)

Abbreviations: DVT, deep venous thrombosis; VTE, venous thromboembolism; HR, Hazard ratio; CI confidence interval

During the study period major bleeding was more frequently observed in patients treated at home: 10 patients (8.3%) versus 1 patient (1.6%, crude HR 5.2; 95%CI 0.67-41). The details of diagnosis and management of the major bleedings are provided in **Table 5**. Of all 11 major bleedings, none occurred during the initial 8 days (mean duration of hospitalization of initially admitted patients) and most occurred after 14 days (82%). Two were fatal (18%), one bleed occurred with concomitant use of aspirin and one bleed occurred in presence of a mild thrombocytopenia. The cumulative incidence of major bleeding in both groups started to divert after day 20 of follow-up (**Figure 1**).

The 3-month incidence of any VTE-related adverse event was 13% in those treated at home versus 19% in the initially hospitalized patients (crude HR 0.48; 95%CI 0.22-1.1; **Table 3a, Figure 1**). Results of the subgroup analysis for cancer-associated PE and DVT separately, are shown in Table 3b and c. Comparable hazard ratios were observed for a 3-month incidence of any VTE-related adverse event with either cancer-associated PE or cancer-associated DVT. We also performed sensitivity analyses after excluding 8 patients with isolated subsegmental pulmonary embolism and found comparable hazard ratios. (data not shown).

In the subgroup analysis of incidental PE, 21 (70%) were treated at home. The 3-month incidence of any VTE-related adverse event was 14% in those treated at home versus 13% in the hospitalized patients (crude HR 1.5; 95%CI 0.14-16.5; **Table 6**).

Secondary outcome

Of all initially hospitalized patients, there were no relevant readmissions due to PE related complications within the 3-month follow-up, whereas 16 patients in the group treated at home were re-admitted (13%). Mean duration until readmission was 30 days (SD 20). Reasons for readmission are shown in **Table 7**, and consisted mainly of major bleeding complications. Notably, 22 (35%) of all initially hospitalized patients died during the index hospitalization or were discharged for palliative end-of-life care with a no-return policy.

All-cause 3-month mortality occurred in 33 patients treated as inpatient (54%) compared to 29 patients treated at home (24%; crude HR 3.1 95%CI 1.9-5.0).

DISCUSSION

In our cohort, two-third of patients with cancer-associated VTE were selected to start anticoagulant treatment at home: 83% of patients with cancer-associated DVT and 55% of patients with cancer-associated PE. Overall, rates of adverse events were high, independent of initial in hospital or home treatment. For patients treated at home, adverse events consisted mostly of major bleeding events, occurring beyond the first 14 days after diagnosis. Reasons for initial admission and rates of VTE-related readmission in our study were comparable to those reported in non-cancer VTE patients.[5,7] The observed higher rate of overall mortality in the patients who were initially admitted can be explained by a more advanced tumor stage. The observed higher rate of VTE-related mortality in the inpatient group can be explained by more severe PE, with a higher prevalence of patients in shock or requiring oxygen therapy. These differences in patients treated at home or in hospital are easily explained by application of the Hestia criteria, selecting lower-risk PE patients eligible for home treatment.

While the higher risk of recurrent VTE and overall mortality in patients who were initially admitted to the hospital was expected considering the more advanced stages of disease of these patients, we did not anticipate the higher risk of major bleeding in patients treated at home. Since the increased risk evolved long after duration of hospitalization of the admitted patients and the majority of bleeding occurred at the cancer site (gastrointestinal tract, urogenital tract or central nervous system) without evidence of supratherapeutic anticoagulant treatment (e.g. incorrect dose, renal insufficiency), we do not think that these bleedings could have been prevented by initial hospitalization. They rather occurred in patients with a very different bleeding risk profile than patients who were initially admitted. Also, the observed higher risk of major bleeding may have been overestimated by competing risk of death. Patients treated at home had a mean time at risk of 82 days compared to 58 days for those who were initially hospitalized (mean difference 24.3; 95%CI 15.7-32.9). Also, one third of initially hospitalized patients were discharged with a no-return policy, which may have caused underreporting of adverse events and by all means, prevented readmissions.

Home treatment in general is currently widely applied in patients with DVT but reserved for selected PE patients at low risk of adverse events. Several studies have demonstrated evident benefits of home treatment of VTE: improved quality of life and patient satisfaction, less use of medical resources and lower healthcare costs. [22-24] Concerns or barriers preventing home treatment are mostly based on fear of early complications, i.e. recurrent VTE, major bleeding and VTE-related mortality.[11] Therefore, the main goals of hospital admission are preventing these early complications as well as observing patients with high risk of bleeding, renal insufficiency, managing other comorbidities and providing support if home circumstances are not appropriate, i.e. oxygen therapy or intravenous analgesia.

These same goals, when deciding on initial treatment, undoubtedly do apply to cancer patients with VTE as well. Because the risk of early mortality in cancer patients with VTE is

Table 4: Details of adjudicated recurrent VTE events.

Pt	Sex	Age	Initial treatment	Incidental or symptomatic VTE finding	Days after index VTE	Specification
No. 1	M	79	At home	Incidental	10 days	Progressive renal vein thrombosis and PE after PE diagnosis during LMWH treatment adequate anti-Xa level (> 2.00 IU/ml) in patient with advanced melanoma. Due to concomitant CRNMB, the anticoagulant treatment remained unchanged.
No. 2	F	76	In hospital	Symptomatic	10 days	Progressive thrombus load in external iliac vein compared to 10 days earlier during LMWH treatment in patient with vulvar carcinoma. LWMH dosage was increased with 17%.
No. 3	F	28	In hospital	Incidental	15 days	New bilateral PE after initial diagnosis of DVT during argatroban treatment (APTT 81.7), (HIT test positive) in patient with advanced cervical carcinoma. No systemic anti-cancer treatment possible due to the condition of the patient.
No. 4	F	41	At home	Incidental	18 days	Incidental PE after initial diagnosis of DVT during edoxaban treatment in patient with advanced colorectal carcinoma treated with palliative chemotherapy. No change made.
No. 5	M	73	In hospital	Symptomatic	23 days	New PE after initial diagnosis of DVT during LMWH treatment with adequate anti-Xa level (1.48 IU/ml) in patient with advanced non-small cell lung cancer. No change in therapy was made.
No. 6.	M	65	In hospital	Symptomatic	34 days	New symptomatic DVT after initial diagnosis of PE during VKA treatment in patient with progressive MDS treated with lenalidomide. VKA was stopped and LWMH started.
No. 7	F	66	At home	Incidental	39 days	Progressive thrombus in superior vena cava after initial diagnosis under VKA treatment (no INR available) in patient with progressive endometrial cancer. No change in treatment made. Palliative treatment started two weeks later
No. 8	F	65	In hospital	Symptomatic	49 days	New symptomatic DVT, several days after temporary stop of LMWH for diagnostic procedure in patient with diffuse large cell B cell lymphoma. LMWH treatment was restarted.
No. 9	M	77	In hospital	Incidental	68 days	Progressive DVT in the inferior vena cava during LMWH treatment with adequate anti-Xa levels (1.67 IU/ml) in patient with progressive melanoma. Treatment was not changed.
No. 10	M	76	At home	Incidental	58 days	New incidental PE after initial diagnosis of DVT during LMWH treatment in patient with SCLC. LWMH dosage was increased with 25%.

Abbreviations: Pt, Patient; VTE, venous thromboembolism; F, female; M, male; DVT , deep venous thrombosis; CRNMB, clinically relevant non-major bleeding; APTT, activated partial thromboplastin time; HIT, heparin induced thrombocytopenia; LMWH, low molecular weight heparin; VKA vitamin K antagonists; MDS, myelodysplastic syndrome; SCLC, small cell lung cancer; NMCRB, non-major clinically relevant bleeding

Table 5: Details of adjudicated major bleeding events.

Patient	Sex	Age	Initial treatment	Time after index VTE	Specification
No. 1	M	69	At home	9 days	Upper GI bleeding requiring transfusion during LMWH treatment in patient with gastric cancer, LMWH treatment was discontinued.
No. 2	F	76	In hospital	12 days	Decrease in the hemoglobin concentration > 2g/dL and transfusion required because of limited bleeding from inguinal wound during LMWH treatment in patient with vulvar carcinoma. Because of concomitant symptomatic progressive DVT, LMWH dosage was increased with 17%.
No. 3	M	66	At home	17 days	Hemodynamically important and ultimately fatal upper GI bleeding in patient with advanced esophageal cancer, LMWH treatment was discontinued.
No. 4	M	87	At home	20 days	Macroscopic hematuria after luxated indwelling catheter requiring transfusion during LMWH treatment in patient with prostate cancer. Treatment remained unchanged.
No. 5	M	41	At home	25 days	Decrease in the hemoglobin concentration > 2g/dL due to post-operative bleed on site of pancreatic anastomosis during LMWH treatment in patient with pancreatic cancer operated with curative intent.
No. 6	F	61	At home	29 days	Intracerebral bleeding during LMWH treatment in patient with advanced glioblastoma. LMWH continued in prophylactic dosage.
No. 7	M	81	At home	42 days	Upper GI bleeding requiring transfusion during LMWH treatment in patient with advanced melanoma. LMWH treatment was discontinued.
No. 8.	M	79	At home	50 days	Intramuscular bleeding with decrease in the hemoglobin concentration > 2g/dL, during therapy with aspirin 100mg once daily and LMWH in patient with advanced melanoma Both drugs were temporary stopped.
No. 9	M	59	At home	50 days	Intracerebral bleed during LMWH treatment in patient with advanced renal cell carcinoma with cerebral metastasis, complicated by focal epileptic insults. Therapeutic LMWH was stopped and the next day continued in prophylactic dosage.
No. 10	M	62	At home	52 days	Persistent haematuria resulting in decrease of hemoglobin concentration > 2g/dL during LMWH treatment in patient with progressive Large cell anaplastic T-cell Lymphoma. LMWH treatment was temporarily discontinued and restarted the next day in a prophylactic dosage.
No. 11	M	41	At home	85 days	Fatal intracerebral bleed during LMWH treatment in patient with cerebral metastasized melanoma, resulting in start terminal palliative treatment. Mild thrombocytopenia $116*10^9$/l at moment of bleeding.

Abbreviations: VTE, venous thromboembolism; F, female; M, male; DVT , deep venous thrombosis; LMWH, low molecular weight heparin; GI, gastrointestinal

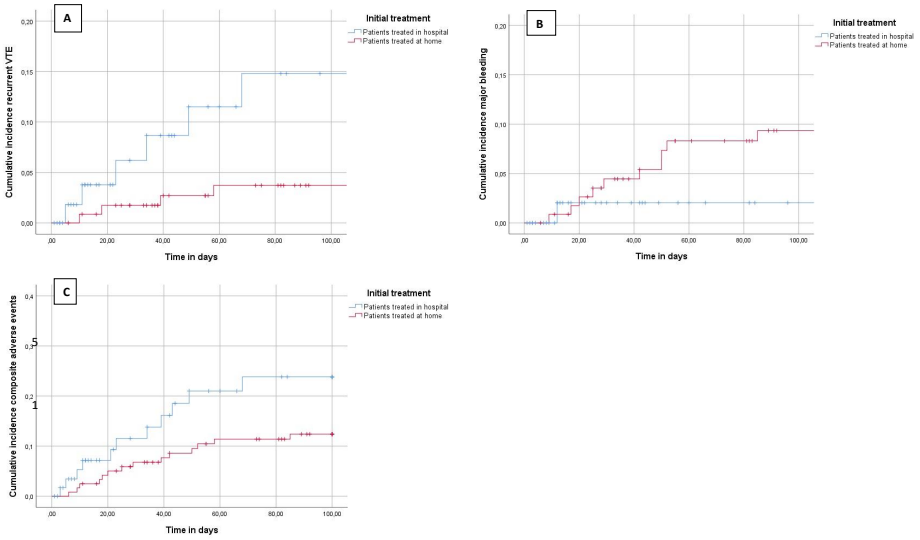

Figure 1: Shown are the cumulative incidence of recurrent VTE within a 3 month period (A), the Kaplan-Meier estimate for major bleeding within a 3 month period (B) and the cumulative composite 3-month outcome of any adverse VTE event (C)

Table 6: VTE-related adverse events in incidental cancer-associated VTE

	Home treatment (n=21)	Initially hospitalized (n=8)	HR	95% CI
1. Suspected VTE-related mortality	N=2	N=1	1.5	0.14-16.5
2. Major bleeding	N=0	N=0	Not applicable	Not applicable
3. Recurrent VTE	N=1	N=0	Not applicable	Not applicable
4. Composite outcome	N=3	N=1	1.5*	0.14-16.5

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism; HR, Hazard ratio; CI confidence interval
* Two adverse events were scored in one patient

Table 7: Reasons of readmission in cancer-associated VTE

	Frequency n= 15	Percent	(Mean) Time until readmission (in days)
1. Thoracic pain	1	6.7	6
2. Dyspnea (without any other explanation than PE)	1	6.7	2
3. Thoracic pain and dyspnea	1	6.7	34
3. Major bleeding	7	47	32
4. Clinically relevant non-major bleeding	2	13	16
5. Recurrent VTE	3	20	50

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism

inherently high, the ESC guideline strongly suggest to hospitalize all patients with PE and cancer. However, should the initial treatment in patients with cancer be only based on the risk of 30-day mortality? In our view, maximizing QOL should be equally important to preventing adverse events. Studies in patients with advanced oncological disease showed significant decline in QOL during hospitalization, especially with longer duration of hospital stay.[14,15] For example, in patients with hematological cancer, the percentage of patients with symptoms of depression more than doubled after hospitalization, with an accompanied increase in fatigue and a clinically significant drop in mean QOL scores.[25] Hence, as initial hospitalization likely does not prevent cancer-associated mortality, we always consider and discuss the possibility of home treatment in all patients in our practice. Notably, the higher incidence of VTE-related readmissions in patients treated at home observed in our study should be taken into account when making the final management decision.

Strong points of our study include the novelty of our data, the completeness of follow-up and the lack of exclusion criteria compared to clinical trials that often exclude patients with the highest risk of bleeding and other adverse outcome. Moreover, all outcomes were adjudicated by independent experts. Main limitation of this study is the retrospective and monocentric design. Therefore, external validity of our findings remains to be proven. However, the comparable rates of adverse events and mortality of our study with the published literature suggest that our results may be widely applicable.[16,17] Furthermore, it is uncertain whether every recurrent incidental PE event was a true recurrence in those who were initially diagnosed with DVT, because no baseline CTPA was performed to exclude for the presence of asymptomatic PE. Lastly, since we did not perform a randomized controlled trial, we cannot judge if home treatment of patients with cancer-associated VTE is better or worse than hospitalization. Because of the inherent differences between the patients treated at home or hospitalized, we specifically chose not to perform multivariate analysis to compare the two treatment strategies but to apply crude comparisons to show the natural course of home treatment in the perspective of patients hospitalized for any reason.

In conclusion, two-third of patients with cancer-associated VTE were selected to start anticoagulant treatment at home. Rates of overall VTE-related adverse events were high, independent of initial in hospital or home treatment, with the vast majority of adverse events in the patients treated at home occurring beyond the first weeks of follow-up. Based on our findings, home treatment may be a good option for selected patients with cancer-associated DVT and/or PE.

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8

Effectiveness and safety of apixaban for treatment of venous thromboembolism in daily practice

Stephan V. Hendriks, Frederikus A. Klok, Wilhelmina J.E. Stenger, Albert T.A. Mairuhu, Jeroen Eikenboom, Anne J. Fogteloo and Menno V. Huisman

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ABSTRACT

Background: Phase 3 trials have shown comparable efficacy of direct oral anticoagulants (DOACs) and vitamin K antagonists in patients with acute venous thromboembolism (VTE), with less major bleeding events in patients randomized to DOAC treatment. With DOACs being increasingly used in clinical practice, evaluation of the DOACs in daily practice-based conditions is needed to confirm their safety and effectiveness.

Aim: To evaluate the effectiveness and safety of apixaban in VTE patients in daily practice.

Methods: In this retrospective cohort study, consecutive patients diagnosed with VTE in two Dutch hospitals (Leiden University Medical Center, Leiden and Haga Teaching Hospital, The Hague) were identified based on administrative codes. We assessed recurrent VTE, major bleeding and mortality during a 3-month follow-up period in those treated with apixaban.

Results: Of 671 consecutive VTE patients treated with apixaban, 371 presented with acute pulmonary embolism (PE) and 300 patients with deep-vein thrombosis. During three months treatment two patients had a recurrent VTE (0.3%; 95%CI 0.08 – 1.1), twelve patients had major bleeding (1.8%; 95%CI 1.0 – 3.2) and 11 patients died (1.6%; 95%CI 0.9 – 2.9), of which one patient with recurrent PE and one because of a intracerebral bleeding.

Conclusions: In this daily practice based cohort, apixaban yielded a low incidence of recurrent VTE, comparable to the phase 3 Amplify study patients. The incidence of major bleeding was higher than in the Amplify-study patients, reflecting the importance of daily practice evaluation and the fact that results from phase III clinical studies cannot be directly extrapolated towards daily practice.

INTRODUCTION

Direct oral anticoagulants (DOACs) inhibit either thrombin (dabigatran) or activated factor X (apixaban, edoxaban and rivaroxaban). Over the last years, DOACS are increasingly being used to prevent ischemic stroke in patients with atrial fibrillation and to treat acute venous thromboembolism (VTE). According to international treatment guidelines, the use of DOACS is being preferred over vitamin-K antagonists (VKA) for these two indications.[1-4] In VTE treatment, phase 3 studies have shown comparable efficacy of DOACs and VKA, with a better bleeding profile.[5-10] Furthermore, at prolonged treatment after the initial 6 months, DOACs have proven to be superior to placebo or aspirin for secondary VTE prevention.[11,12]

Importantly, as phase 3 trials dictate to have strict in- and exclusion criteria both efficacy and bleeding rates may be underestimated because patients at higher risk of bleeding are usually excluded. With DOACs being increasingly used in clinical practice, evaluation of the DOACs using practice based data sources is needed to better delineate their effectiveness and safety. Such data focusing on safety of apixaban for treatment of venous thromboembolism are scarce.

In this study we evaluated the efficacy and safety of apixaban in patients with VTE treated in two hospitals in the Netherlands.

METHODS

Design and patients

In this retrospective cohort follow-up study, consecutive patients diagnosed with venous thromboembolism between January 2016 and December 2018 in two Dutch hospitals (Leiden University Medical Center, Leiden and Haga Teaching Hospital, The Hague) were identified via the hospitals' administrative system. Patients were eligible for inclusion if they were 18 years or older and had established acute symptomatic or incidental pulmonary embolism (PE) involving subsegmental or more proximal pulmonary arteries confirmed by computed tomography pulmonary angiography (CTPA), or symptomatic or incidental deep vein thrombosis (DVT) of the lower or upper extremities, involving the popliteal, femoral, iliac, subclavian, axillary or brachial vein or the inferior vena cava, diagnosed by compression ultrasound or CT venography, or by a positive signal on magnetic resonance direct thrombus imaging (DTI) indicative of fresh thrombus in the proximal veins of the leg.[13-15]

Patients were included in this study when the physician had the intention to start with apixaban treatment. In the LUMC the treatment protocol recommended patients to be treated with apixaban 10 mg twice daily for one week after which apixaban 5 mg BID was initiated. In the Haga Teaching Hospital the treatment protocol recommended patients to be initially treated with approximately one week of therapeutic weight based low molecular-weight heparin (LMWH) after which apixaban 5 mg twice daily was given. Protocol deviations in both hospitals

were common, truly reflecting practice based medicine. Thus, the decision which of the two treatment regimens was initiated, depended on the discretion of the treating physician.

Patients who completed at least 3 months of anticoagulant therapy or met a study endpoint in that period were included in this current analysis. Follow-up data were retrieved from the patient chart. Due to the retrospective study design, the need for informed consent was waived by the institutional review boards of both hospitals.

Aims and outcomes

The primary aim of this study was to evaluate the efficacy and safety of apixaban in VTE patients in daily practice. The primary efficacy outcome was recurrent VTE and all-cause mortality during a 3-month follow-up period after index VTE. The primary safety outcome was the 3-month incidence of major bleeding.

Secondary outcomes in this study were 1) the reported side effects of apixaban as noted by the treating physician in the patient chart and 2) the primary outcomes in the first week of treatment.

Definitions

Recurrent VTE was defined as a new intraluminal filling defect on computed tomographic pulmonary angiography, confirmation of a new PE at autopsy or a new intraluminal filling defect on computed tomographic angiography in other venous beds. Recurrent lower extremity DVT was defined as new non-compressibility by ultrasonography or as an increase in vein diameter under maximal compression, as measured in the abnormal venous segment, indicating an increase in thrombus diameter (≥ 4 mm), or by a positive signal on magnetic resonance direct thrombus imaging (DTI) indicative of fresh thrombus in the proximal veins of the leg.[13-15]

Major bleeding was defined as according to the ISTH criteria as any bleeding resulting in death, symptomatic bleeding in a critical organ (intracranial, intra spinal, intraocular, retroperitoneal, intra articular and pericardial bleeding and muscle bleeding resulting in compartment syndrome) or symptomatic bleeding resulting in a decrease in the hemoglobin concentration of at least 2g/dL or resulting in the transfusion of at least two packs of red blood cells.[16]

In case of death, information was obtained from the hospital records. VTE-related mortality was defined as death within 7 days of PE diagnosis, PE confirmed as cause of death during autopsy, or sudden unexpected death with no other explanation. All events were adjudicated by 2 independent experts who were unaware of the initial management decision. Any disagreement between the 2 independent experts was resolved by a third expert.

Statistical analysis

For the presentation of the baseline characteristics, categorical data are presented as percentages or as proportion and continuous variables as means with standard deviation (SD). The main outcomes of the study are expressed by frequency and proportion with corresponding

95% confidence interval (95%CI). All adverse events were included in the primary analysis. The secondary outcome reported side effects is provided as frequencies and proportion. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

Between January 2016 and December 2018, 671 consecutive patients were diagnosed with VTE and treated with apixaban, of whom 300 (45%) had DVT and 371 (55%) had PE with or without DVT. The baseline demographic and clinical characteristics of all 671 patients are summarized in **Table 1**. Their mean age was 60 years (SD 16), 48% was female and 6.3% had active malignancy at time of diagnosis. The median weight in this cohort was 85 kg (SD 18.6) with 84 patients (13%) having a weight above 100kg. Renal insufficiency (creatinine clearance < 50 ml/min) was present in 60 patients (8.9%). Thirteen patients had severe renal insufficiency, a creatinine clearance e-GRF < 30 ml/min (1.9%). The vast majority of the patients (74%) were treated as outpatient after initial index VTE, this was 93% for those with DVT and 58% for those with PE with or without DVT. For the patients treated initially in hospital, the median admission duration was 5.0 days (interquartile range 7).

Outcomes

During three months follow-up, two patients experienced a recurrent VTE (0.30%; 95%CI 0.08-1.1**; Table 2**). A 71 year old patient had progressive iliac vein thrombosis, three days after diagnosis of a DVT of the femoral vein and start of apixaban, in the presence of a myelodysplastic syndrome. Another 49 year old patient was diagnosed with symptomatic segmental PE, one month after initial DVT diagnosis, in the presence of a progressive stage IV non-small cell lung carcinoma.

A total of 12 patients (1.8%; 95%CI 1.0 – 3.2) experienced major bleeding. The details of the major bleeding, its management and outcome are provided in **Table 3.** Of the 12 major bleedings, three occurred during the first week, including two major bleedings during LMWH therapy. One possible intracranial bleeding under LMWH was fatal, another major bleeding occurred in the presence of thrombocytopenia (platelet count 23X10*9/L); three patients (25%) had a malignancy.

Eleven patients (1.6%; 95%CI 0.9 – 2.9) died during the three months follow-up (**Table 4**). One patient on apixaban died of the index PE within 24 hours of the initial PE diagnosis. Seven patients (64%) had active malignancy at time of death and all died after initiation of palliative care at home or hospice because of metastasized end-stage disease. One patient died due to a possible intracerebral bleed; apixaban was already stopped and LMWH had been started.

Secondary outcomes

The most frequent reported side effects of apixaban were headache (2.5%) and abdominal discomfort (2.4%). The following less frequent side-effects were reported by the treating physician: nausea (0.9%), rash/hypersensitivity (0.4%), itching (0.8%), hair loss (0.3%), paraesthesia (0.3%) and dizziness (0.3%; **Table 5**) causing switch to an alternative anticoagulant in 13% of all 53 patients with side effects. All adverse events within the first week of anticoagulant treatment strategies are provided in **Table 6.**

DISCUSSION

In this practice-based study we observed a lower rate of recurrent VTE (0.3% during 3 months) in patients treated with apixaban than that observed in the phase 3 AMPLIFY clinical trial (2.3% during six months). In contrast, the incidence of major bleeding (1.8% during 3 months) was higher than in the apixaban treated patients in the Amplify study (0.6% during 6-month follow-up).

The low rate of recurrent VTE could be explained by the difference in the follow-up duration in the phase 3 AMPLIFY clinical trial, which was twice as long. Moreover, a considerable percentage of recurrent VTE was adjudicated as death for which PE could not be ruled out. We

Table 1: Baseline characteristics of patients with VTE treated with apixaban

	N=671
Demographics	
Age, mean (SD)	60 (16)
Male sex, no (%)	347 (51.7)
Weight in kg, mean (SD)	84.7 (18.6)
<60 kg — no. (%)	26 (3.9)
60-100 Kg — no. (%)	354 (53)
>100 Kg — no. (%)	84 (13)
Missing — no. (%)	207 (31)
Body Mass Index, mean (SD)	27.3 (5.1)
Missing — no. (%)	276 (41)
Creatinine clearance — no. (%)	
<30 ml/min	13 (1.9)
30-50 ml/min	47 (7)
50-80 ml/min	239 (36)
>80 ml/min	319 (48)
Missing — no. (%)	53 (8)
VTE risk factors	
Previous venous thromboembolism — no. (%)	145 (22)

Table 1: Baseline characteristics of patients with VTE treated with apixaban (continued)

	N=671
COPD — no. (%)	65 (9.7)
Heart failure — no. (%)	21 (3.1)
Estrogen use — no. (%)	67 (10)
Immobilisation — no. (%)	174 (26)
Active malignancy no. — no. (%)	42 (6.3)
Recurrent or metastatic cancer — no. (%)	21 (3.1)
VTE presentation	
Qualifying diagnosis of VTE — no. (%)	
PE with or without DVT	371 (55)
DVT only	300 (45)
Incidental PE no. (%)	16 (2.4)
Extent of qualifying PE no. (%)	
Subsegmental	37/371 (10)
Segmental	162/371 (44)
Central	165/371 (44)
Could not be assessed	7/371 (2)
Treatment	
Outpatient treatment	496 (74)
Readmissions	121 (18)
Apixaban without prior anticoagulant treatment	348 (52)
Apixaban with prior LMWH usage	323 (48)

Abbreviation: SD, standard deviation; VTE, venous thromboembolism; DVT, Deep vein thrombosis; PE, pulmonary embolism; COPD, Chronic obstructive pulmonary disease; LMWH, low-molecular-weight heparin

therefore think, VTE recurrence rates in both studies are likely comparable. Overall, the baseline characteristics in our cohort were comparable to those of the AMPLIFY study except that the proportion of patients included with a DVT was higher in the AMPLIFY study compared to 45% in this cohort. Moreover, more than half (52%) of our patients started apixaban without prior anticoagulant treatment, while this rate was 13% in the AMPLIFY study patients. Notably, the proportion of patients with initial LMWH treatment decreased over time, as experience and knowledge with apixaban treatment increased during the observation period.

Table 2: VTE-related adverse events of patients treated with apixaban

	Number	proportion	95% CI
1. Overall mortality	11	1.6	0.9 – 2.9
2. Major bleeding	12	1.8	1.0 – 3.2
3. Recurrent VTE	2	0.30	0.08 – 1.1

Abbreviations VTE, venous thromboembolism, 95% CI, 95% confidence interval

The most notable difference of this analysis compared to the AMPLIFY study was the incidence of major bleeding. Taking a closer look at the patients who experienced a major bleeding episode elucidates the difference between our practice based study and the phase 3 Amplify study. First of all, two patients suffered from a hematooncological disease, with one being shortly after a hematopoietic stem cell transplantation, at time of bleeding. Overall, three out of 12 patients (25%) who experienced major bleeding had an active malignancy. Treatment of cancer-

Table 3: Detailed information of major bleeding

Patient	Sex	Age	Initial event	Time to adverse event	Major bleeding specified	Management and outcome
No. 1	F	74	PE	2 days	Decrease in the hemoglobin concentration > 2g/dL and requiring transfusion 3 days post-operatively after total knee replacement on operative site during LMWH treatment .	Management: Conservative, LMWH treatment was continued twice daily in therapeutic dosage followed by apixaban Outcome: Resolved without sequalae
No. 2	F	83	PE	5 days	Small traumatic intracerebral bleeding after a fall in the first week with LMWH treatment.	Management: anticoagulant treatment was ceased. Temporary administration of prophylactic dosed LMWH. Apixaban was started 7 days later Outcome: Resolved without sequalae
No. 3	M	61	PE	7 days	Gastrointestinal bleeding resulting in decrease in the hemoglobin concentration > 2g/dL, colonoscopy showed post colon polypectomy bleeding. Received infusion of thrombolytic drugs because of high-risk PE in beginning of admission 7 days prior.	Management: administration of 3 packed red blood cells and 2000 IU prothrombin complex concentrate. Apixaban was temporary stopped with temporary administration of prophylactic dosage LMWH. Apixaban was restarted after successful clip closure of the post polypectomy bleed Outcome: apixaban was restarted 2 days after bleeding, patient was discharged 3 days after bleeding

Table 3: Detailed information of major bleeding (continued)

Patient	Sex	Age	Initial event	Time to adverse event	Major bleeding specified	Management and outcome
No. 4	M	69	PE	8 days	Macroscopic haematuria resulting in decrease in the hemoglobin concentration > 2g/dL after Millin prostatectomy.	Management was started with operative evacuation of clots and continuous irrigating of the bladder via an indwelling catheter. Apixaban was switched to LMWH in a lower therapeutic dosage. After 26 days apixaban was restarted in the outpatient clinic Outcome: Resolved without sequalae
No. 5.	M	71	DVT	14 days	Bleeding in pancreas from pancreatic pseudoaneurysm	Management: coiling, anticoagulation was temporary stopped, temporary prophylactic dosage of LMWH was administered Outcome: discharged 1 day after coiling with the restart of anticoagulant treatment
No. 6	F	46	DVT	21 days	Abnormal menstrual bleeding resulting in decrease in the hemoglobin concentration > 2g/dL after stopping oral contraceptives	Management: oral contraceptives restarted, tranexamic acid was refused by patient Outcome: Resolved without sequalae, apixaban was continued during the complete follow-up
No. 7	F	37	PE	37 days	Abnormal menstrual bleeding resulting in decrease in the hemoglobin concentration > 2g/dL	Management: administration of tranexamic acid and iron infusion. Due to extent of bleeding, embolization of the uterine artery was necessary Outcome: Resolved without sequalae, after three days of cessation on anticoagulants, therapeutic dosages of LMWH were administered for 2 months, after which apixaban was continued

Table 3: Detailed information of major bleeding (continued)

Patient	Sex	Age	Initial event	Time to adverse event	Major bleeding specified	Management and outcome
No. 8	M	62	DVT	42 days	A decrease in the hemoglobin concentration > 2g/dL requiring transfusion because of gastrointestinal bleeding on due to diffuse vulnerable mucous membrane seen on endoscopic examination, post allogenic bone marrow transplantation due to myelodysplastic syndrome. (platelet count 23X10*9/L)	Management: thrombocyte transfusion, start of proton pump inhibition intravenously Outcome: no gastrointestinal bleed was objectified after 3 days of conservative therapy, anticoagulant treatment was continued.
No. 9	M	82	PE	55 days	Progressive subdural haematoma and progressive subdural hygroma (both present before apixaban was started)	Management: anticoagulation was discontinued indefinitely Outcome: after initial progression of subdural fluid collection resulting in unilateral paresis of the arm, dexamethasone was administered, resulting in partial clinical recovery and regression of the fluid collection on CT
No. 10	F	76	PE	56 days	Gastrointestinal bleeding resulting in decrease in the hemoglobin concentration > 2g/dL and transfusion required: clinical diagnosis diverticular bleeding, endoscopic examination showed no focus	Management: administration of intravenous tranexamic acid and 3500 IU prothrombin complex concentrate, anticoagulation was temporary stopped Outcome: resolved without sequelae after an admission of 3 days, apixaban was restarted the day after discharge
No. 11	F	57	PE	75 days	Ruptured spleen in patients with diffuse Large B-cell lymphoma with splenic localisations. Also, a large amount of haemorrhagic pleural effusion was drained by thoracentesis.	Management: anticoagulation was discontinued indefinitely Outcome: patient also received first line of therapy for DLBCL and was discharged after an admission of 45 days.

Table 3: Detailed information of major bleeding (continued)

Patient	Sex	Age	Initial event	Time to adverse event	Major bleeding specified	Management and outcome
No. 12	M	59	DVT	81 days	Possible intracerebral bleeding in presence of progressive oesophageal cancer while treated with LMWH. Symptoms of headache, nausea and vision loss. Patient refused further treatment and decided to receive end-of-life care at home.	Management: palliative treatment Outcome: patient died 5 days later

Abbreviations: M, male; F, female; CT, computed tomography; LMWH, light molecular weight heparin; DLBCL, diffuse Large B-cell lymphoma; IU, international units

Time to adverse event: time from initial events (and subsequent start of anticoagulant therapy) until occurrence major bleeding

associated VTE is not only challenging due to a higher risk of recurrent VTE and mortality, but also because of higher incidences of major bleeding.[17] The added value of DOAC therapy in patients with cancer-associated thrombosis has already been established with the publication of the SELECT-D3 and Hokusai VTE Cancer trials, with consideration for the risk of bleeding in certain tumor types (e.g. gastrointestinal, urogenital) [18,19] International guidelines currently

Table 4: Detailed information of deaths

Patient	Sex	Age	Time to event	Specified
No. 1	F	93	0 days	Patient presented at ER with stridor and hypoxia. CT showed an incidental subsegmental PE. One single administration of apixaban was ordered. She died several hours after presentation with stridor, severe hypoxia and laryngeal spasms. At autopsy, no good explanation was found for the upper airway narrowing as cause of death.
No. 2	F	81	1 day	Patient using apixaban died of fatal PE, occurring one day after initial PE diagnosis with symptoms of progressive oxygen requirement and signs of exhaustion. Resection of a meningioma was the initial reason for admission, which was complicated by a pneumonia and acute PE. Due to severe comorbidity, i.e. advanced age with frailty, severe emphysema and a refractory delirium, palliative treatment was started.
No. 3	M	87	10 days	Patient died due to progressive cerebral ischemia, on admission also an incidental segmental PE was diagnosed. Due to neurological deterioration and advanced age, a palliative treatment was started
No. 4	M	46	14 days	Patient was diagnosed with incidental PE in presence of a progressive stage IV non-small cell lung carcinoma (NSCLC) with obstruction of the right upper lobe bronchus, lymphangitis carcinomatosis and pleural fluid. One day after initiation of palliative treatment, patient died

Table 4: Detailed information of deaths (continued)

Patient	Sex	Age	Time to event	Specified
No. 5.	M	71	26 days	Patient died in a nursing home after neurologic deterioration due to progressive hydrocephalus. Initial admission was because of a subarachnoid bleeding treated with coiling of its aneurysm and extra ventricular drainage. During hospital admission PE was diagnosed. Palliative treatment was initiated after neurological deterioration.
No. 6	M	49	46 days	Patient died at home after initiation of palliative treatment. Multiple cerebral ischemic events occurred in presence of a progressive stadium IV NSCLC resulting in a severe thrombophilic condition. Patient was also diagnosed with recurrent VTE during the 3-month follow-up.
No. 7	M	57	56 days	Palliative treatment was initiated after admission of a subtotal ileus in presence of metastasized gastric cancer with peritonitis carcinomatosis. Care was provided by the general practitioner
No. 8	F	64	74 days	Died at home after initiation of palliative treatment due to advanced stage NSCLC with bone and myogenic metastasis with progressive pleural carcinomatosis
No. 9	M	62	83 days	Patient died because of infectious complications after a hematopoietic stem cell transplantation due to myelodysplastic syndrome. Patient was admitted because of respiratory insufficiency after an aspergillus pneumoniae. After almost 3 months of admission patient died one day after initiation of palliative treatment
No. 10	M	59	86 days	Patient died due to a possible intracerebral bleed. Patient also mentioned in major bleeding section: No. 12. Symptoms of nausea, headache and hemianopsia were reported at home in the presence of progressive esophageal carcinoma without further treatment option. Apixaban was already ceased and patient was treated with LMWH. Palliative care was initiated by the general physician
No.11	M	67	89 days	Patient died after initiation of palliative treatment after small bowel ileus in presence of a metastasized urothelial carcinoma with peritonitis carcinomatosis

Abbreviations: M, male; F, female; ER, emergency room; CT, computed tomography; PE, pulmonary embolism; NSCLC, non-small cell lung carcinoma

advise to consider the use of DOACs in cancer-associated thrombosis with caveats for these gastrointestinal and urogenital tumours.[4] In this respect, the fact that DOACs were sometimes prescribed in patients with cancer-associated VTE in this cohort, reflects anticoagulant therapy in current daily practice. Secondly, in two patients bleeding occurred shortly after intervention, one patient already had a subdural fluid collection and one patient experienced bleeding within

a week after prior treatment of thrombolytic therapy. These patients would have been excluded in phase 3 trials as they dictate strict in- and exclusion criteria.

Table 5: Other reported side-effect of apixaban

	Frequency n=43	proportion
1. Headache	17	2.5
2. Nausea	6	0.89
3. Abdominal discomfort	16	2.4
4. Itching	5	0.75
5. Hypersensitivity/ Rash	3	0.45
6. Hair loss	2	0.30
7. Paresthesia	2	0.30
8. Dizziness	2	0.30

Table 6: VTE-related adverse events in the first week according to initial treatment strategy

	Direct apixaban n=348	Initial treatment with LMWH n=323
1. Overall mortality	2 (0.6%)	0
2. Major bleeding	1 (0.3%)	2 (0.6%)
3. Recurrent VTE	1 (0.3%)	0

Abbreviations VTE, venous thromboembolism; LMWH, low molecular-weight heparin

We observed two heavy menstrual bleedings in this cohort. Treatment with factor Xa inhibitors is indeed associated with an increased risk of abnormal uterine bleeding, particularly heavy menstrual bleeding in premenopausal women when compared to treatment with VKA.[20-24] The observation that these women were admitted because of heavy menstrual bleeding, although it was not specifically monitored in this cohort, underlines the relevance of monitoring and counseling the risk of heavy menstrual bleeding in premenopausal women after initiating DOAC therapy.

Interestingly, in the management of major bleeding, prothrombin complex concentrate (PCC) was only used twice in patients with gastrointestinal bleeding, while all other patients with major bleeding were treated conservatively by only stopping the apixaban. This observation that most major bleeding events were managed conservatively, without the use of PCC, was also observed in the Dresden NOAC registry (PCC administered in 6.7% of all major bleeding events).[25]

Overall, the rate of major bleeding in our cohort is comparable to rates of other practice based cohorts in current literature. A systematic review including 5 large observational cohorts showed a 0.6 to 3.6% three months major bleeding rate in patients treated with apixaban for acute VTE. [26] Same proportions of major bleeding associated with DOAC therapy (3.3% during

a mean follow-up of 85 days) were observed in a large practice-based multicenter, population study, although most DOAC users in this study used rivaroxaban.[27]

The main limitation is the presence of selection bias as we do not know in how many patients (and why) another anticoagulant strategy than apixaban was chosen. Of note, apixaban was the first choice in anticoagulant therapy in both hospital protocols for VTE management. Therefore, we consider our results representative for daily practice since patients from both an academic and a non-academic teaching hospital were studied and we observed rates of adverse events and mortality comparable to the published literature. Two of the major bleedings occurred on LMWH treatment in the first week of anticoagulant treatment, while the treating physician continued with apixaban treatment after the initial LMWH course. According to the intention to treat principle, we included those adverse events in the final analysis, which may have led to an overestimation of the apixaban associated rate of major bleeding. Strengths include the completeness of follow-up and the lack of exclusion criteria compared to clinical trials. Moreover, all outcomes were adjudicated by independent experts and we could provide detailed data on management and outcome for each adverse event.

In conclusion, Apixaban yielded a low incidence of recurrent VTE in our large practice-based patient cohort. The incidence of major bleeding was however higher than in the Amplify-study, reflecting the importance of daily practice evaluation and the fact that results from phase III clinical studies cannot be directly extrapolated towards daily practice.

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9

Home treatment compared to initial hospitalization in normotensive patients with acute pulmonary embolism in the Netherlands: a cost analysis

Stephan V. Hendriks, Wilbert B. van den Hout, Thomas van Bemmel, Ingrid M. Bistervels, Michiel Eijsvogel, Laura M. Faber, Herman M.A. Hofstee, Tom van der Hulle, Antonio Iglesias del Sol, Marieke J.H.A. Kruip, Albert T.A. Mairuhu, Saskia Middeldorp, Mathilde Nijkeuter, Menno V. Huisman and Frederikus A. Klok, *for the YEARS investigators*

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ABSTRACT

Background: Venous thromboembolism constitutes substantial healthcare costs amounting to about 60 million euros per year in the Netherlands. Compared to initial hospitalization, home treatment of pulmonary embolism (PE) is associated with a cost reduction. An accurate estimation of cost savings per patient treated at home is currently lacking.

Aim: The aim of this study was to compare healthcare utilization and costs during the first 3 months after a PE diagnosis in patients who are treated at home versus those who are initially hospitalized.

Methods: Patient-level data of the YEARS cohort study, including 383 normotensive patients diagnosed with PE, was used to estimate the proportion of patients treated at home, mean hospitalization duration in those who were hospitalized and rates of PE-related readmissions and complications. To correct for baseline differences within the two groups, regression analyses was performed. The primary outcome was the average total healthcare costs during a 3-month follow-up period for patients initially treated at home or in hospital.

Results: Mean hospitalization duration for the initial treatment was 0.69 days for those treated initially at home (n=181) and 4.3 days for those initially treated in hospital (n=202). Total average costs per hospitalized patient were €3.209 and €1.512 per patient treated at home. The adjusted mean difference was €1,483 (95%CI €1,181 – 1,784).

Conclusions: Home treatment of hemodynamically stable patients with acute PE was associated with an estimated net cost reduction of €1,483 per patient. This difference underlines the advantage of triage-based home treatment of these patients.

INTRODUCTION

Venous thromboembolism (VTE), consisting of pulmonary embolism (PE) and deep vein thrombosis (DVT), constitutes a major global health issue. It represents the third leading cause of vascular disease with nearly 10 million annual cases worldwide.[1-3] Therefore, the yearly economic burden of VTE is substantial. In the Netherlands costs of VTE related medical care in 2015 amounted to nearly 60 million euros, not including the costs of VTE-associated intensive care admissions, which accounted for another 8 million euro.[4]

Home treatment of VTE is associated with improvement of quality of life and prevention of hospital overcrowding. Moreover, the potential reduction of healthcare costs is a frequently suggested argument in favor of home treatment compared to initial hospitalization.[5,6] For DVT, the strategy to treat patients at home has been widely accepted since the introduction of low molecular weight heparins.[7,8] For PE, there has been a change over the last decade, as the safety and feasibility of home treatment have been shown in several large trials.[9-16] With the recent introduction of direct oral anticoagulants (DOACs) that have a better safety profile than conventional anticoagulants[17], the threshold to treat a PE patient at home has been further lowered.[18] A reduced length-of stay and resultant decrease in total hospital costs in patients treated with a DOAC has already been demonstrated.[19-21] An accurate estimation of cost saving per patient when choosing for home treatment is currently however still lacking.

We therefore aimed to evaluate the healthcare utilization and medical costs of home treatment compared to initial hospitalization in the treatment of acute PE in the setting of Dutch clinical practice.

METHODS

Patient selection

This was a post-hoc analysis of the YEARS study, performed in 12 academic and non-academic centers across the Netherlands.[22] For the present analysis, data of all normotensive outpatients who were diagnosed with acute PE and in whom home treatment may have been considered were studied, reflecting daily practice circumstances. The YEARS study was a prospective, multicenter, diagnostic management study between October 2013 to July 2015 in the Netherlands that aimed to validated the safety and efficacy of the YEARS algorithm in the diagnostic management of suspected PE.[22] Patient level data from the YEARS study was used to estimate the mean hospitalization duration of patients with confirmed PE, as well as the rates of PE-related scheduled and unscheduled readmissions. Further, we extracted details of home treatment and discharge from the original patient charts. Lastly, demographic data of PE patients in the YEARS cohort was used to adjust the health economic model for baseline characteristics and to estimate pharmaceutical costs.

Study objectives and outcomes

The primary aim of this study was to compare healthcare utilization and costs of normotensive PE patients treated at home to those treated initially in hospital. The primary outcome of this analysis was the amount of average total healthcare costs during a 3-month follow-up period.

Definitions

Acute PE was defined as intraluminal filling defects of the subsegmental or more proximal pulmonary arteries confirmed by computed tomographic pulmonary angiography (CTPA).[23] Home treatment was defined as hospital discharge within 24 hours after diagnosis of VTE. A PE-related readmission was defined as any scheduled or unscheduled visit to the outpatient clinic, emergency room or readmission in hospital due to PE-related complications, such as thoracic pain, dyspnea, major bleeding, clinically relevant non-major bleeding or (suspected) recurrent VTE.

Medical costs are reported in Euros at price level 2018 (updated using the general consumer price index, if necessary) and include pharmaceutical, radiological, and hospital costs. These reference prices are designed to reflect realistic costs and to standardize health-economic evaluations in the Netherlands.

Pharmaceutical costs

For the calculation of medication costs in the 3-month period following the PE diagnosis, we included the costs of the medication itself (including VAT) and an additional €6 pharmacy delivery costs per regular delivery.[24] Deductibles were not included in this analysis as they have to be paid by the patients themselves and are the same for both the in-hospital and outpatient treated patients. Because no individual data on types of anticoagulant were available, data on anticoagulant use were obtained from IQVIA's Real-World Data Longitudinal Prescription database (LRx, Amsterdam, The Netherlands). From anonymous patient prescription records, data on basic patient characteristics, dispensing (e.g. pharmacy, prescription date and duration), medication (e.g. generic and brand name, dosage, dosing regimen) and prescriber information were collected. The database covers approximately 75% of all prescriptions dispensed in the Netherlands, represented by both retail pharmacies and dispensing general practitioners. The price per day of apixaban use was €4.49 for the first 7 days and €2.25 thereafter. For rivaroxaban the price per day was €4.71 for the first 21 days and €2.35 thereafter. The prices per day of dabigatran and edoxaban were €2.44, with a recommended prior 5 day use of low molecular weight heparin (LMWH). For the cost of vitamin k antagonists (VKA), we included €0.09 per day, plus a 7-day run-in period with LMWH. The price of LMWH was based on the price of nadroparin, the most used LMWH in the Netherlands.[25] We used the price per day of €10.34, for a 0.8mL 19,000IE/mL syringe, closest to the recommend 171 IE/ml per kilogram for an average weight of 86 kilograms, derived as mean weight from the YEARS study cohort.[22]

Additional costs when carrying out vitamin K antagonist controls were obtained from annual reports of the Dutch thrombosis service and included the average annual costs for diagnostics and treatment in a primary care setting. For the patients with venous thromboembolism the yearly average additional costs were €333, corresponding with a 3-month costs of €83. We conservatively assumed no cost difference for treatment options and monitoring of VKA when initial therapy was started in a clinical setting or at home.[26]

Radiological costs

The costs of radiological imaging were set at € 183 and € 43 per CTPA and chest X-ray respectively.[27,28] Every PE patient in the YEARS study was diagnosed with CTPA. X-ray testing had been performed in 86% of all patients diagnosed with PE in the initial diagnostic assessment.[29]

Laboratory costs

Laboratory costs were obtained by the price level 2018 (updated using the general consumer price index, if necessary) and were derived from laboratory analysis of the 12 academic and non-academic centers and included costs for: complete blood count, kidney function, liver function, electrolytes, inflammatory markers and d-dimer.

Hospital costs

Hospital days, outpatient visits and emergency visits were valued in accordance with the reference prices from the Dutch guidelines for economic evaluations in health care, at €495, €95 and €269 respectively. This includes costs for administration, specialist time and nursing care.[27,28] Estimated hospital costs did not include ICU care, since patients with high-risk PE were not included in the YEARS study and these patients cannot be treated at home. Total hospital costs were based on the average costs per hospital day multiplied by the length of stay, as diagnosis-related group based reimbursement systems in the Dutch healthcare setting have to the substantiated with interventions and days of admission to reach to the total amount of costs.

The proportion of patients who needed an unscheduled visit to the ER or outpatient clinical ward was obtained from a post-hoc analysis of the YEARS study.[30] If patients were readmitted, we assumed a mean readmission duration of 5.0 days, obtained from previous publications.[31] The price per day for a readmission was assumed equal to the initial hospitalization. To calculate the number of planned outpatient clinic visits, we used the hospitals protocol for VTE management for patients after home treatment or initial hospitalization. As detailed data was lacking, we could not take visits to the general practitioner into account.

Statistical analysis

Total medical costs were calculated for each patient in the YEARS study cohort. For the presentation of the baseline characteristics, categorical data are presented as percentages or

as proportion and continuous variables as means with standard deviation (SD). To compare average costs of home treatment to initial hospitalization, costs for the mean hospitalization duration were compared for both treatment modalities. In multivariate analysis we will provide the adjusted cost differences with a 95% confidence interval as well as adjusted p-values for significance. To correct for baseline differences within the two groups, regression analyses will be performed to estimate a proper estimation between those initially treated at home or after hospitalization. We also planned a sensitivity analysis restricted to those patients who were admitted but discharged after 2 and 3 days, respectively, as these are likely patients that are most comparable to those treated at home. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

RESULTS

Study patients

Of all 383 normotensive patients diagnosed with PE, 181 (47%) were treated at home. Overall, the mean age was 59 years (standard deviation (SD) 17), 50% was female and 12% had active malignancy at time of diagnosis. Patients initially treated at home were younger with a mean age of 56 years versus 62 years in those initially hospitalized (mean difference 6.9 years (95%CI 3.6-10.2)), and the prevalence of cardiopulmonary comorbidity was higher among those with initial hospitalization. Other baseline patient characteristics between those treated at home and initially hospitalized were comparable. Of note, relevant inter-hospital differences were observed in the proportion of patients treated initially at home treatment with percentages ranging from 13% to 83%.

Healthcare utilisation

All patients diagnosed with acute PE visited the emergency room at initial diagnosis and were subjected to laboratory testing and CTPA. The mean hospitalization duration of those treated at home was 0.69 days, whereas patients with initial hospitalization had a mean hospitalization duration of 4.3 days. The 3-month rate of total PE-associated unscheduled readmissions in patients treated at home was 9.7% versus 8.6% for initially hospitalized patients. Proportions for each type of unscheduled visit are shown in **table 1**. As part of the hospitals' VTE management protocol, all patients who required in hospital care were followed at the outpatient clinic two times at week 6 and after 3 month. For those with initial home treatment, an additional visit in the first two weeks after the index event was scheduled. The most frequent prescribed anticoagulant was rivaroxaban (56%), followed by apixaban and VKA (both 17%). Dabigatran and edoxaban were each prescribed in 5% of patients .

Healthcare costs

Initial costs for an emergency room visit with subsequent laboratorial costs were €269 and €35, respectively, independent of initial treatment modality. Average total radiological costs for each patient amounted to €220. An overview of the pharmaceutical costs are provided in **table 2.** Average hospital admission costs per patient were € 342 for home treatment compared to average cost per patient treated initially in hospital of € 2,148. Readmission costs were calculated separately for hospital readmissions, emergency room visits or unscheduled visits to the outpatient clinic. An overview of these specific extra costs are summarized in **table 2.** No relevant differences were found in total readmission costs for home treatment compared to initial hospitalization, for a mean difference of €34 (95%CI €-79 to €146).

Primary outcome

Total average costs per hospitalized patient were €3,209 and €1,512 per patient treated at home. Thus, the crude average reduction per PE patient in a 3-month follow-up period was €1,697 when selecting for home treatment. The adjusted mean difference was €1,483 (95%CI €1,181 - €1,784).

We also performed sensitivity analyses for those with a mean admission duration of two or three days, and still found considerable mean differences compared to home treatment: the adjusted mean differences were €414 (95%CI €268 - €560) and €1,115 (95%CI €900 - €1,330) respectively.

DISCUSSION

In this analysis we estimated a €1,483 reduction per acute normotensive PE patient if they were treated at home, instead of initial hospitalization. The decrease in total costs was adjusted for relevant patient characteristics and mainly driven by the reduction in costs for hospital admission. No relevant differences were found in costs for pharmacological treatment and readmissions in patients with home treatment versus those with initial hospitalization.

Global growth in healthcare expenditure demands effective cost-containment policies to keep healthcare payable. Introducing home treatment of PE as standard of care is likely to result in considerable cost savings. For example, it is estimated that US health care costs could be reduced by $1 billion per year if home treatment would have been applied properly.[32] These numbers reflect an US perspective, with globally the highest healthcare costs and also with early hospital discharge initiated in the vast minority of all PE patients.[5] Our data support these US data by showing that significant healthcare cost reductions can be realized by treating PE patients at home. Current evidence suggests that as much as 30% to 55% of patients with acute PE could be selected for home treatment, which could lead to a considerable global cost reduction.[32,33]

Table 1: Baseline characteristics and outcome for patients with acute pulmonary embolism of the YEARS study

		Home treatment (n=181)	Initial hospitalization (n=202)
Demographics			
Age, mean (SD)		56 (16)	62 (16)
Male sex, no (%)		92 (51)	96 (49)
Weight in kg, mean (SD)		85 (17)	86 (18)
Body Mass Index, mean (SD)		28 (5.4)	28 (5.3)
VTE risk factors			
COPD (%)		6 (3.3)	13 (6.6)
Heart failure (%)		2 (1.1)	6 (3.1)
Previous VTE no. (%)		49 (27)	41 (21)
	DVT	19 (11)	13 (6.6)
	PE +/- DVT	26 (14)	28 (14)
Estrogen Use (%)		23 (13)	17 (8.7)
Active malignancy no. (%)		20 (11)	26 (13)
Treatment			
Admission days, no (%)			
	0	56 (31)	
	1	125 (69)	
	2		62 (32)
	3		51 (26)
	4		21 (11)
	5		23 (12)
	6-28		38 (19)
	>28		1 (0.5)
Readmissions, no (%)			
	outpatient visit	-	2 (1.0)
	ER visit	9 (5.0)	7 (3.6)
	Admission	9 (5.0)	9 (4.6)
Diagnostic imaging performed for suspected VTE recurrence, no (%)		3 (1.7)	3 (1.5)
Major bleeding , no (%)		4 (2.2)	4 (2.0)

Abbreviations: PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism; DVT, Deep vein thrombosis
Data of admission days was 7 missing for seven patients

This is the first analysis focusing on costs in a detailed patient level with an accurate estimation of costs per patient. The validity and robustness of our model depends on the impact of uncertainties in key input variables. First of all, not all PE patients are candidates for home treatment. Even despite the fact that high-risk PE patients were not taken into account, not all patients who were admitted were candidates for home treatment, which is among others

Table 2: Average healthcare utilization and costs during a 3-month follow-up period, for patients initially treated at home or in hospital

Type of healthcare		Unit price	Home treatment		Hospitalization		Cost difference	Adjusted cost difference*	95% CI	p-value adjusted
			Volume	Costs	Volume	Costs				
Initial ER visit		€ 269	1	269	1	€ 269	-	-	-	-
Laboratory testing		€ 35	1	€ 35	1	€ 35	-	-	-	-
Radiological imaging	X-ray	€ 43	0.88	€ 38	0.88	€ 37.4	€ 0.03	€ 2.5	-0.7 – 5.7	0.13
	CTPA	€ 186	1	€ 186	1	€ 186	-	-	-	-
Room and board		€ 495	0.69	€ 342	4.34	€ 2,148	€ -1,806	€ -1.612	-1,900 to -1,324	< 0.001
Pharmacy		€ 228	1	€ 228	1	€ 228	-	-	-	-
PE-related readmission	Admission	€ 2,475	0.05	€ 124	0.046	€ 113	€ 11	€ 55	-55 – 164	0.33
	ER	€ 269	0.05	€ 13	0.036	€ 9	€ 4	€ -2.6	-15 – 10	0.68
	Outpatient visit	€ 95	-	0	0.01	€ 1	€ 1	€ 0.8	-2.4 – 0.78	0.31
Outpatient clinic		€ 95	3	€ 285	2	€ 190	€ 95	-	-	-
All costs				**€1,512**		**€ 3,209**	**€ -1,697**	**€ -1,483**	**€-1,784 to -1,181**	**< 0.001**

Abbreviations: CI, confidence interval; ER, emergency room; PE, pulmonary embolism; CTPA, computed tomography pulmonary angiogram

* Adjusted for : age, gender, COPD, heart failure, kidney injury, malignancy, tachycardia, oxygen administration

Definitions:

Heart failure: A history of known heart failure requiring active treatment

Kidney injury: MDRD < 60ml/min

Malignancy: Active cancer was defined as a diagnosis of cancer that occurred within 6 months before the diagnosis of index VTE (excluding basal-cell or squamous-cell carcinoma of the skin), or any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer

Tachycardia: Heart rate > 100 beats/min

shown by relevant differences in baseline characteristics. These differences reflect the selection of PE patients by the Hesta criteria, selecting lower-risk PE patients eligible for home treatment.[11] With regression analysis we performed a correction for relevant baseline characteristic differences, but we acknowledge that still some degree of residual confounding may be present. Comorbid conditions that may prolong the hospital stay, e.g. delirium, were not available in the original YEARS database, and could therefore have a potential effect on the cost difference between patients treated at home or in the hospital. Even so, we think that our present cost estimate is accurate. Moreover, the clear heterogenicity of initiated home treatment between hospitals (ranging from 13% to 83%) suggest the eligibility of home treatment in a considerable proportion of PE patients with current hospitalization, which is favorable to the validity our analysis. Due to the design of our study, it was not possible to distinguish hospitalized patients who may have been candidates for home treatment from those who were not. Therefore, we performed sensitivity analysis for PE patients with a short hospitalization duration, in which still considerable cost savings were calculated.

Secondly, readmission costs did not include costs for the treatment of adverse events, i.e. major bleeding or recurrent VTE, which could underestimate the total readmission costs. However, adverse events occurred similarly in both groups and costs for readmission will largely be determined by the length of hospital admission, which was taken into account. Considering the comparable readmission rates between each initial treatment strategy, we think that our present cost estimate is reasonably accurate.

Thirdly, we could not provide differences in pharmaceutical costs between patients treated initial in hospital or at home due to lack of detailed data on medication use. However, total pharmaceutical costs were relatively low compared to the other costs and potential excessive differences within this category between both initial treatment strategies are not expected. Therefore we do not think no major changes in outcome for this analysis are expected.

Lastly, this analysis reflects a the Dutch health care setting. Cost estimates of hospitalization for VTE vary by country; for example, a study estimating costs per hospitalization for PE estimated the cost to be over $8700 in the US (where healthcare costs are generally highest globally) and over €3400 in Italy and Belgium.[34] Therefore, the generalizability of this analysis remains to be proven. We have provided our cost analysis calculator in the supplementary materials to be adapted based on local circumstances elsewhere.

To our knowledge this is the first economic comparison for home treatment of PE patients in the current literature. Strengths of this analysis include the detailed estimation of costs per patient working towards total average costs. In contrast to most research on health care and health economics using ICD-10 codes to select for patient eligibility, our database does not contain flaws caused by imperfect coding practice. Further, with patient data of both academic and non-academic centres, including smaller and larger peripheral hospitals, we consider our results representative for a daily practice cohort in the Netherlands. Lastly, although these results must be interpreted within the framework and limitations of findings of the YEARS study,

a management study with possible underrepresentation of high-risk subgroups, the YEARS algorithm was implemented as standard diagnostic strategy in all participating hospitals. Therefore, we consider the YEARS study patients representative.

In conclusion, home treatment of hemodynamically stable patients with acute PE was estimated to result in a net cost reduction of €1,483. Although, this could be a slight overestimation of real cost difference, it certainly shows the potential for major cost savings on regional or national level, if patients eligible for home treatment for acute PE are not hospitalized. Of note, we only included direct medical costs in this analysis, indirect medical costs (e.g., loss of productivity in hospitalized patients) would probably further increase the cost difference between patient treated initially in-hospital or as outpatient. 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.

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10

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.

II

Nederlandse samenvatting

Dit proefschrift beschrijft verschillende studies die gericht zijn op het verbeteren van de risicostratificatie van thuisbehandeling bij patiënten met een longembolie. Daarnaast beschrijft dit proefschrift de huidige situatie van thuisbehandeling bij patiënten met een longembolie in de Nederlandse praktijk en is het gericht op de veiligheid van antistolling bij de behandeling van een longembolie. Tenslotte wordt een overzicht gegeven van de mogelijkheid van thuisbehandeling bij mensen met een veneuze trombo-embolie (VTE) en kanker. **Hoofdstuk 1** bevat een algemene introductie over longembolieën en de toekomstperspectieven in de behandeling van longembolieën.

DEEL 1. RISICO-INSCHATTING VAN THUISBEHANDELING BIJ PATIËNTEN MET EEN ACUTE LONGEMBOLIE

Hoofdstuk 2 geeft een overzicht van de recente ontwikkelingen op het gebied van thuisbehandeling bij patiënten met een longembolie in de laatste decade. Daarnaast beschrijft dit hoofdstuk de huidige methodes die worden gebruikt om mensen te selecteren voor thuisbehandeling. Patiënten met een longembolie werden voorheen in het ziekenhuis behandeld vanwege de noodzaak tot parenterale toediening van antistolling. Ondanks verbeteringen in de risicostratificatie en de introductie van de directe orale anticoagulantia (DOAC's) wordt thuisbehandeling echter nog steeds niet op grote schaal toegepast, terwijl wordt geschat dat 30 tot 50% van alle patiënten met een longembolie veilig thuis behandeld kunnen worden. In dit overzicht wordt een grote variatie in lengte van ziekenhuisopnames in Europa beschreven. Dit toont aan dat de keuze voor thuisbehandeling of ziekenhuisopname niet puur gebaseerd is op enkel patiëntkenmerken en risicostratificatie, maar ook sterk afhankelijk is van locoregionale voorkeuren. De belangrijkste onderzoeken van thuisbehandeling worden besproken en inzicht wordt gegeven in de optimale strategie om patiënten met een longembolie te selecteren voor thuisbehandeling. In het kort, er worden momenteel twee gevalideerde klinische beslisregels gebruikt om te selecteren voor thuisbehandeling. Als eerste de Pulmonary Embolism Severity Index (PESI) -score of de versimpelde versie (sPESI) ervan, die de kans op overlijden binnen 30 dagen voorspelt bij gehospitaliseerde patiënten met een longembolie. Ten tweede de Hestia-criteria, een klinische beslisregel die rechtstreeks patiënten selecteert die veilig thuis kunnen worden behandeld. Andere risicoscores zoals de BOVA- en FAST-risicoscores zijn zowel niet extern als in uitkomstonderzoeken gevalideerd en kunnen derhalve niet worden toegepast.

In de twee volgende hoofdstukken onderzochten we eventuele verbeteringen in risicostratificatie bij patiënten die in aanmerking komen voor thuisbehandeling. In **hoofdstuk 3** is gekeken naar de toegevoegde prognostische waarde van een cardiale biomarker, troponine-T additioneel aan de Hestia-criteria in een cohort van 347 thuis behandelde longembolie patiënten. Het troponine-T was verhoogd bij 58 patiënten (17%). We hebben gekeken naar ongewenste uitkomsten binnen een periode van 30 dagen, gedefinieerd als cumulatieve incidentie van hemodynamische

instabiliteit, IC opname en overlijden als gevolg van een longembolie of ernstige bloeding. Deze ongewenste uitkomsten traden op bij één van de 58 (1,7%) longembolie patiënten met een verhoogde troponine-T waarde versus twee van de 289 (0,70%) patiënten met normale waarden. Dit verschil was niet significant vanwege het zeer lage totaal aantal ongewenste uitkomsten en de brede betrouwbaarheidsintervallen. Hoewel dit de belangrijkste beperking was in dit cohort, veroorzaakt door de sterke preselectie van de Hestia-criteria, bevestigde dit resultaat wel de kracht van deze klinische beslisregel om de juiste longembolie patiënten met een laag risico te selecteren voor thuisbehandeling. Bovendien sluit een normale troponine-T waarde niet uit dat er longembolie geassocieerde complicaties plaatsvinden. Tenslotte bleek dat patiënten met een verhoogd troponine-T geen significant hoger risico hadden op overlijden: één patiënt met een verhoogde troponine waarde (1,7%) versus vijf patiënten met normale waarde (1,7%) overleden (odds ratio van 1.0; 95% betrouwbaarheidsinterval (BI) 0.11-8.7). Daarom kon de toegevoegde prognostische waarde van troponine-T bovenop de Hestia-criteria voor het selecteren van longembolie patiënten voor thuisbehandeling niet worden vastgesteld.

In aanvulling op de combinatie van een cardiale biomarker met een klinische beslisregel, kan beeldvormend onderzoek ook worden gebruikt voor de identificatie van laagrisico patiënten. In de volgende twee hoofdstukken wordt de toegevoegde waarde van rechterkamer overbelasting, beoordeeld op computertomografie met pulmonaire angiografie, verder onderzocht als hulpmiddel bij de risicostratificatie voor de ernst van longembolieën. In **Hoofdstuk 4** hebben we de incidentie van CT-gemeten rechter ventrikel (RV) overbelasting onderzocht en de impact hiervan op klinische uitkomsten van thuis behandelde longembolie patiënten op basis van afwezigheid van de Hestia-criteria. Hiervoor werd een grote post-hoc analyse uitgevoerd op individueel patiëntniveau uit de gecombineerde databases van de prospectieve Hestia en Vesta studies. De studie omvatte in totaal 1474 patiënten, waarvan 752 thuis werden behandeld. Hiervan hadden 225 patiënten (30%) een Rechter Ventrikel/ Linker ventrikel (RV/LV)- diameterverhouding boven de 1,0. De incidentie van ongewenste uitkomsten, oftewel terugkerende VTE en mortaliteit, was 2,7% bij degenen met een RV/LV-diameterverhouding van boven de 1,0 die thuis werden behandeld, vergeleken met 2,3% bij patiënten met een normale RV/LV-ratio, resulterend in een Odds Ratio van 1,2 (95% BI 0,44-3.2). Uit de groep thuis behandelde patiënten met een ongewenste uitkomst stierven vijf (2,2%) patiënten met een RV/LV-diameterverhouding > 1,0, vergeleken met vijf patiënten (0,9%) zonder tekenen van RV-dilatatie. Bij nadere beschouwing van de overlijdens bij de thuis behandelde patiënten met tekenen van RV dilatatie, hadden vier van de vijf patiënten een uitgezaaide maligniteit en alle sterfgevallen vonden plaats na de eerste 14 dagen na de diagnose. Deze bevindingen tonen impliciet aan dat een standaard beoordeling van de RV-functie niet verplicht zou moeten zijn in de behandelstrategie van alle patiënten met een laag risico op longembolie.

Van alle Hestia-items is er één subjectief, d.w.z. "medische of sociale reden voor behandeling in het ziekenhuis gedurende meer dan 24 uur", waardoor de behandelend arts alle patiënt specifieke omstandigheden kan meewegen in de uiteindelijke beslissing.

In **hoofdstuk 5** hebben we de redenen voor ziekenhuisopname volgens de Hestia-criteria geëvalueerd. Specifiek hebben we de redenen voor de toepassing van het subjectieve Hestia-criterium onderzocht. Daarnaast hebben we geëvalueerd of beoordeling van de ernst van de longembolie relevant is bij het toekennen van het subjectieve Hestia-criterium als argument voor ziekenhuisopname. Van de 600 opgenomen patiënten was de meest voorkomende reden voor ziekenhuisopname de noodzaak tot zuurstof toediening (45%), terwijl 38% werd opgenomen uitsluitend op basis van het subjectieve Hestia-criterium. Bij de nadere analyse van deze groep werd bij 22% de longembolie als te ernstig beoordeeld om thuisbehandeling te overwegen: die 22% had een aanzienlijk hogere RV/LV-ratio (gemiddelde verschil +0.30, 95% BI 0.19-0.41) evenals een hogere hartslag (+18/min, 95% BI 10-25) ten opzichte van de thuis behandelde patiënten met RV-dilatatie. Deze observatie suggereert dat het hemodynamisch profiel van een patiënt, d.w.z. de ernst van RV-dilatatie en de resulterende hemodynamische respons in plaats van alleen een abnormale RV/LV-ratio, intrinsiek wordt meegenomen in de beslissing om patiënten in het ziekenhuis of thuis te behandelen bij het toepassen van de Hestia-criteria.

DEEL II. HUIDIG BELEID IN THUISBEHANDELING EN DE VEILIGHEID VAN ANTICOAGULANTIA BIJ LONGEMBOLIEËN

De trend in het afgelopen decennium was om longembolie patiënten met een laag risico op vroege ongewenste uitkomsten thuis te behandelen. Gesuggereerd wordt dat tot 55% van de patiënten met een acute longembolie in aanmerking kan komen voor ambulante behandeling. Deze percentages zijn echter gebaseerd op prospectieve uitkomststudies juist gericht op thuisbehandeling.

In **Hoofdstuk 6** evalueren we derhalve het huidige beleid in de praktijk en de uitkomst van thuisbehandeling van patiënten met een longembolie in 12 Nederlandse ziekenhuizen. In deze post-hoc analyse van de YEARS-studie, een prospectieve, multicenter, diagnostische managementstudie, werd bij in totaal 456 patiënten een longembolie gediagnosticeerd. We zagen dat 46% van alle patiënten met een longembolie thuis werden behandeld. De overige 54% werd in het ziekenhuis behandeld met een mediane opnameduur van 3,0 dagen (interkwartielafstand 2,0-5,0). Interessant is dat er relevante verschillen waren tussen ziekenhuizen onderling, met het percentage thuisbehandeling variërend van 13% tot 83%. De incidentie van nadelige uitkomsten voor degenen die thuis werden behandeld was laag (3,8%), uitgesplitst in twee terugkerende veneuze trombo-embolieën, drie ernstige bloedingen en twee niet-longembolie-gerelateerde overlijdens. Bovendien was het percentage longembolie-geassocieerde ongeplande heropnames niet verschillend tussen patiënten die initieel thuis of in het ziekenhuis werden behandeld (ruwe hazard ratio (HR) van 1,1 (95% BI 0,57-2,1)). Deze bevindingen ondersteunen de grootschalige trend om patiënten met een longembolie thuis te behandelen.

In de huidige literatuur is het bewijs voor de behandeling van patiënten met kanker en VTE in de thuissetting zeer schaars, aangezien alle thuisbehandelstudies slechts een kleine minderheid van patiënten met kanker geassocieerde VTE hebben geïncludeerd. Volgens de sPESI score worden alle patiënten met kanker als hoog risico op complicaties en overlijden gecategoriseerd, wat inhoudt dat al deze patiënten in eerste instantie in een ziekenhuisomgeving moeten worden behandeld.

Hoofdstuk 7 geeft een overzicht van thuisbehandeling bij patiënten met kanker-geassocieerde VTE in de Nederlands praktijk en de nadelige effecten hiervan. Van de 183 patiënten bij wie een kanker-geassocieerde VTE werd vastgesteld, hadden 114 een longembolie (± diep veneuze trombose (DVT)) en 69 hadden een DVT. Thuisbehandeling werd gestart bij 83% van de patiënten met een kanker-geassocieerde DVT en in 55% van de gevallen met kanker-geassocieerde longembolieën. VTE-gerelateerde mortaliteit binnen een follow-up periode van 3 maanden trad op bij 2 patiënten die thuis werden behandeld (1,7%) en bij 5 patiënten die initieel in het ziekenhuis werden behandeld (7,9%; ruwe HR 0,32; 95% BI 0,06-1,6). In de thuis behandelde groep kregen vier patiënten (3,3%) een symptomatisch recidiverende VTE tijdens de follow-up versus 6 patiënten die aanvankelijk gehospitaliseerd werden (9,5%; ruwe HR 0,33; 95% BI 0,09-1,2). De meest nadelige uitkomst bij de groep thuis behandelde patiënten was echter het aantal ernstige bloedingen (n=10, 8,6%), die optraden na de eerste 14 dagen na diagnose. De meerderheid van deze bloedingen was gerelateerd aan de lokalisatie van de tumor zonder bewijs van doorgeschoten antistolling. Bovendien ontstonden de meeste bloedingen lang na de gemiddelde opnameduur van de opgenomen patiënten. Daarom is het onwaarschijnlijk dat deze bloedingen voorkomen hadden kunnen worden door een initiële ziekenhuisopname. Alles in overweging nemend, waren de percentages van bijwerkingen hoog, maar onafhankelijk van de initiële behandeling in het ziekenhuis of thuis. Deze studie toonde aan dat thuisbehandeling een goede optie zou kunnen zijn voor geselecteerde patiënten met kanker-geassocieerde DVT en/of longembolie.

Hoofdstuk 8 was gericht op het onderzoeken van de veiligheid van apixaban in een praktijkgerichte setting bij patiënten die meestal thuis werden behandeld. Van de 671 opeenvolgende VTE-patiënten die met apixaban werden behandeld, werden 371 gediagnosticeerd met een longembolie en 300 patiënten hadden een DVT. Tijdens een follow-up periode van drie maanden hadden twee patiënten (0,3%) last van recidiverende VTE, kregen 12 patiënten (1,8%) ernstige bloedingen en overleden 11 patiënten (1,6%). Van de overleden patiënten hadden er zeven (64%) een actieve maligniteit. Alle zeven overleden na aanvang van palliatieve zorg thuis of in een hospice vanwege een eindstadium van de gemetastaseerde ziekte. Het meest opvallende verschil in deze analyse in vergelijking met de fase 3 Amplify-studie was de incidentie van ernstige bloedingen: respectievelijk 1,8% gedurende een periode van 3 maanden versus 0,6% tijdens een follow-up van 6 maanden. Zowel de werkzaamheid als het aantal bloedingen kan worden onderschat in fase 3-onderzoeken, omdat patiënten met een hoger risico op bloedingen over het algemeen worden geëxcludeerd. Dit onderzoek bevestigt daarom het belang van dagelijkse

praktijkevaluatie en het feit dat resultaten van fase-3 klinisch onderzoek niet één op één kan worden vertaald naar de dagelijkse praktijk.

In **hoofdstuk 9** hebben we de economische impact van thuisbehandeling beoordeeld. Kostenreductie is een vaak genoemd argument voor thuisbehandeling, maar een nauwkeurige schatting van een eventuele kostenbesparing per patiënt ontbreekt momenteel nog in de literatuur. In deze analyse, met behulp van gedetailleerde patiëntgegevens van de YEARS-studie, werd een reductie van € 1.483 geschat per acute normotensieve patiënt met een longembolie indien thuisbehandeling werd geïnitieerd in plaats van een ziekenhuisopname. De daling van de totale kosten werd voornamelijk gedreven door lagere kosten voor ziekenhuisopname. Omdat de veiligheid en haalbaarheid van thuisbehandeling al is bewezen bij zorgvuldig geselecteerde patiënten met een longembolie, onderstreept dit verschil het voordeel van op triage gebaseerde thuisbehandeling van deze patiënten.

TOEKOMSTPERSPECTIEF

De risicostratificatie bij patiënten met een longembolie die in aanmerking komen voor thuisbehandeling is de afgelopen decennia sterk geëvolueerd. De introductie van klinische beslisregels heeft de mogelijkheid gecreëerd om patiënten te selecteren voor thuisbehandeling. Daarbij worden (beeldvormende) biomarkers aanbevolen om deze risicostratificatie verder te optimaliseren. De introductie van DOAC's, inclusief hun meer praktische toepasbaarheid, heeft ervoor gezorgd dat de drempel voor de behandelend arts om een patiënt met een longembolie patiënt thuis te behandelen verder is verlaagd. Het uitgebreide en toenemende gebruik van DOAC's zal in de nabije toekomst waarschijnlijk meer thuisbehandeling initiëren. Dit zal eveneens zeer relevant worden voor mensen met kanker-geassocieerde VTE, aangezien recente grote fase III-onderzoeken, HOKUSAI-VTE CANCER trial en CARAVAGGIO trial, de mogelijkheid van DOAC-gebruik in deze specifieke subgroep heeft aangetoond. Waarschijnlijk worden DOAC's in de nabije toekomst de eerstelijnstherapie voor mensen met kanker-geassocieerde VTE.

De optimale strategie om patiënten te identificeren voor thuisbehandeling, wordt verder onderzocht met de HOME-PE-studie, die tot doel had twee klinische beslisregels, de sPESI en de Hestia-regel, te vergelijken om kandidaten te selecteren voor vroegtijdig ontslag. Ondanks dat bij meer patiënten in de sPESI-groep dan in de HESTIA-groep werd afgeweken van de triagebeoordeling voor thuisbehandeling door de verantwoordelijk arts, werd bij meer dan een derde van de patiënten thuisbehandeling gestart met daarbij een lage incidentie van complicaties. Een vergelijkbare veiligheid en werkzaamheid werd aangetoond voor de strategie op basis van de Hestia-regel versus de strategie op basis van sPESI, waarbij de Hestia-regel oudere patiënten en patiënten met actieve kanker niet a priori uitsluit van thuisbehandeling.

Verder prospectief onderzoek is nodig met betrekking tot de aanvullende rol van cardiale biomarkers en beeldvormende biomarkers in combinatie met klinische beslisregels. In het al-

gemeen zal het toevoegen van cardiale biomarkers en/of de beoordeling van rechterventrikel disfunctie aan klinische criteria waarschijnlijk de gevoeligheid van de risicostratificatie verhogen ten koste van een lagere specificiteit, d.w.z. leidend tot meer patiënten met een lager risico die worden geselecteerd voor thuisbehandeling, maar ook leidend tot een toename van het aandeel van patiënten dat wordt opgenomen in een ziekenhuis. Om het voortdurende debat over de relevantie van selectie van patiënten met een rechterventrikeldisfunctie voor thuisbehandeling te beantwoorden, zal een gerandomiseerde studie moeten worden gestart die zich richt op patiënten met een laag risico op bijwerkingen, dwz patiënten zonder Hestia-criteria, maar een RV/LV-ratio > 1. Het onderzoek moet worden opgezet als een non-inferioriteitsonderzoek met een primair eindpunt gericht op vroege bijwerkingen, bijv. symptomatisch terugkerende VTE, longembolie-gerelateerde overlijdens binnen een maand, hemodynamische instabiliteit, IC-opnames en het aantal heropnames als gevolg van VTE.

Naast het identificeren van de optimale selectie voor patiënten die in aanmerking komen voor thuisbehandeling, kan eveneens de behandeling van sommige aspecten van longembolie worden verbeterd. In dit proefschrift hebben we aangetoond dat 9,7% van alle thuis behandelde patiënten met een longembolie opnieuw wordt opgenomen vanwege longembolie-gerelateerde problemen, met thoracale pijn als de meest voorkomende reden. Daarentegen zijn er momenteel geen duidelijke richtlijnen beschikbaar voor de optimale farmacologische behandeling van thoracale pijn bij deze patiënten, waarschijnlijk veroorzaakt door pleuritis. Een prospectieve studie ter evaluatie van pijnbestrijding, waarbij niet-steroïde middelen worden vergeleken met opiaten, kan hierbij helpen. Betere kennis over de preventie en optimale behandeling van aanhoudende pijn op de borst leidt waarschijnlijk tot een hogere patiënttevredenheid en lagere zorgkosten, dit laatste gedreven door minder heropnames.

Ten slotte is het te verwachten dat met de opkomende opties in eHealth een betere monitoring van thuis behandelde patiënten zal worden geïntroduceerd. In de eerste dagen na een longembolie diagnose zou het interessant zijn om te zien of gezondheidsbewakingsapparatuur met een smartphone kan helpen bij het opsporen van vroege ongewenste uitkomsten, maar ook bij het verbeteren van de therapietrouw en het voorkomen van longembolie-gerelateerde ongeplande heropnames.

Appendices

List of publications
Dankwoord
Curriculum vitae

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DANKWOORD

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CURRICULUM VITAE

Stephan Vincent Hendriks werd geboren op 6 oktober 1986 te Woerden, waar hij ook opgroeide. In 2004 behaalde hij zijn atheneumdiploma aan het Kalsbeek College te Woerden. In datzelfde jaar startte hij met de studie Geneeskunde aan de Universiteit Leiden. In 2008 begon hij met zijn coschappen in Leiden. Na het afronden van zijn studie geneeskunde startte hij als arts-assistent bij de interne geneeskunde in het Groene hart ziekenhuis (GHZ) te Gouda. Na een periode als arts-assistent in het Maasstad Ziekenhuis te Rotterdam begon hij in 2014 aan zijn opleiding tot internist in het Leids Universitair Medisch Centrum (LUMC). Na zijn eerste opleidingsjaar in het LUMC, keerde hij voor twee jaar terug naar het GHZ voor het vervolg van zijn opleiding. Begin 2018 begon hij met zijn differentiatie tot internist acute geneeskunde in het LUMC. Medio 2018 onderbrak hij zijn opleiding om gedurende twee jaar fulltime promotieonderzoek te verrichten in het LUMC te Leiden (onder begeleiding van Prof. dr. M.V. Huisman en Dr. F.A. Klok) en het Hagaziekenhuis te Den Haag (onder begeleiding van dr. A.T.A. Mairuhu). De resultaten van deze werkzaamheden zijn beschreven in dit proefschrift. Tijdens het afronden van zijn promotie heeft hij zijn opleiding tot internist per 2021 afgerond. Na een korte periode als internist-acute geneeskunde in het LUMC vervolgde hij zijn loopbaan als internist-acute geneeskunde in het Haaglanden Medisch Centrum.