Evaluation of patients with low-risk pulmonary embolism

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Abstract

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) affects 5% of the population during their lifetime. Patients with VTE are treated with anticoagulant (AC) therapy for a minimum of 3 months to prevent thrombus extension, embolization, and reccurences. Hereafter the decision to stop or continue treatment depends on the balance between the risk of reccurence (1-10%/year) and bleeding (2-4%/year). Treatment of acute PE is traditionally hospital based and associated with high costs. The lesser need for monitoring with the increasingly used direct oral anticoaugulants (DOAC) in comparison to warfarin potentially facilitates outpatient treatment of PE in low risk patients. Treatment of PE patients outside of hospital might be hampered by fears concerning patient's anxiety and wellbeing, however, and it is therefore important to ensure that outpatient treatment is associated with favorable outcomes on health-related quality of life (HRQoL). Furthermore, the need for anticoagulation therapy in patients with subsegmental pulmonary embolism (SSPE) diagnosed with computer tomography of the pulmonary arteries has been questioned as these patients run low risk for reccurent VTE during 3 months of follow-up.

In this thesis we evaluated patients with low risk PE.

Study I; the aim was to evaluate the safety of withholding AC therapy in 54 patients with SSPE diagnosed by ventilation/perfusion single photon emission computed tomograpy (V/P SPECT). During 90 days follow-up there were no deaths or recurrent PE. Seven patients were readmitted to the hospital, however, wherof 4% (2/54) were diagnosed with DVT necessitating AC therapy.

Study II; aimed to evaluate the efficacy and safety of outpatient treatment of low-risk PE patients with DOAC. Outpatient treatment was defined as discharge from the emergency department (ED) within 24 hours. Comorbidities, risk factors, and simplified pulmonary embolism severity index (sPESI) were evaluated for all 245 patients at baseline. Death, recurrent VTE, and bleeding was recorded during 6 months of follow-up. There were no deaths related to VTE and no recurrent VTE, whereas one patient experienced major bleeding, and five patients experienced minor bleedings.

Study III; evaluated the health care costs in patients with low risk PE. Health care costs were analysed in 223 patients treated as outpatients and 287 patients treated in hospital. Total cost per patient was 2,088 EUR in the outpatient group, and 7,334 EUR in the inpatient group ($p<0.001$).

Study IV: aimed to evaluate HRQoL in outpatient treated PE patients in comparison to HRQoL in DVT patients. Patients were invited to complete disease specific questionnaires and a generic HRQoL tool within 72 hours, six weeks, and six months after diagnosis. A total of 29 PE and 63 DVT patients were enrolled and completed follow-up forms. No difference in HRQoL was observed between PE and DVT patients in the acute phase or at six weeks whereas PE patients had a significantly lower EQ-5D index than DVT patients after six months. Furhtermore, all domains of Pemb-QoL were significantly improved during follow-up.

In conclusion; Withholding AC therapy in patients with SSPE cannot be recommended. Outpatient treatment with DOAC in selected low risk PE patients is efficient and safe. Better adherence to current international guidelines recommendning outpatient treatment with DOAC in low risk PE would potentially lead to significant savings in healthcare expenditure. The overall self-rated health status in low risk PE patients is comparable to in outpatient treated DVT patients.

Key words Low-risk pulmonary embolism; direct oral anticoagulation; efficacy and safety; cost savings; health related quality of life

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What we speak becomes the house we live in.

-Hafez

To my beloved family

Table of Contents

Thesis at glance

Paper in thesis	Study design	Main research question	Main findings
Paper I, Small PE n= 54	Retrospective	Is it possible to withhold AC therapy in small PE?	No, recurrence rate was high. AC therapy is recommended
Paper II, Safety and efficacy n= 245	Retrospective	Is outpatient treatment in PE patients safe when using our selection criteria?	Yes, there was no VTE mortality or recurrent VTE
Paper III, Health economics n= 510	Retrospective	Is outpatient treatment of low-risk PE patients associateda with cost savings?	Yes, savings were observed
Paper IV, Quality of life n=92	Prospective	Is QoL comparable in outpatient treated low-risk PE and DVT patients?	Yes, QoL was comparable initially

List of publications

This thesis is based on the following papers, referred to by their Roman numerals and reprinted with consent from the respective publishers.

I. R. Ghazvinian, A. Gottsäter, J. L. Elf. Is it safe to withhold long-term anticoagulation therapy in patients with small pulmonary emboli diagnosed by SPECT scintigraphy? Thromb J 2016;14:12

II. R. Ghazvinian, A. Gottsäter, J. L. Elf. Efficacy and Safety of outpatient treatment with direct oral anticoagulation in pulmonary embolism. J Thromb Thrombolysis 2018;45:319-24

III. R. Ghazvinian R, J. L. Elf, S. Löfvendahl, J. Holst, A. Gottsäter. Outpatient treatment in low-risk pulmonary embolism patients receiving direct acting oral anticoagulants is associated with cost savings. Clin Appl Thromb Hemost 2020;26:1-8

IV. R. Ghazvinian, A. Gottsäter, C. Kumlien, S.K. Thörn, I. Timberg, J. L. Elf. Health related quality of life in outpatient treatment of pulmonary embolism. *Manuscript from interim analysis*

Abbreviations

AC	Anticoagulation
BMI	Body mass index
BNP	B-type natriuretic peptide
CO	Cardiac output
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomographic pulmonary angiography
DOAC	Direct oral anticoagulants
DVT	Deep vein thrombosis
ECG	Electrocardiographic
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-3L	Euro quality of life 5 dimensions and 3 levels
HAC	Hospital acquired complication
HRQoL	Health related quality of life
INR	International normalized ratio
IQR	Interquartile range
LMWH	Low molecular weight heparin
LOS	Length of stay
LRPE	Low-risk pulmonary embolism
LV	Left ventricle
MI	Myocardial infarction
Msv	Millisieverts
NT	N-terminal

PAP	Pulmonary arterial pressure
PE	Pulmonary embolism
PEITHO	Pulmonary embolism thrombolysis trial
PEmb-QoL	Pulmonary embolism Quality of Life
PESI	Pulmonary embolism severity index
PERC	Pulmonary embolism rule-out criteria
PFO	Patent foramen ovale
PIOPED	Prospective investigation of pulmonary embolism diagnosis
PVR	Pulmonary vascular resistance
QoL	Quality of life
rtPA	Recombinant tissue-type plasminogen activator
RV	Right ventricle
SD	Standard deviation
sPESI	simplified Pulmonary embolism severity index
SSPE	Subsegmental pulmonary embolism
TAPSE	Tricuspid annular plane systolic excursion
UFH	Unfractionated heparin
VKA	Vitamin K antagonists
V/P SPECT	Ventilation/perfusion single photon computed tomography
V/Q	Ventilation/perfusion
VTE	Venous thromboembolism

Introduction

History

Venous thromboembolism (VTE) was first demonstrated in the 18th Century by Giovanni Batista Morgagni who identified large clots in the pulmonary arteries at autopsy of patients having suffered sudden death from pulmonary infarction. Laennec in 1819 first described the pathologic features of haemorrhagic pulmonary infarction and differentiated it from other causes of haemoptysis[1] but was not able to explain the disease origin. A contemporary of Laennec, Jean Cruveilhier, hypothesized that the cause of all disease was phlebitis. He reached this conclusion by observing blood clots at autopsy[2]. It was Rudolph Virchow who subsequently defined the pathophysiology of pulmonary embolism (PE) by realizing that a venous thrombus could break loose from its origin, travel through the blood stream, and lodge in the vessels of other organs[3]. Virchow observed two types of thrombi associated with PE. One arising from a systemic vein, thereafter embolizing to the lung, and another arising in the pulmonary artery distal to the embolus as a result of stagnant blood flow. Virchow's triad was defined as constituting of 1) stasis of blood, 2) venous injury, and 3) a state of hypercoagulability. These three factors are considered as being the underlying mechanisms of thrombosis formation [4].

Epidemiology

There are almost 10 million yearly cases of VTE globally[5]. The disease has substantial morbidity and mortality, and is one of the three major cardiovascular causes of death, along with myocardial infarction and stroke[5]. The annual incidence of VTE is 1 to 2 events per 1,000 individuals in the general population[6]. National inpatient data from Sweden (The National Board of Health and Welfare's statistical database for diagnoses) revealed that the number of admissions for PE increased from 3,752 in 1998 (42.4 per 100,000) to 7,415 in 2021 (71.2 per 100,000)[7]. Corresponding figures from the US between 1993 and 2012 were 60,000 (23 per 100,000) and 202,000 (65 per 100 000). In contrast to the increasing incidence of PE, however, there was a decreasing incidence of massive and hospital related PE mortality over the same period[8 9 10 11]. This is probably a result of increased disease awareness and availability of enhanced imaging techniques, for example computed

tomography pulmonary angiography (CTPA) and ventilation/perfusion single photon emission computed tomography (V/P SPECT), in combination with improved diagnostic algorithms as for example Wells score[12]. Furthermore, national inpatient data from Sweden revealed a decreasing length of stay (LOS) for inpatient treatment of PE, from 8.7 days in 1998 to 4.3 days in 2021[7]. Corresponding data regarding hospitalization for acute PE patients in the US by National Inpatient sample database between 2002 to 2014 revealed a median LOS of 5 days (IQR 3-9)[13]. VTE incidence is age-related in a disproportionate manner; in subjects older than 70 years the incidence is three times higher than in those aged 45 to 69 years, in whom the incidence is three times higher than in individuals aged 20 to 44 years. The lifetime incidence of VTE does not differ by sex, but women have higher risk during the ages of 20-40 years reflecting exposure to reproductive factors, whereas men have higher risk in older age groups[14]. PE accounts for between 5 to 10% of in-hospital deaths[15]. A VTE diagnosis, either PE or DVT, is also associated with significant mortality, the case fatality rate of a VTE event is approximately 10% at 30 days, increasing up to 15% within 3 months, and 20% by 1 year[11 16 17].

Risk factors

All VTE risk factors can be summarized by the above-mentioned Virchow's triad and can be divided into inherited and acquired factors.

Table 1. Inherited risk factors for venous thromboembolism.

Inherited risk factors	Prevalence in the population (%)	Prevalence in patients with VTE (%)	Increased risk for VTE (fold)
Factor V Leiden mutation in heterozygote form [19-21]	5-10	20-30	3-5
Factor V Leiden mutation in homozygote form [19-22]	0.1	3-4	7-20
Prothrombin gene mutation in heterozygote form [19-21]	2	6-7	3-5
Prothrombin gene mutation in homozygote form [19-21]	0.01	unknown	unknown
Antithrombin deficiency [23-25]	0.02	0.8	10-20
Protein C deficiency [23-25]	0.2	1	5-10
Protein S deficiency [23-25]	0.1	1	5-10

Inherited risk factors

The inherited risk factors are genetic conditions which increase the risk of VTE. Prothrombin gene mutation increases the risk of thrombosis threefold and is found in around 2%, almost only in Caucasians[18]. The mutation can be detected in approximately 6% of patients with VTE[19 20 21]. Homozygosity for the prothrombin gene mutation is rare, however, but confers a 30 times increased risk for VTE [19 20 21]. A more common mutation leading to hypercoagulability is the factor V Leiden mutation which is associated with a 5-fold increased risk of VTE in its heterozygote form, and a 20-fold increased risk in homozygote form [19 20 21 22]. The prevalence of carriers is 5-10% among Caucasians, 20-30% among VTE patients, and approximately 50% in patients with familial thrombophilia[19 20 21]. Deficiencies in protein C, protein S, and antithrombin[23 24 25] are both more infrequent and more potent, and confer a 5- to 10-fold increase in VTE risk.

Acquired risk factors

Pregnancy is a natural hypercoagulable state with the purpose to decrease the risk of haemorrhage during childbirth[26]. This is mediated by increase in coagulation factors VII, VIII, X, von Willebrand factor, and fibrinogen, together with a decreased level of protein S and acquired activated protein C resistance[26 27]. VTE rate increases four- to fivefold during pregnancy, and up to twentyfold during the three months following delivery[28 29]. Oestrogen therapy increases the risk of VTE three- to fourfold[30], especially during the first year of treatment and particularly the first three months. Hereafter, the risk does not increase further, however, and cessation of therapy will eliminate the risk[31].

The risks of thrombosis related to trauma and surgery are known, in particularly in patients undergoing orthopaedic surgery with elective hip or knee replacement without prophylactic anticoagulation (AC) therapy[32]. Hip replacement following trauma is associated with a corresponding risk both preoperatively and postoperatively[33], mediated mainly by immobility during and after the surgery as well as by direct venous injury and inflammation. Pharmacological thromboprophylaxis is therefore recommended[11]. Immobility increases the risk of VTE mediated primarily by stasis of blood flow, occurring with hospitalization, prolonged travel, and joint immobility[34 35 36].

Age is an important risk factor for VTE with increasing risk from the fourth and fifth decades and a marked increase in those older than 60 years[37]. This is largely caused by increased rates of malignancy, comorbidities, obesity, and decreased mobility[38].

Patients with severe obesity (body mass index (BMI) ≥ 35) have a sixfold increased risk of VTE compared to those with normal BMI[39].

Antiphospholipid syndrome is characterized by recurrent venous and arterial thrombosis, with DVT and PE manifestations being the most frequent. Patients with this syndrome having a 5 to 8% higher risk of VTE than the normal population[40 41].

Prior VTE events could also be considered as a risk factor, as the rate of recurrency during the first 5-years after stopping AC therapy can be 25% or higher in patients with idiopathic or unprovoked events[42].

Pathogenesis and pathophysiology

The formation of a thrombus is explained by disturbances in one or several of the factors in Virchow's triad as depicted in Figure 1. Most thrombi originate from the deep veins of the lower extremities. Thromboses most often develop in the calf or femoropopliteal veins, and less frequently in the iliac veins[43]. Favourable locations for thrombus formation are regions with decreased blood flow, such as valve cusps and bifurcations. The thrombus might propagate due to local hypercoagulability caused by hypoxia and haemoconcentration[44 45]. Upper extremity deep vein thrombosis is a less common VTE event, usually associated with central venous catheters, intracardiac devices, malignancy, or venous related trauma[46]. PE is most likely to occur as a consequence of lower extremity DVT, whereas upper extremity DVT causes only 6% of PE cases[47 48 49].

A PE usually results from detachment of an embolus from its point of origin in the deep venous system. The thrombus travels through the systemic venous system, through the right heart ventricle and into the pulmonary arterial system. This might lead to gas exchange abnormalities and hypoxemia, but it is the potential haemodynamic consequences of the PE which explain the increased morbidity and mortality associated with the condition. Therefore, understanding of the pathophysiology of PE is important for decision making regarding AC therapy, and consideration of for example systemic thrombolytic or catheter-directed therapies such as thrombolysis, mechanical thrombectomy, or surgical intervention[50 51].

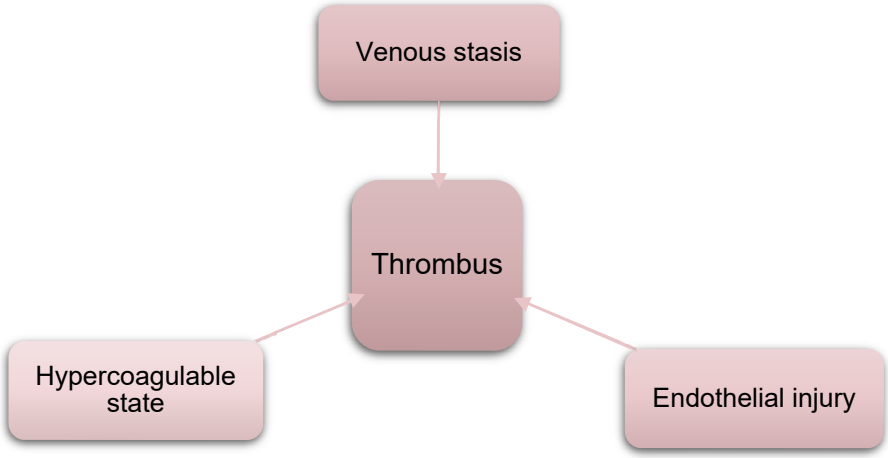

Figure 1. The pathophysiology of thrombus formation, also known as Virchow's triad.

Hypoxemia

Hypoxemia caused by ventilation-perfusion inequalities and shunts is the most common physiological result of an acute PE[52] [53] [54]. The PE there causes redistribution of cardiac output (CO) and blood flow from obstructed regions of the pulmonary vascular bed to non-affected regions. This results in a mismatch of gas exchange in areas with low ratios of perfusion to ventilation (PE areas), whereas non-affected areas will have a compensatory increased ratio of ventilation to perfusion resulting in further mismatch contributing to hypoxaemia. In areas where the blood flow is retained but no ventilation exists, such as atelectasis due to the loss of surfactant or areas with pulmonary infarction or haemorrhage, shunting might occur. In the setting of acute PE, the increased right atrial pressure might open a patent foramen ovale (PFO) and cause a right-to-left intracardiac shunt. Inversion of the pressure gradient may lead to severe hypoxaemia, paradoxical embolization, and stroke[55]. Massive obstruction of the pulmonary vascular bed can cause reduced cardiac output, which in turn will lead to a low mixed venous oxygen saturation. The combination of mixed venous oxygen saturation with ventilation to perfusion mismatch from the PE might further exacerbate hypoxemia. Eventually, areas with vascular obstruction will lead to increased dead space as the lungs continue to ventilate despite reduced/absent perfusion[56]. Medullary receptors sense the increase in partial pressure of carbon dioxide, however, resulting in increased minute ventilation. Acute PE is therefore often accompanied by respiratory alkalosis[57].

Haemodynamics

The haemodynamic effects of an acute PE are related to the size and location of the embolus and the presence of pre-existing cardiopulmonary disease. Patients with non-massive PE are usually normotensive and have a normal right ventricular (RV) function. Patients with sub-massive PE are generally clinically stable, but evidence of RV dysfunction are evident on CT or ultrasonography. Patients with massive PE usually present with haemodynamic instability from RV failure, and risk both morbidity and mortality. The choice of correct treatment in these different situations is therefore fundamental for the patient[57].

Obstruction of the pulmonary arterial vasculature by thrombotic material leads to increased pulmonary vascular resistance (PVR) when >30-50% of the vascular bed is affected[58]. This increase is due to both mechanical obstruction and the release of vasoconstrictive agents from platelets, such as serotonin and thromboxane-a2, from plasma (thrombin), and from the tissue (histamine and endothelin)[59 60]. The sudden increase in PVR increases the preload of the RV, which will dilate its myocytes altering its contractile properties, resulting in a more forceful systolic contraction as a result of the Frank-starling mechanism. RV dilatation confers inotropic and chronotropic stimulation, and temporarily stabilises the systemic pressure in combination with the systemic vasoconstriction. However, the thin-walled RV is unable to generate a mean pulmonary arterial pressure (PAP) >40 mmHg in patients without prior cardiopulmonary disease[59 61]. Prolonged RV contraction will therefore lead to bowing of the interventricular septum into the left ventricle[62] and desynchronization of the ventricles which may also be exacerbated by right bundle branch block. As a result, the prolonged increased preload of the RV will impinge the left ventricle (LV), leading to reduced cardiac output, systemic hypotension and haemodynamic instability[59 62 63].

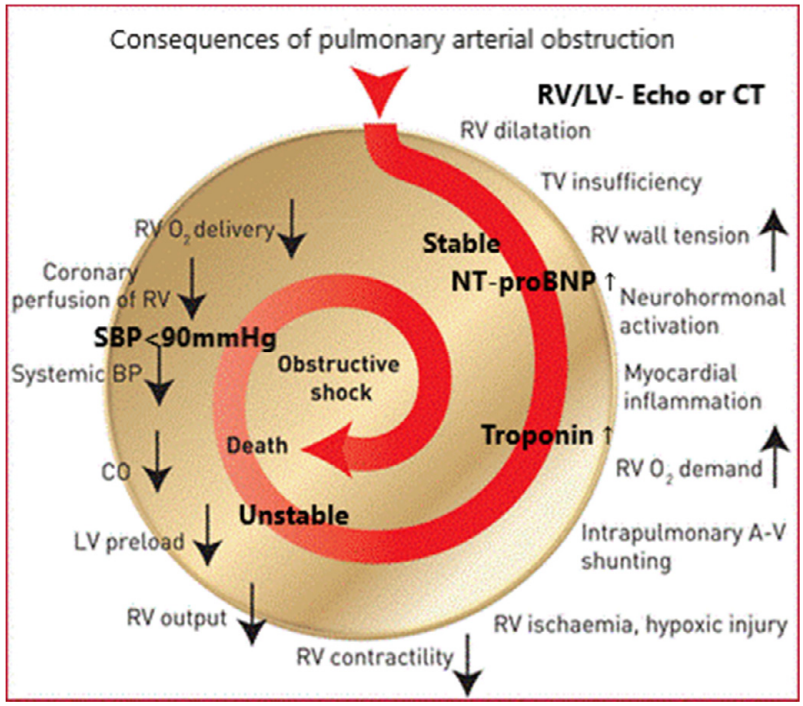

Figure 2. Factors contributing to haemodynamic collapse and death in acute pulmonary embolism (modified from Konstatinides et al[64]).
AV = Arterio-venous; BP = Blood pressure; CO = Cardiac output; LV = Left ventricle; NT-proBNP = N-terminal prohormone of brain natriuretic peptipe; O2 = oxygen; RV = Right ventricle; SBP = Systolic blood pressure; TV = Tricuspid valve.

Diagnosis

PE is one of three major causes of cardiovascular death, and might present with a wide spectrum of symptoms ranging from asymptomatic cases to patients suffering sudden death[5]. The increased awareness of VTE and the increased availability of imaging testing such as CTPA have led to a higher tendency to suspect and exclude PE in low probability patients. This is well illustrated by the decreasing number of test-positive patients in clinical studies. PE incidences as low as 5% have been reported in recent North American studies, in contrast to the approximately 50% incidence reported in early 1980s[65]. The characteristic signs and symptoms of PE such as tachycardia, dyspnoea, cough, chest pain, syncope, hypoxemia, and shock are non-specific, however, and may be present in many other conditions such as for example acute myocardial infarction (MI), congestive heart failure, or pneumonia[66]. Therefore, the diagnosis of PE depends largely on the clinical likelihood of PE and the stability of the patient. To identify the likelihood of PE, the clinical presentation

and medical history of the patient need to be combined with widely used diagnostic tools such as the Wells criteria or the Geneva score[67].

Clinical presentation

Patients with pulmonary embolism obstructing the pulmonary vascular bed most often present with dyspnoea, chest pain, pre-syncope/syncope, or haemoptysis[68 69 70]. Syncope and haemodynamic instability are rare but important clinical presentation, and indicate more severe obstruction caused by central or massive PE with highly reduced haemodynamic reserve. Syncope is associated with haemodynamic instability and RV dysfunction[71]. Chest pain is frequent in PE and usually caused by pleural irritation due to distal emboli causing pulmonary infarction[72]. In centrally positioned PE chest pain might be anginal reflecting possible RV ischaemia, necessitating a differential diagnosis from acute coronary syndrome or aortic dissection[73]. Dyspnoea may present as both acute and severe in central PE, whereas patients with small peripheral PE often have mild and even transient dyspnoea. In patients with prior cardiopulmonary disease such as heart failure, worsening of the dyspnoea may be the only indication of PE[73]. In the prospective investigation of pulmonary embolism diagnosis II (PIOPED II) trial, common signs were tachypnoea (54%) and tachycardia (24%). The most usual symptoms were onset of dyspnoea within seconds, at rest or with exertion (73%), pleuritic pain (44%), calf or thigh swelling (41%), and cough (34%)[67].

Diagnostic approach

The clinical probability of the disease increases with the number of predisposing factors. As approximately 60% of patients with PE have predisposing factors[73], clinical probability tests might help increase the accuracy of PE diagnosis.

Wells criteria and Geneva score

Validated scoring systems such as Wells criteria and Geneva score[68] are used in order to estimate the likelihood of PE. These scoring systems classify the clinical likelihood of PE into two or three categories with increasing incidence of PE[74 75] (as PE being either unlikely or likely, or as the patient having low, intermediate, or high clinical probability of PE). The above-mentioned scoring systems have been validated in two meta-analyses, which confirmed the validity of the original and simplified versions of the Wells criteria and the revised Geneva scores[76 77]. Prospective direct comparison between these rules has confirmed that their diagnostic performance is equal[78]. Table 2 summarizes the validated versions of the Geneva score and Table 3 summarizes the Wells prediction rules for PE. Regardless of the scoring system, and when a three-level classification is used, the proportion of patients with confirmed PE may be expected to be approximately 10% in the low-

probability category, 30% in the moderate-probability category, and 65% in the high-probability category[77]. When using a two-level classification, the proportion of patients with confirmed PE is approximately 12% in the PE-unlikely category and 30% in the PE-likely category[77].

Table 2. Original and simplified versions of the revised Geneva score

Revised Geneva score	**Original version[79]**	**Simplified version[80]**
Age > 65 years	1	1
Previous DVT or PE	3	1
Surgery or fracture within 1 month	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Haemoptysis	2	1
Heart rate		
75-94 bpm	3	1
≥ 95 bpm	5	2
Pain on lower limb deep vein palpation and unilateral oedema	4	1
Clinical probability		
Three-level score		
Low	0-3	0-1
Intermediate	4-10	2-4
High	≥ 11	≥5
Two-level score		
PE unlikely	0-5	0-2
PE likely	≥ 6	≥ 3

DVT= deep vein thrombosis; PE=pulmonary embolism; bpm=beats per minute

Table 3. Original and simplified version of Wells score

Wells score	Original version[81]	Simplified version[82]
Previous PE or DVT	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Cancer	1	1
Haemoptysis	1	1
Heart rate > 100 bpm	1.5	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Three-level score		
Low	0-1	NA
Intermediate	2-6	NA
High	≥ 7	NA
Two-level score		
PE unlikely	0-4	0-1
PE likely	> 4	≥ 2

DVT= deep vein thrombosis; PE=pulmonary embolism; bpm=beats per minute; NA= not available

Pulmonary embolism rule-out criteria

Pulmonary embolism rule-out criteria (PERC) were established to identify patients in the ER having such a low risk of PE that diagnostic workup should not be initiated[83]. These rule-out criteria comprise eight clinical variables which notably are associated with an absence of PE: age<50 years, pulse<100 beats per minute, oxygen saturation>94%, no unilateral leg swelling, no haemoptysis, no recent trauma or surgery, no history of VTE, and no hormonal use. Safe exclusion of PE in low clinical probability patients using PERC was validated in a prospective study[84] and in a randomized non-inferiority management study[85]. The overall prevalence of PE in these studies was low (< 5%) and the generalizability of the results can therefore be questioned.

Chest radiography

Chest radiography of the lungs in PE is frequently abnormal, but findings are often non-specific such as oligemia (Westermark's sign), peripheral wedged-shaped density above the diaphragm (Hampton's hump), and enlargement of the right descending pulmonary artery (Palla's sign). The major role of chest radiography in this situation is therefore identification of alternative diagnoses[86].

Electrocardiography

The most frequent abnormality in the electrocardiogram (ECG) is the S1Q3T3 pattern indicating RV strain. The ECG shows an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III. Other ECG changes may include inversion of T waves in leads V1-V4, QR pattern in V1, and incomplete or complete right bundle branch block[87]. Sinus tachycardia occurs in approximately 40% of patients with PE, and another arrhythmia which might be associated with PE is atrial fibrillation[88].

D-dimer

D-dimer is the degradation product of cross-linked fibrin, the levels of which rise due to simultaneous activation of coagulation and fibrinolysis in patients with acute onset of a thrombotic disease. There are numerous available assays for D-dimer with different characteristics[88]. However, quantitative enzyme-linked immunosorbent assay (ELISA) or ELISA-derived assays have the highest diagnostic sensitivity (over 95%) and a specificity around 40%[89 89]. PE can be ruled out in patients with low or intermediate pre-test probability in combination with a negative quantitative D-dimer. Furthermore, studies have shown that a negative D-dimer test in combination with low clinical probability might exclude the disease in 30% of outpatients with suspected PE[90 90 91 92]. In outcome studies, the risk of VTE during three months was <1% in patients with low or intermediate clinical probability who were left untreated on a basis of a negative D-dimer[90]. As mentioned above the low specificity of D-dimer results in a low positive predictive value, since increased D-dimer levels are seen in a variety of conditions such as cancer, inflammation, infection, chronic kidney failure, pregnancy, previous VTE, and advancing age[93 94 95]. Age is an important factor as the specificity of D-dimer in suspected PE decreases steadily to 10% in patients >80 years of age[95]. Therefore, use of age-adjusted cut off levels have been shown to improve accuracy of D-dimers in the elderly. In a multinational prospective management study D-dimer cut-off increased the number of patients in whom PE could be excluded from 6.4% to 30% without additional false-negative findings[96].

Pulmonary angiography

Pulmonary angiography is an invasive method to diagnose PE and has historically been the “gold standard” for the diagnosis or exclusion of acute PE. It is rarely performed nowadays, however, as the less invasive alternative CTPA offers similar diagnostic accuracy[97]. Invasive catheter-based diagnostic testing is reserved for patients in whom an interventional catheter-directed thrombolysis or embolectomy is planned. PE is visualized as intraluminal filling defects or as an amputation of a pulmonary arterial branch[98]. Thrombi as small as 1-2 mm within subsegmental arteries can be visualized, however, with high interobserver variability at this level[99 100]. As angiography is an invasive investigation which may require high radiation

dose, up to 10-20 millisieverts (mSv), it is not risk-free. In a study of approximately 1,000 patients, the procedure mortality was 0.5%, major non-fatal complications occurred in 1%, and minor complications in 5%[101]. Haemodynamic instability or respiratory failure were the major causes of death in this study.

Computed tomographic pulmonary angiography

Multidetector CTPA is the principal imaging test for diagnosis of PE allowing visualization of the pulmonary arteries at subsegmental levels[102 103 104] In the PIOPED II study the sensitivity of CTPA for PE diagnosis was 83% and the specificity was 96%[105]. This study also highlighted that the negative predictive value for PE in patients with low or intermediate clinical probability of PE and a negative CTPA was high (96% and 89%). The negative predictive value, however, was only 60% if the clinical probability was high[106]. In the same study, a positive CTPA had a positive predictive value of 92-96% in patients with an intermediate or high clinical probability, whereas the predictive value was as low as 58% in patients with a low pre-test likelihood of PE[106]. On these grounds the clinicians should consider further testing in case of negative CTPA but a high clinical suspicion of PE. However, the Christopher management study revealed that in patients having a likely or high probability of PE, or a positive D-dimer test who underwent CTPA, the CTPA had a negative predictive value of 98%[106].The European Society of Cardiology considers a negative CTPA as enough for exclusion of PE in patients with low or intermediate clinical probability. But it remains controversial whether patients with a negative CTPA and a high clinical probability should undergo further investigation[50].

Lung scintigraphy

Ventilation/perfusion lung scintigraphy (V/Q scan) is a non-invasive technique enabling an indirect diagnosis of PE. In this imaging technique perfusion scans are combined with ventilation studies, and the purpose of the ventilation scan is to increase the specificity in acute PE. The diagnosis is confirmed when ventilation is normal and hypoperfusion occurs in the same area, a condition also referred to as "mismatch". As V/Q scan has lower radiation and is a contrast medium sparing procedure it is particularly suitable in patients with severe renal failure, contrast medium-induced anaphylaxis, and young female patients, especially during pregnancy[107]. Classification criteria for planar V/Q scans were originally defined in the PIOPED study[108], but have later been revised[109 110 111]. To enhance the communication between clinicians, scans are defined as normal (excluding PE), high probability (considered diagnostic of PE), or non-diagnostic[112 113 114]. In the PIOPED II study it was suggested that a high probability V/Q scan could confirm PE[106]. This has been questioned in patients with a low clinical probability, however[115 116]. Several studies indicate that imaging for PE with V/P SPECT may decrease the proportion of non-diagnostic scans to 0-5%[114 117 118 119]. Unfortunately, the retrospective design of these studies has led to uncertainties regarding the

accuracy of V/P SPECT[119 120 121]. Therefore, large scale prospective studies are needed for further validation of the utility of V/P SPECT.

Assessment of pulmonary embolism severity

It is of great importance to assess pulmonary embolism severity in order to offer the patient appropriate surveillance and therapeutic management. The initial risk stratification is based on the clinical signs and symptom of haemodynamic instability, the latter indicating high risk of early death[5]. Risk stratification is of high importance also in the remaining group of patients presenting without haemodynamic instability.

Risk stratification

The focus of risk stratification is the evaluation of RV function, a critical determinant of the outcome in patients with acute PE. There are different risk stratification tools, imaging and laboratory tests which are helpful for the physician when choosing the right level of care and therapeutic management[50].

Pulmonary embolism severity index or simplified pulmonary embolism severity index

Pulmonary embolism severity index (PESI, table 4) is one of the most validated scores to assess PE severity, comorbidities, overall mortality risk, and early outcomes of patients with acute PE[122 123 124 125]. The original PESI score[126] included 11 variables whereas the simplified version of PESI (sPESI) has six variables[127]. One of the main strengths of the PESI and sPESI scores, observed in a randomized trial and confirmed in observation studies, is their reliability for identification of patients with low mortality within 30 days[125 128].

Table 4. Original and simplified Pulmonary Embolism Severity Indices (PESI).

Parameter	Original version[127]	Simplified version[128]
Age	Age in years	1 point (if age>80 years)
Male sex	+10 points	-
Cancer	+30 points	1 point
Chronic heart failure	+10 points	
Chronic pulmonary disease	+10 points	1 point
Pulse rate > 110 bpm	+20 points	1 point
Systolic BP <100 mmHg	+30 points	1 point
Respiratory rate > 30 breaths per minute	+20 points	-
Temperature<36° C	+20 points	-
Altered mental status	+60 points	-
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
Risk strata	Class I: ≤65 points Very low 30-day mortality (0-1.6%) Class II: 66-85 points Low mortality risk (1.7-3.5%) Class III: 86-105 points Moderate mortality risk (3.2-7.1%) Class IV: 106-125 points High mortality risk (4.0-11.4%) Class V: > 125 points Very high mortality risk (10.0-24.5%)	0 points = 30-day mortality risk 1.0% (95% CI 0.0-2.1%) ≥1 point(s) = 30-day mortality risk 10.9% (95% CI 85-13.2%)

Hestia criteria

The Hestia criteria (table 5) constitute a checklist of 11 clinical parameters or questions which all can be obtained bedside. This checklist contains aspects of PE severity, comorbidities, and the feasibility of home treatment. Home treatment is considered as being not possible if one of the exclusion criteria is met[129]. The three months recurrence rate of VTE in a single arm management trial using Hestia criteria for home treatment of acute PE patients was 2.0% (0.8-4.3%), which was considered acceptable[130]. Other studies have shown that the Hestia criteria enable reliable identification of PE patients at low risk and therefore can be used for clinical triage[130].

Table 5. Hestia exclusion criteria for outpatient management[130].

Is the patient haemodynamically unstable? *	Yes	No
Is thrombolysis or embolectomy necessary?	Yes	No
Active bleeding or high risk of bleeding? †	Yes	No
More than 24 hours 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 hours?	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^{-1}? ‡	Yes	No
Does the patient have severe liver impairment? §	Yes	No
Is the patient pregnant?	Yes	No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes	No

Hestia exclusion criteria for outpatient management of pulmonary embolism[130]. If the answer to one or more of the questions is 'yes', then the patient cannot be treated at home.
*Include the following criteria but leave them to the discretion of the investigator: systolic blood pressure< 100 mmHg with heart rate> 100 beats, min^{-1}; condition requiring admission to an intensive care unit. † Gastrointestinal bleeding in the preceding 14 days, recent stroke (< 4 weeks ago), recent operation (< 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count< 75 x 109 L^{-1}), uncontrolled hypertension (systolic blood pressure> 180 mmHg or diastolic blood pressure> 110 mmHg). ‡Calculated creatinine clearance according to Cockroft-Gaul formula. §Left to the discretion of the physician.

Echocardiography and cardiac biomarkers

Echocardiography visualizes RV dilatation in ≥ 25% of unselected PE patients, and is a useful non-invasive imaging method for early risk stratification of patients with PE[131]. RV dysfunction on echocardiography is associated with short-term mortality in haemodynamically stable patients, but has a low positive predictive value for PE-related death (<10%)[132]. This is mainly due to the lack of echocardiographic parameters standardized for PE[133 133]. Echocardiography is widely recognized as a valuable tool for distinguishing the function and morphology of the RV and assessment of the prognosis in normotensive PE patients, however[133 134]. An RV/LV diameter ratio ≥1.0 and a tricuspid annular plane systolic excursion (TAPSE) < 16 mm are findings associated with unfavorable prognosis[133]. Echocardiography is also useful for diagnosing of right-to-left shunts, such as patent foramen ovale, and right heart thrombi, conditions associated with increased mortality in acute PE[56 134]. A patent foramen ovale in a patient with acute PE has also been proven to increase the risk of ischemic stroke due to paradoxical embolism[135 136].

As previously mentioned (Figure 2), RV overload due to acute PE is associated with myocardial stretch leading to release of B-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP. Plasma levels of these peptides therefore reflect the severity of RV overload due to acute PE[137]. In a meta-analysis, 51% out of 1,132 unselected

patients with acute PE had elevated BNP or NT-proBNP at admission, indicating a 10% risk of early death and a 23% risk of adverse clinical outcome[138]. These peptides have low specificity and positive prediction values for early mortality in normotensive patients[139], however, but low plasma levels of BNP and or NT-proBNP were capable of excluding an unfavorable clinical outcome with high sensitivity and negative predictive value in a multicenter management study[134]. Likewise, elevated plasma concentrations of cardiac troponins I or T in both unselected and selected patients with acute PE were associated with a worse prognosis[140]. The interpretations of troponin I or T levels depend on the assay used, however, a meta-analysis[141] has shown that between 30% (using conventional assays) and 60% (using high sensitivity assays) of patients with acute PE have elevated cardiac troponin I or T [141 141 142 143]. As mentioned regarding BNP or NT-proBNP, elevated cardiac troponins have a low specificity and positive predictive value for mortality in haemodynamically stable PE patients, but nevertheless cardiac biomarkers in combination with clinical assessment and imaging findings may improve risk stratification in PE[144].

Treatment

As one of the first features of severe PE is hypoxemia, administration of oxygen therapy is indicated in patients with oxygen saturation <90%. An atrial septal defect or a patent foramen ovale could contribute to severe hypoxemia[56], a condition for which other oxygen therapies such as high-flow oxygen or non-invasive or invasive mechanical ventilation might be necessary[144 145]. These oxygenation techniques are mainly used in extreme cardiopulmonary instability, however. Such patients are often hypotensive or have a high risk of developing hypotension during induction of anesthesia, intubation, and positive-pressure ventilation. Mechanical ventilation should therefore be used with care as adverse haemodynamic effects such as positive intrathoracic pressure may reduce venous return and worsen low CO due to RV failure in patients with high-risk acute PE[145 146].

Low systemic output caused by acute RV failure is the main cause of death in patients with high-risk PE. Modest volume loading is the treatment of choice when the central venous pressure is low[146], however, it can also lead to an overdilatation of the RV which will lead to drop in systemic blood pressure[147]. Assessment of central venous pressure by ultrasound of the inferior vena cava could therefore be helpful to guide cautious volume loading when arterial pressure is low[148].

In high-risk PE patients the use of vasopressors is often necessary for stabilization of the patient before non-invasive or invasive treatment. Norepinephrine is used as vasopressor in acute PE and cardiogenic shock, leading to improvement of ventricular systolic interaction and coronary perfusion without causing increased

PVR[148]. Dobutamine is mainly considered in patients with a low cardiac index and normal blood pressure, but the fact that an increase in cardiac index may aggravate the ventilation/perfusion mismatch by redistribution of blood flow from obstructed to unobstructed vessels must be taken into consideration[149].

Extracorporeal membrane oxygenation (ECMO) and thrombolysis may be used in patients with high-risk PE and circulatory collapse or cardiac arrest. As this approach is associated with a high risk of complications, and vascular access is needed, it has been considered as controversial[150 151].

Initial and long-term treatment

Heparinoids

Low molecular weight heparin (LMWH) is the drug of choice in patients with high or intermediate clinical probability of PE. Treatment should be initiated already when the patient is awaiting the result of diagnostic tests[50]. This can be accomplished either by weight adjusted subcutaneous LMWH, fondaparinux, or intravenous unfractionated heparin (UFH). However, LMWH and fondaparinux are preferred over UFH, as they are associated with lower risk of major bleeding and heparin-induced thrombocytopenia, and do not necessitate monitoring of anti-Xa[152 153 154 155]. In patients with overt haemodynamic instability treated with reperfusion treatment, UFH is preferred at diagnosis. Unfractionated heparin is also recommended for patients with severe renal impairment (creatinine clearance ≤30 mL/min) or severe obesity[154]. LMWH can be prescribed in patients with renal impairment and creatinine clearance 15-30 mL/min and in need of long-term therapy, however, adapted dosing should be used[154].

Vitamin K-antagonists

Vitamin K antagonists (VKA) have been the golden standard for treatment of VTE for more than 50 years. They should be administered simultaneously with LMWH or other subcutaneous anticoagulation for ≥5 days, and until the international normalized ratio (INR) value has reached 2.0-3.0 for two consecutive days[156]. Warfarin may be started at a dose of 10 mg in patients aged <60 years, and in otherwise healthy older patients at a dose of ≤5 mg[154]. Over the next five to seven days the daily dose is adjusted according to the INR level. Therefore, implementation of an anticoagulation clinic is of high importance and has been proved to increase time in therapeutic range as well as clinical outcome, compared to regulation of VKAs by a general practitioner[157 158].

Direct oral anticoagulation (DOAC)

DOAC, also known as non-vitamin K antagonist oral anticoagulants (NOAC), are small molecules that inhibiting an activated coagulation factor. Dabigatran inhibits thrombin whereas other DOAC (apixaban, edoxaban, and rivaroxaban) affect factor Xa.[159]. In contrast to VKA, DOAC can be given at fixed doses without routine laboratory control, mainly due to their well-known bioavailability and pharmacokinetics[160]. In addition, VKA are more prone to interact with other drugs[154]. It has also been shown that treatment with DOAC leads to a significantly reduced rate of major bleeds compared to VKA, but is non-inferior regarding VTE recurrence rate[160]. However, patients with severe renal impairment were excluded in phase III DOAC trials in VTE, and DOAC can therefore only be used in patients with mild to moderate renal dysfunction (CrCl from 15 or 30 to 60 mL/min)[161].

Reperfusion treatment

Thrombolysis

Systemic thrombolysis in the acute setting of high-risk PE leads to faster resolution of pulmonary obstruction, improvement PAP, PVR, and RV dilatation in comparison to treatment with LMWH or UFH[161 162 163 164]. Streptokinase and urokinase were introduced as the first thrombolytic agents, but intravenous administration of recombinant tissue-type plasminogen activator (rtPA) is preferable to prolonged infusion of the first-generation thrombolytic agents[50]. Thrombolytic treatment may be performed in patients who have had symptoms for 6-14 days, but the greatest benefits is observed when treatment is instituted within 48 hours[165]. Significant reductions of mortality and recurrent PE have been observed in a meta-analysis of thrombolysis in high-risk PE patients, defined mainly as presence of cardiogenic shock. Treatment also conferred a 9.9% rate of severe bleeding and 1.7% rate of intracranial haemorrhage, however[166]. In the pulmonary embolism thrombolysis (PEITHO) trial, thrombolytic therapy in normotensive intermediate-risk PE patients was associated with significant reduction of haemodynamic collapse, however, patients in the thrombolysis group also ran an increased risk of severe extracranial and intracranial bleeding, and no benefit could be demonstrated in terms of mortality[167]. Long term follow-up after the PEITHO-trial showed similar rates of residual dyspnoea and RV dysfunction.

Thrombectomy

This approach can be performed either by percutaneous catheter-directed treatment or surgical embolectomy.

The first approach is less invasive, as catheter insertion into the pulmonary arteries is performed via the femoral route. Different types of catheters can be used for mechanical fragmentation, thrombus aspiration, or pharmacomechanical approach.

The latter is a combination between mechanical or ultrasound fragmentation of the thrombus alongside with reduced-dose thrombolysis[168 169]. A meta-analysis showed that the overall success rates of this percutaneous catheter-based therapy reached 87%[170]. One randomized control trial compared conventional heparin-based treatment and a catheter-based therapy combining ultrasound clot fragmentation in patients with intermediate-risk PE, showing that the invasive approach was more successful in decreasing the RV/LV diameter ratio at 24 hours without increased risk of bleeding[171]. Two prospective studies of intermediate- and high-risk PE patients corroborate that this approach leads to improvement in RV function[172 173]. These studies should be interpreted with caution, however, as they have not directly compared catheter-directed therapy with systematic thrombolysis, and the number of patients treated was limited[50].

A much more invasive approach in acute PE is surgical embolectomy, which is carried out with cardiopulmonary bypass, without aortic cross-clamping or cardioplegic cardiac arrest. This is followed by incision of the main pulmonary arteries and the removal of the thrombus [50]. This approach is more appropriate for high-risk PE patients with or without cardiac arrest and in selected cases of intermediate-risk PE[174]. In an observational retrospective study of 174,322 patients hospitalized for PE between 1999 and 2013, 2,854 underwent systemic thrombolysis and 257 underwent surgical embolectomy. The overall 30-day mortality with these two therapeutic strategies were 15% and 13%, respectively, but thrombolysis was associated with a higher risk of stroke and reintervention at 30 days[175]. The less invasive approach was also associated with a higher rate of recurrent PE requiring readmission, 7.9 vs 2.8%, whereas there was no difference in 5-year survival between groups[175].

Treatment strategies

High-risk pulmonary embolism

As mentioned above, the treatment of high-risk PE patients is mainly focussed on stabilization of the patient and treatment of the RV failure. This is primarily accomplished by the treatment of choice in these cases, systemic thrombolysis[50]. Percutaneous catheter-directed thrombolysis or surgical pulmonary embolectomy are other alternatives to create reperfusion of the affected area in patients with contraindications to thrombolysis[50]. After the patients have been haemodynamic restored, oral anticoagulation is the drug of choice.

Intermediate-risk pulmonary embolism

In patients without haemodynamic instability the drug of choice in most cases is parenteral or oral anticoagulation[50]. Within this group, however, normotensive patients with one indicator of elevated PE-related risk such as comorbidities or

aggravating conditions or signs of RV dysfunction on echocardiography or CTPA accompanied by a positive cardiac biomarker should be monitored over the first hours or days[168]. These patients with intermediate-high PE-risk should receive LMWH over the first two to three days, and assessment of the haemodynamic situation is of great importance. If haemodynamic instability occurs in this patient group, treatment should be offered in accordance with the above guidelines for high-risk PE patients[168 50].

Low-risk pulmonary embolism

Home treatment of low-risk PE patients is recommended if the risk of early PE-related death or serious complications is low, patients do not have comorbidities or conditions that mandate hospitalization, proper anticoagulation treatment can be provided, and good compliance can be assured[50]. As previously mentioned, both the Hestia criteria and PESI or sPESI are adequate tools for a physician to estimate safety and feasibility of early discharge or home treatment[125 126 130 131 175].

Cost-benefits of early discharge in low-risk pulmonary embolism

In the United States PE is estimated to cause annual costs ranging from 8.5 to 19.8 billion US dollars[176]. Dasta et al reported that the daily cost for inpatient PE treatment started at 2,034 US dollars and was highest during the first three days, and that the total mean daily cost for inpatient care of PE was 1,735 US dollars[177].

LaMori and colleagues showed that outpatient treatment of low-risk PE (LRPE) was associated with potential savings, as the economic burden incurred by PE is lower in patients with short length of stay (LOS)[178]. Furthermore, patients with short LOS run a noticeable lower risk for hospital acquired conditions (HAC)[179]. Since the introduction of DOACs as first line treatment[180 181 182 183 184 185] of PE, outpatient treatment of VTE has potentially been facilitated as the need for monitoring of DOAC treatment is less than for warfarin. Coleman et al[186] showed that rivaroxaban use was associated with a 1.36-day shorter length of stay (LOS) and 2,304-dollar reduction in total cost compared to parenteral bridging during institution of warfarin. This cost reduction was achieved without increasing the short-term risk of adverse events including readmission for VTE or major bleeding[187].

Similarly, Bookhart and colleagues[187] showed that rivaroxaban use resulted in a 1.7-day mean reduction in LOS compared with treatment with enoxaparin and vitamin K antagonists, enabling a reduction of total hospital cost of 3,000 dollars per patient. DOAC treatment of low-risk PE patients selected with validated risk stratification tools therefore seems to be a promising strategy to decrease the economic burden to society caused by the disease.

Subsegmental pulmonary embolism

PE can be classified according to the most proximal location of the emboli or graded according to the percentage of the pulmonary vascular bed affected[188]. The use of multiple-detector CTPA has led to an increased number of diagnosed subsegmental pulmonary emboli (SSPE), accounting for around 5-15% of PE cases. The mortality of PE though, has remained consistent or decreasing[189]. These findings highlight the question whether AC-therapy is required for such additionally detected PE´s[190 191]. In a cross-sectional survey on clinician's opinions on SSPE[192], it was shown that physicians are comfortable with withholding of therapy if the three months risk for recurrent VTE is <2%. Recently, Le Gal G et al prospectively assessed 90-days outcome in 292 patients with isolated subsegmental PE in whom AC therapy was withheld. They observed a recurrence rate of 3.1% which was, however, lower in younger patients and patients with single subsegmental PE[193].

Duration of anticoagulation therapy

Anticoagulation therapy in patients with PE should be recommended for a minimum of 3 months to prevent thrombus extension, embolization, and recurrences[51 194]. Hereafter, the decision to stop or continue treatment depends on the balance between the risk of recurrence (1-10% per year) and bleeding (2-4% per year)[51].

The most important determinants of the risk of recurrence are whether the VTE was unprovoked or provoked and whether the provoking factor was transient or permanent[195 196 197] (Figure 3).

The estimated risk for long-term recurrence of PE could be defined as low, intermediate, or high. Low recurrence risk (<3% per year) is mostly associated with transient risk factors such as surgery with general anesthesia for more than 30 minutes, hospitalization or immobilization ≥ 3 days, and trauma with fractures[50 198]. Intermediate risk (3-8% per year) is associated with risk factors such as minor surgery <30 minutes, admission to hospital for <3 days, oestrogen therapy, pregnancy, reduced mobility ≥ 3 days, long-haul flights, inflammatory bowel disease, or active autoimmune disease[50 198]. High risk (>8% per year) is associated with persistent risk factors such as cancer, one or more previous VTE episodes in absence of provocative factor, and antiphospholipid syndrome[198]. These factors should be weighed against the bleeding risk of every individual patient when deciding upon the appropriate duration of anticoagulation.

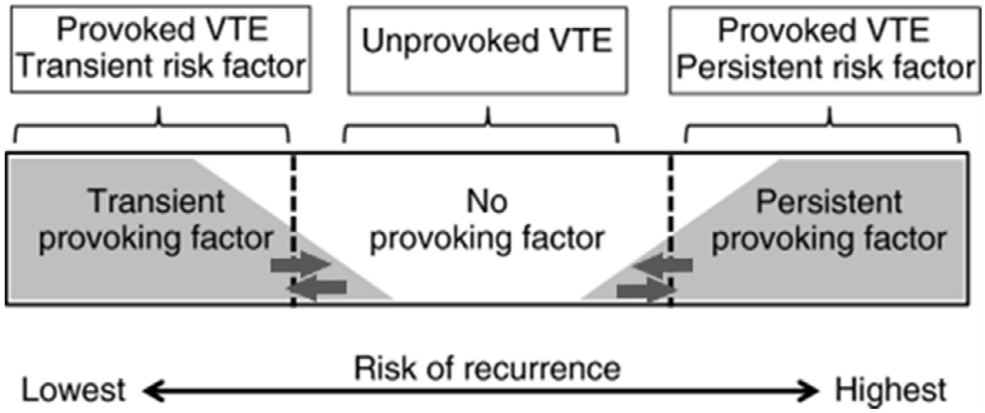

Figure 3. Perspectives regarding risk of recurrence of VTE and risk factors (modified from Kearon et al[198]).

Prognosis

In most PE survivors, the pulmonary vascular bed is restored within the first few months following an acute PE episode. However, in rare cases the thrombus might remain persistent and organized, which might become life-threatening due to obstructive vasculopathy, also called CTEPH[198]. The most common residual symptoms six months to three years after an acute PE are persistent or deteriorating dyspnoea and poor physical performance[199]. At six months follow-up there is a high variability (20-75%) regarding patient's health status compared to the time of actual PE diagnosis[200 201 202]. There are some baseline parameters which could be used as predictors of exertional dyspnoea at long-term follow-up: cardiopulmonary comorbidity, advanced age, high body mass index, history of smoking, RV dysfunction at PE diagnosis, high PAP, and residual pulmonary obstruction at discharge[201 203 204]. In a prospective Canadian study aiming to determine predictors of exercise limitation after PE and its association with health-related quality of life (HRQoL) and dyspnoea, 100 patients were enrolled for evaluation of cardiopulmonary exercise testing at 1 and 12 months, quality of life, dyspnoea 6-min walking distance, residual clot burden, and both cardiac and pulmonary function during follow-up[205]. Significantly reduced functional outcome during cardiopulmonary exercise testing was noted in 47% of patients, and HRQoL, dyspnoea scores, and 6-min walking distance were related to this functional outcome [206]. In both patients with and without reduced maximal aerobic capacity, however, pulmonary function tests and echocardiography results at follow-up were largely within normal limits. Independent predictors for reduced functional exercise capacity and quality of life were female sex, higher body mass index, history of lung disease, higher PAP, and higher main pulmonary artery diameter on CTPA at baseline[206]. In a study of 20 patients with massive or sub-massive PE, there was no

association between exercise impairment and persistent RV dilatation[207]. Both older and more recent studies suggest that body weight and cardiopulmonary comorbidity are largely responsible for the frequently reported dyspnoea and other signs of exercise limitation after acute PE[50].

Health related quality of life

As mentioned above, PE severity and long-term outcomes vary[50 197]. HRQoL is a concept that refers to how a person perceives their overall health status and how it affects their daily life, which can be significantly impacted by PE [207 208]. Patients with PE may experience symptoms such as shortness of breath, chest pain, cough, and fatigue, which can interfere with their ability to perform daily activities and affect their emotional well-being[201 204 207]. Furthermore, the treatment of PE with AC therapy can also have side effects and impact HRQoL[208 209]. Several studies have assessed HRQoL in PE patients using various tools[209 210 211 212]. Decreased QoL has generally been observed in patients with PE compared to the general population, however, the explanation for this has not been fully clarified[209 210 211 212]. Therefore, effective management of PE should not only focus on preventing complications and improving clinical outcomes but also aim to improve the patient's overall quality of life.

Aims

Paper I: To retrospectively evaluate the safety of withholding anticoagulation therapy in patients with subsegmental PE diagnosed by V/P SPECT.

Paper II: To evaluate the safety and efficacy of outpatient treated acute PE patients treated with DOAC.

Paper III: To evaluate whether outpatient treatment in DOAC treated low-risk PE patients is associated with cost savings.

Paper IV: To evaluate HRQoL in outpatient treated low-risk PE patients in comparison to outpatient treated DVT patients and the standard general population.

Patients and methods

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For paper I ethical approval was obtained by the local ethics committee of Lund University dnr 2006/324.

For papers II, III, and IV ethical permission was obtained from the ethics committee in Lund, Sweden, dnr 2015/143 and 2018/909.

Selection criteria

Selection criteria for outpatient treatment in paper I-IV are illustrated in Figure 4.

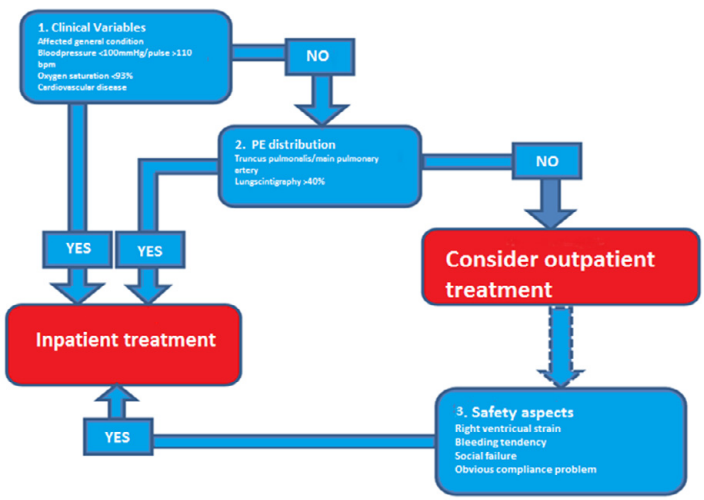

Figure 4. Selection criteria for outpatient treatment of pulmonary embolism (PE) at Skåne University Hospital.

Paper I

Between 2007 and 2011, 898 (Figure 5) patients were diagnosed with acute PE by V/P SPECT at Lund University Hospital and clinically assessed according to our selection criteria for outpatient treatment (Figure 4).

Conventional long-term AC treatment was defined as therapeutic doses of LMWH or VKA for at least three months, and was withheld by the physician if the V/P SPECT result was interpreted as follows:

1. Falsely positive for technical reasons (low probability).
2. The perfusion defect was thought to represent an old and no longer clinically relevant embolization.
3. The embolization was thought to be too clinically irrelevant to merit treatment.

Withholding of long-term treatment also required that patients were haemodynamically stable, did not have clinical signs or symptoms of DVT, and that the extension of perfusion defects on the V/P SPECT images comprised ≤ 20 % of the pulmonary vascular bed. Based on these criteria, 54 patients did not receive conventional long-term AC therapy.

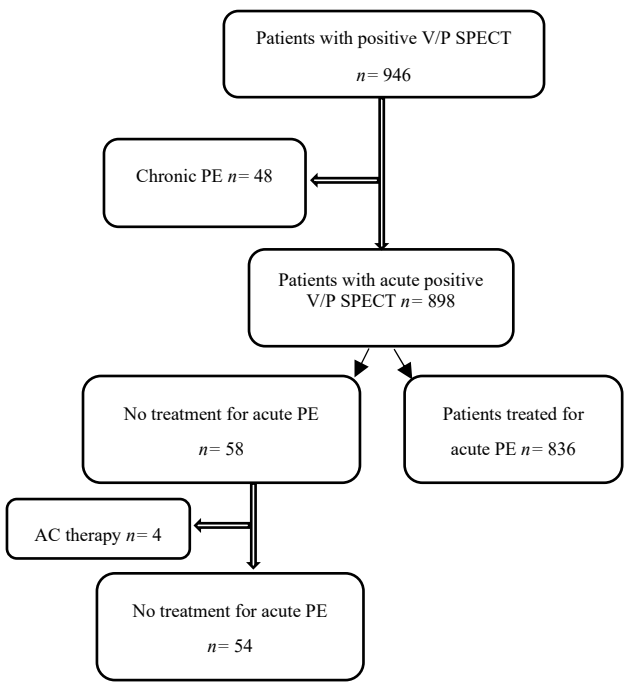

Figure 5. Flow diagram of patient selection in Paper I.

Papers II and III

Both papers II and III (Figure 6) report a retrospective multicenter cohort study in consecutive patients treated for acute PE with DOAC in the emergency departments of all eight hospitals in Sweden's southernmost health care region with 1.3 million inhabitants. The eight hospitals in the region, out of which one is a tertiary academic hospital, used pragmatic criteria for selection of PE patients suitable for outpatient treatment (Figure 4). We extracted data from AuriculA (Swedish quality register for anticoagulation) for all 881 patients between 2013 and 2015, and reviewed digital patient files and imaging databases. The following main baseline data were retrieved for paper II: symptoms, comorbidities, diagnostic method, sPESI score, malignancies diagnosed prior to or at diagnosis of PE, use of central venous catheters or oral contraceptive pills, pregnancy or postpartum state, and family history defined as VTE in first or second degree relatives, immobilization defined as ≥ 3 days of bedrest, trauma or major surgery, flight travel of > 5h, cast therapy within the previous month, thrombophilia, d-dimer (defined as positive if >0.25 mg/L), troponin T (defined as positive if>5 ng/L). Data on mortality, recurrent VTE, and bleeding complications defined according to the international Society on Thrombosis and Haemostasis during 6 months after diagnosis had been adjudicated by AuriculaA officers before entry into the registry.

In paper III all 881 patients were retrospectively assessed according to the risk stratification score sPESI[128]. As many factors might affect decisions on hospitalization, we restricted our comparison of out- and inpatients to low-risk PE patients with sPESI 0 and 1.

The cost data were obtained from the central economic unit of the administrative body of our Health Care Region, and are those debited to an insurance company or an external region. The cost data which were obtained are listed below:

1. Daily cost for hospitalization: 554 EUR (based on the average cost for room and staff, imaging, laboratory tests, and medication).
2. Outpatient visits to physicians: 175 EUR.
3. Outpatient visits to nurses: 131 EUR.
4. As the costs for the initial ED visit (435 EUR) and CT examination (255 EUR) was the same in both groups, these figures were not included in the calculations.
5. Cost for telephone appointments is not debited in our region.

In both papers II and III, PE patients were offered an appointment or telephone appointment with a nurse in a vascular unit within 72 hours and an appointment with a vascular physician within 4-6 weeks.

In paper II only descriptive statistics were calculated. In paper III we compared the in- and outpatient subgroups by Mann-Whitney tests. Multivariable analyses were performed regarding costs. Results were expressed as n (%), mean ± standard deviation (SD), or median and interquartile range (IQR) as indicated. Analyses were performed using SPSS for Windows, version 23.0 (SPSS Inc, Chicago, IL).

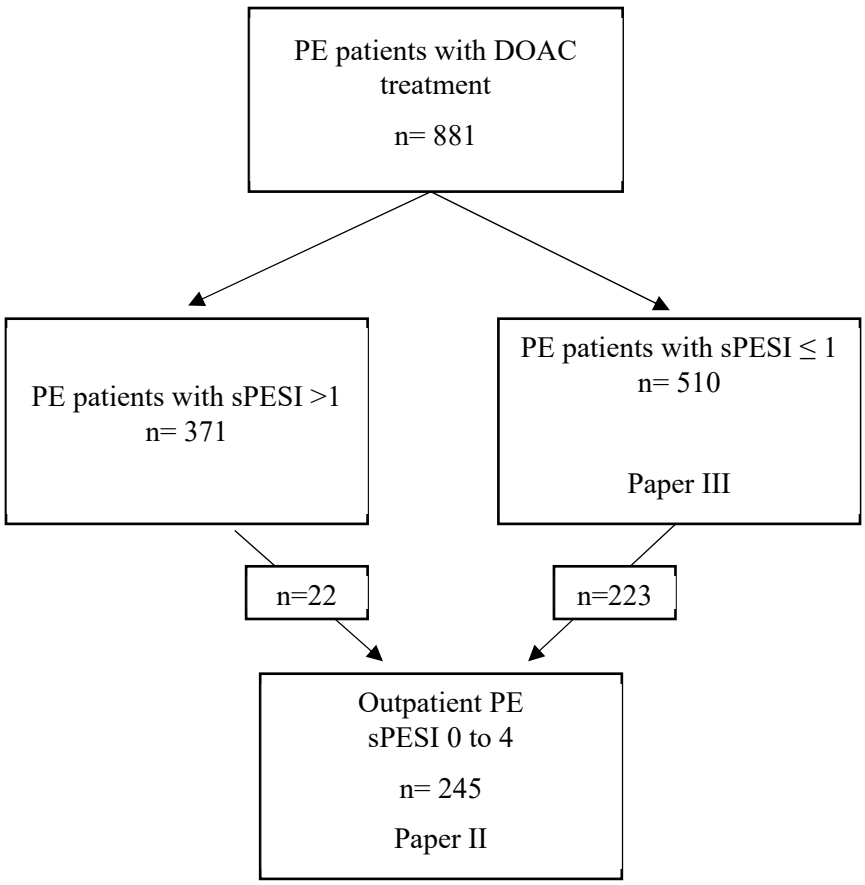

Figure 6. Flow chart illustrating patients with pulmonary embolism (PE) diagnosed between 2013 to 2015 in Swedens southernmost healthcare region treated with direct oral anticoagulants (DOAC). Retrospective calculation of simplified pulmonary embolism severity index (sPESI) describing patient selection in paper III and all outpatient treated PE patients in paper II.

Paper IV

Between November 2020 and December 2022, we performed a multicenter prospective cohort study involving three Vascular Medicine units in Region Skåne; Skåne University Hospital and two general hospitals, Kristianstad and Hässleholm, with a total catchment population of about 715,000 inhabitants. Patients with PE were selected for outpatient treatment (<24 h) at the ED in accordance with our regional selection criteria (Figure 4). DVT patients were selected for outpatient treatment in accordance with international guidelines[213]. PE patients were invited to complete a Pulmonary Embolism Quality of life (PEmb-QoL)[211] questionnaire, whereas both PE and DVT patients received a questionnaire aimed to evaluate the general well-being, EQ-5D-3L[214] instrument, including EQ-VAS within one week, after six weeks, and six months after diagnosis.

A power calculation (alpha 0.05, power 80%), indicated that 63 low-risk PE patients and 63 DVT patients were needed to evaluate a 15% difference in QoL in outpatient treated low-risk PE in comparison to DVT.

All patients were offered an appointment with a nurse within 72 hours and with a vascular physician within six weeks after diagnosis. Patients were excluded if they were aged <18 or >90 years or deemed incapable of complying with study procedures due to language barriers, disturbances of vision, dementia, or major psychiatric diagnoses. As background EQ-5D health status index is not available for the Swedish population, we used Danish data obtained by the EuroQoL website as a substratum for the calculation of the EQ-5D health profile. As no Swedish version of the PEmb-QoL questionnaire was available, we performed a forward-backward translation from the Norwegian version into Swedish, according to recommendations[215].

Inclusion of PE patients was severely delayed due to the COVID-19 pandemic. At the time of the interim analysis, 57 patients had been offered inclusion in the study, whereof 28 had been excluded due to lack of informed consent, length of stay in the ED > 24 h, or loss to follow up. The corresponding figures for DVT patients were 87, whereof 24 patients had been excluded. In total, 63 DVT patients and 29 PE patients were included in the analysis.

PEmb-QoL and EQ-5D-3L are provided in the appendix, page 73-81.

Statistics

Normally distributed variables are presented as mean and standard deviation (SD) and non-normally distributed variables as median (range). Descriptive analysis in

both PE and DVT groups, as well as comparative analyses between the two groups were performed using the Mann-Whitney U-test and the Wilcoxon signed-rank test.

Results

Paper I

At the time of withholding AC-therapy the majority of patients had risk factors predicting a high-risk PE i.e., malignancy, heart failure, COPD or elevated cardiac biomarkers, and only one patient had undergone ultrasound examination which was not repeated.

During 90 days of follow-up no deaths occurred. Seven patients were readmitted to hospital, however, only in five cases for suspected VTE. Four patients underwent phlebography or ultrasound of the lower extremities, whereof two patients (4%) were diagnosed with DVT necessitating long-term AC therapy.

The first patient with recurrent VTE was a 71-year-old patient who had received AC for 24 hours. He was readmitted 38 days after the final AC dose due to swelling of the left leg, and ultrasound confirmed a DVT extending up to the external iliac vein, provoked by plaster cast immobilization due to a tibial fracture. The second patient with recurrent VTE was a 92-year-old woman who had received AC for 20 days and was readmitted 52 days after the final dose of AC therapy due to swelling of the right leg. Ultrasound confirmed DVT extending up to the common femoral vein.

Paper II

Baseline characteristics and main findings at the six months follow-up are shown in Figure 7.

Two of our patients were in week nine of pregnancy at the time of PE diagnosis, contraindicating DOAC therapy[184 185 186]. In both these patients, pregnancy was terminated.

The majority of patients (97%) were treated for six months, whereas DOAC therapy was stopped after three months in seven patients. During six months of follow-up, one 72-year-old patient died with cardiac arrest of unknown cause during ongoing treatment with rivaroxaban. Autopsy was not performed, but acute echocardiography during resuscitation showed no dilatation of the right ventricle.

In total, nine patients underwent objective imaging for suspected recurrent PE during follow-up, but no patient was diagnosed with recurrent VTE.

One 61-year-old patient experienced major bleeding during DOAC therapy. The patient was admitted due to haemothorax caused by pneumonia and long-lasting cough. This caused a reduction of 20 g/L in haemoglobin level, but the patient was haemodynamically stable. However, investigation for underlying malignancy was negative, and treatment was changed from DOAC to LMWH.

Minor bleedings occurred in five (2%) patients during DOAC therapy, one patient with epistaxis, one with increased menstrual bleeding, two with macroscopic hematuria, and two with minor gastrointestinal bleeding.

During six months of follow-up, previously unknown malignancies were unveiled in three patients.

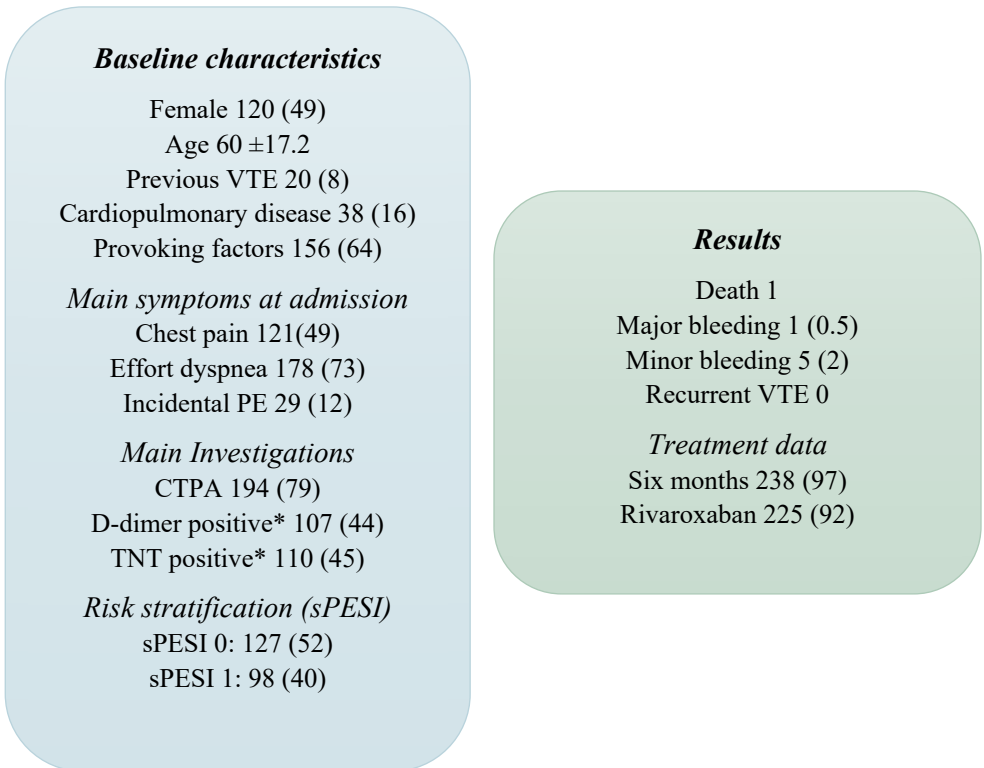

Figure 7. Baseline characteristics and six months follow-up of 245 outpatients in the Skåne Region treated with direct oral anticoagulants (DOAC) because of pulmonary embolism during 2013-2015, n (%) or mean±SD
CTPA= computed tomography of pulmonary arteries, sPESI = simple Pulmonary Embolism Severity Index, VTE = venous thromboembolism
*percentages of patients analyzed

Paper III

Among outpatients with PE, 97 (43%) had sPESI score 0 and 126 (57%) sPESI score 1, whereas the proportions in those selected for inpatient treatment were 112 (39%) and 175 (61%) respectively.

Inpatients were generally older ($p<0.001$, table 5), whereas gender distribution was equal. The cost in EUR per patient for hospital stay and outpatient visits during 6 months before and after diagnosis of low-risk PE (sPESI ≤1) was as following:

1. Inpatients had a mean stay of 7.4 days incurring a cost of 4,100 EUR for the index PE.
2. Inpatients had a higher number of hospital days six months before the acute PE episode leading to a cost difference between groups, 1,330 EUR in inpatients versus 720 EUR in outpatients ($p<0.001$).
3. Inpatients had a higher number of hospital days than outpatients during six months after PE diagnosis, 1,939 EUR versus 720 EUR ($p<0.001$).
4. The number of outpatient nurse- and physician visits during six months before and six months after the acute PE episode was also higher in the inpatient group ($p<0.001$, table 5), leading to a significantly higher total cost in the inpatient group 8,293 EUR versus 2,176 EUR in outpatients ($p<0.001$).
5. No mortality, recurrent VTE, or major bleeding episodes were observed during six months of follow-up in either group.
6. In multivariate analysis, type of treatment (in- or outpatient, $p<0.001$) and sPESI group (0 or 1, $p<0.001$) were both significantly associated with a total cost below or above median, whereas age or gender were not (table 6).

Subgroup analysis of sPESI 0 and sPESI 1

sPESI 0

Among the 238 patients with sPESI 0, 112 (47%) patients were hospitalized and 126 (53%) were treated as outpatients.

1. Inpatients had a mean of 7 days of hospital stay for the index PE incurring a cost of 3,933 EUR ($p<0.001$).
2. Total cost in the inpatient group (6,503 EUR) was higher compared to for outpatients (1,957 EUR, $p<0.001$).

sPESI 1

Among the 272 patients with sPESI 1,175 (64%) were treated in hospital and 97 (36%) as outpatients.

1. Inpatients had a mean stay of 7.6 days, incurring a cost of 4,210 EUR.
2. Inpatients had a significantly higher cost both at 6 months after the index PE (2,493 EUR versus 886 EUR, p=0.002) and when total cost was calculated (9, 440 EUR versus 2,922 EUR, p<0.001).

Table 5. Comparison of patients with pulmonary embolism (PE) and simplified pulmonary embolism score index (s-PESI) 0 and 1 treated with direct acting oral anticoagulants as outpatients or inpatients during 2013-2015. Costs in EUR per patient for hospital stay and outpatient visits during the six months before and after diagnosis of PE. N (%) or mean (IQR). LOS= length of stay.

All patients (n=510)	Inpatients (n=287)	Outpatients (n=223)	P-value	sPESI 0 (n=238)	Inpatients (n=112)	Outpatients (n=126)	P-value	sPESI 1 (n=272)	Inpatients (n=175)	Outpatients (n=97)	P-value
Age (years)	69 (SD 17)	65 (SD 15)	<0.001		60 (SD 15)	54 (SD 18)	0.007		69 (SD 15)	65 (SD 13)	0.011
Male gender	146(51)	111 (49)	0.806		48% (male)	45% (male)	0.976		53% (male)	50% (male)	0.652
LOS at PE diagnosis (days)	7.4 (3-8)				7.1 (3-5.8)		<0.001		7.6 (3-9)		<0.001
LOS 6 months prior to PE diagnosis (days)	2.4 (0-1)	1.3 (0-1)	<0.002		1.4 (0-1)	1.2 (0-1)	0.271		3.1 (0-3)	1.4 (0-1)	0.368
LOS 6 months post PE diagnosis (days)	3.5 (0-1)	1.3 (0-1)	<0.001		1.8 (0-1)	1.1 (0-1)	0.100		4.5 (0-3)	1.6 (0-1)	0.002
Total LOS (days)	13.1 (3-15)	3.0 (0-2)	<0.001		10.1 (3-8)	2.7 (0-1)	<0.001		15.1 (4-19)	3.3 (0-3)	<0.001
Nurse appointments 6 months prior to PE diagnosis	0.7 (0-1)	0.6 (0-1)	0.005		0.5 (0-0)	0.3 (0-0)	0.113		0.8 (0-1)	1.2 (0-1)	0.740
Physician appointments 6 months prior to PE diagnosis	1.3 (0-2)	1.5 (0-2)	0.001		1.1 (0-2)	1.1 (0-2)	0.601		1.5 (0-2)	2.1 (0-3)	0.055
Nurse appointments 6 months post PE diagnosis	1.0 (0-1)	1.0 (0-1)	<0.001		0.9 (0-1)	0.5 (0-1)	0.025		1.1 (0-1)	1.6 (0-1)	0.166
Physician appointments 6 months post PE diagnosis	2.7 (1-4)	2.5 (1-3)	0.014		2.4 (1-4)	2.2 (1-3)	0.500		2.9 (1-5)	3.0 (1-4)	0.462
Mortality	0	0			0	0			0	0	
Health care costs 6 months prior to PE diagnosis	1330	720	<0.001		776	665	0.271		1717	776	0.368
Health care costs at PE diagnosis	4100				3933				4210		
Health care costs 6 months after PE diagnosis	1939	720	<0.001		997	609	0.100		2493	886	0.002
Total hospital costs	7369	1440	<0.001		5706	1274	<0.001		8420	1662	<0.001
Nurse appointment costs prior to PE diagnosis	92	79	0.005		66	39	0.113		105	157	0.740
Physician appointment costs prior to PE diagnosis	228	263	0.001		193	193	0.601		263	368	0.055
Nurse appointment costs after PE diagnosis	131	131	<0.001		118	66	0.025		144	210	0.166
Physician appointment costs after PE diagnosis	473	263	0.014		420	385	0.500		508	525	0.462
Total cost	8293	2176	<0.001		6503	1957	<0.001		9440	2922	<0.001

Table 6. Multivariate analysis of factors influencing whether total treatment cost was above or below median in patients with pulmonary embolism (PE) and simplified pulmonary embolism score index (s-PESI) 0 and 1 treated with direct acting oral anticoagulants as outpatients or inpatients during 2013-2015.

	ß	P-value	OR	95% CI
Age	0.004	0.565	1.004	0.990-1.018
sPESI 0 or 1	-0.768	<0.001	0.464	0.301-0.715
Gender	-0.283	0.177	0.753	0.499-1.136
In or outpatient treatment	2.180	<0.001	8.842	5.793-13.496

Paper IV

From November 2020 to December 2022, a total of 29 PE and 63 DVT patients were enrolled and completed the questionnaire in the acute phase. The median age was 58 (48-73) years in PE patients and 64 (54-73) years in DVT patients. Male gender was predominant in both groups, 59% in PE and 62% in the DVT group.

Analysis of quality-of-life questionnaires

PE patients compared to DVT patients

1. No difference in HRQoL (EQ-5D-3L) was observed between patients with PE and DVT neither in the acute phase nor at six weeks.
2. At six months PE patients had a significantly lower EQ-5D index, mainly due to worse outcome in “pain/discomfort” and “anxiety/depression” domains, p=0.004 (Figures 8 and 9).

EQ-5D-3L questionnaire in PE patients

1. No significant improvements were noted in EQ-VAS and EQ-5D index.
2. EQ-VAS improved numerically throughout all follow-ups; 75 (50-85), 78 (69-90), 85 (50-90), and were numerically comparable to in the standard Danish population, 81.
3. EQ-5D index scores were numerically slightly worse during all follow-up stages compared to the value of 0.86 in the Danish population (Table 7).

Pulmonary embolism quality of life (PEmb-QoL) questionnaire

1. Significant improvements were seen in in FOC, ADL and WRP dimensions of the PEmb-QoL questionnaire at all three occasions (Table 7 and Figure 10).
2. No improvements were seen in SL, IOC, or EC between six weeks and six months of follow-up (Table 7).

EQ-5D-3L questionnaire in DVT patients

1. The EQ-5D index score was significantly better in the acute setting than after six weeks and six months follow-up, 0.77 vs 0.82 vs 1 ($p<0.001$).
2. EQ-VAS were also significantly better in the acute setting than after six weeks and six months follow-up, 75 vs 80 vs 80 ($p<0.05$, $p<0.05$).
3. No improvements were seen in EQ-5D index score or EQ-VAS when comparing results at six weeks and six months follow-up.
4. Both EQ-5D-3L and EQ-VAS were similar to the Danish background population (0.86 and 81) (Table 7).

Table 7. Health related quality of life in pulmonary embolism (PE) patients during follow-up. Pulmonary embolism Quality of life (PEmb-QoL) divided into dimensions and presented as median (range). EuroQoL 5 domains and 3 levels (EQ-5D-3L) and EuroQol visual analog scale (EQ-VAS) are presented as median (range) in PE and deep vein thrombosis (DVT) patients.

PE PATIENTS	ACUTE	ACUTE VS 6 WEEKS (P-VALUE)	6 WEEKS	6 WEEKS VS 6 MONTHS (P-VALUE)	6 MONTHS	ACUTE VS 6 MONTHS (P-VALUE)	
PEMBQOL	MEDIAN (IQR)		MEDIAN (IQR)		MEDIAN (IQR)		
FOC	0.80 (0.40-1.00)	p<0.001	1.00 (0.60-1.00)	p<0.001	1.00 (0.80-1.00)	p<0.05	
ADL	0.67 (0.67-1.00)	p<0.001	1.00 (0.67-1.00)	p<0.001	1.00 (0.67-1.00)	p<0.001	
WRP	0.50 (0.50-1.00)	p<0.05	1.00 (0.50-1.00)	p<0.05	1.00 (0.50-1.00)	p<0.001	
SL	0.40 (0.20-0.60)	p<0.05	0.20 (0.20-0.40)	p>0.05	0.20 (0.20-0.50)	p<0.05	
IOC	0.33 (0.17-0.67)	p<0.05	0.33 (0.17-0.50)	p>0.05	0.33 (0.17-0.33)	p<0.001	
EC	1.00 (0.67-1.00)	p<0.05	1.00 (0.83-1.00)	p>0.05	1.00 (0.83-1.00)	p<0.05	
EQ-5D-3L							Danish Population
PE PATIENTS							
EQ-5D	0.76 (0.68-1.00)	p>0.05	0.82 (0.76-1.00)	p>0.05	0.76* (0.19-0.76)	p>0.05	0.86
EQ-VAS	75 (50-85)	p>0.05	77.5 (68.7-90)	p>0.05	85 (50-90)	p>0.05	81
DVT PATIENTS							
EQ-5D	0.77 (0.66-0.82)	p<0.001	0.82 (0.76-1.0)	p>0.05	1 (0.82-1.0)	p<0.001	
EQ-VAS	75 (60-90)	p<0.05	80 (70-90)	p>0.05	80 (70-95)	p<0.05	

*p<0.05 in PE versus DVT patients.
FOC = Frequency of complaints, ADL = Activity of daily living, WRP = Work related problems, SL = Social limitations, IOC = Intensity of complaints, EC = Emotional complaints

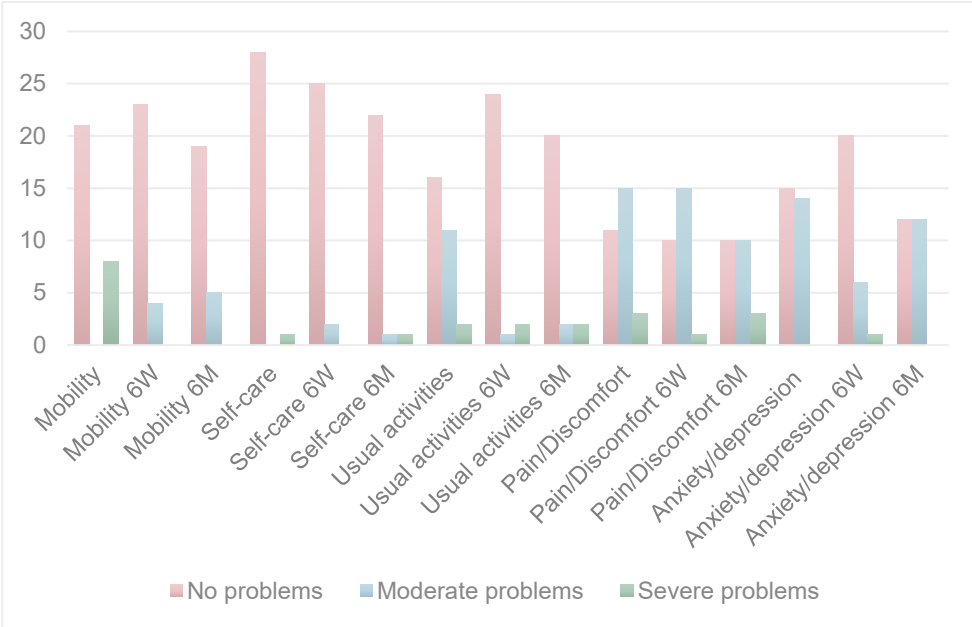

Figure 8. Bar chart showing EuroQoL-5 dimension and 3 levels (EQ-5D-3L) in 29 pulmonary embolism (PE) patients at diagnosis, 27 at six weeks, and 24 at six months. Y-axis=number of patients

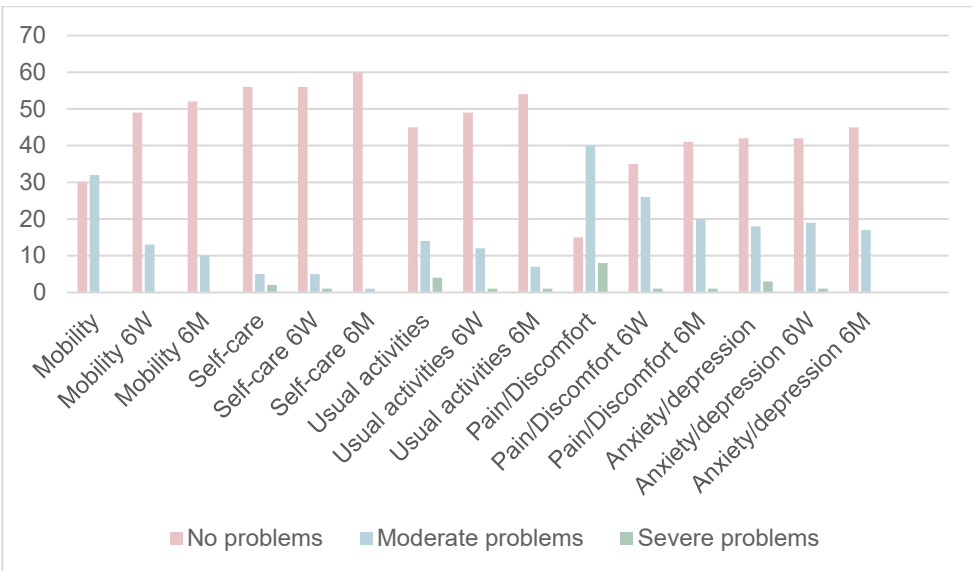

Figure 9. Bar chart showing EuroQoL-5 dimensions and 3 levels (EQ-5D-3L) in 63 deep vein thrombosis (DVT) patients at diagnosis, 62 at six weeks and six months follow-up. Y-axis=number of patients.

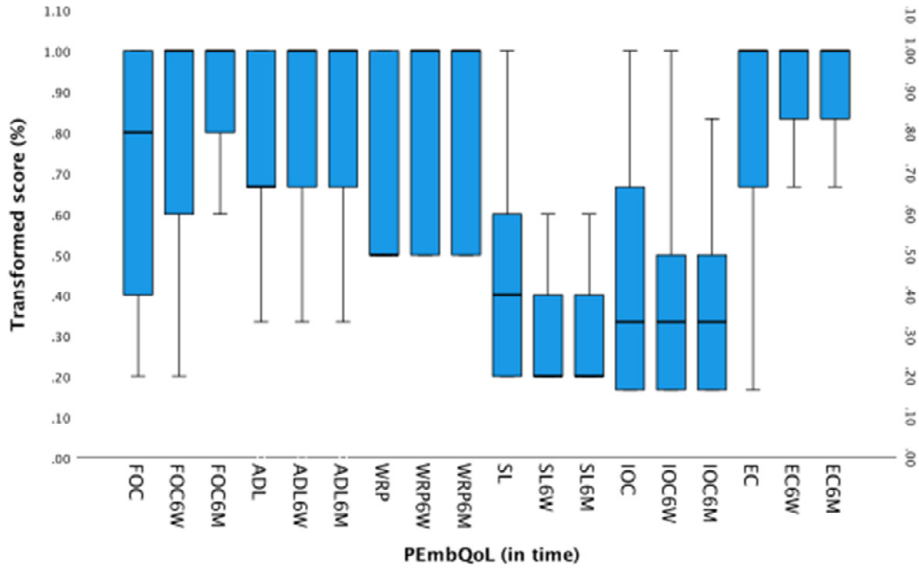

Figure 10. Boxplot of Pemb-QoL dimension and summary scores in 29 low-risk pulmonary embolism (PE) at diagnosis, after six weeks and after six months of follow-up. Median (IQR), min, max. In FOC, ADL, WRP, and EC a high score indicates a better quality of life, whereas in SL and IOC a low score indicates a better quality of life. Health state index scores range from 0-1, where 0 is a health state equivalent to death and 1 is equivalent to perfect health. FOC = Frequency of complaints, ADL = Activity of daily living, WRP = Work related problems, SL = Social limitations, IOC = Intensity of complaints, EC = Emotional complaints

Discussion

In this thesis we attempted to recognize some clinically relevant questions as listed below.

Paper I - Is it safe to withhold AC therapy in low-risk PE patients?

A cross-sectional survey[193] on clinician's opinions showed that physicians are comfortable with withholding of AC therapy if the three months risk for recurrent VTE is <2%.

In paper I, withholding of conventional long-term AC therapy in small PE patients diagnosed by V/P SPECT was associated with a recurrence rate of VTE in 2/54 (4%), however, neither recurrent PE nor deaths were observed. These figures are higher than retrospectively reported by Goy et al[216], who experienced no recurrences among 30 SSPE patients at three months follow-up. Similar results were reported by Carrier and co-workers who observed no recurrences in 60 patients with SSPE[217]. Furthermore, the bleeding risk in patients with AC therapy is approximately 2-4%/year[51], and Goy and colleagues[217] observed major bleeding events in 2/43 SSPE patients on AC therapy. Surprisingly, den Exter et al[218] reported 3.5% recurrences in 116 SSPE patients during AC therapy.

Le Gal et al[194] reported a recurrence rate of VTE in 3.1% in 266 patients without AC therapy in a multicentre prospective cohort study. These results are comparable to our study, however, in their study[194] all participants underwent bilateral lower-extremity venous ultrasonography at diagnosis which was repeated one week later if results were negative at diagnosis. In addition, they reported that the incidence of recurrent VTE was 2.1% in patients with single SSPE, 5.7% in those with multiple SSPE, 1.8% in patients aged ≤65 years, and 5.5% in older patients.

Future studies with a cutoff of <5% or <10% for the extent of perfusion defects in V/P SPECT (compared <20% in our study) and bilateral lower-extremity venous ultrasonography at diagnosis might perhaps result in lower risk for recurrent VTE.

As current international guidelines suggest long-term therapy in patients with unprovoked VTE, withholding of AC-therapy could be considered as a "protocol

violation"[50 51 213]. However, the matter could perhaps still be discussed in patients with an asymptomatic SSPE provoked by a strong transient risk factor without any inherited risk factors? Furthermore, the different properties of individual risk factors need to be taken into account, increasing age is linearly correlated to increased risk for VTE[14 37] whereas other risk factors such as trauma or surgery are transient [32 33]. If this question is to be answered, systematic prospective investigation of patients with acquired, inherited, transient, or persistent risk factors[196 198] need to be performed. In such studies, frequent diagnostic investigations during the follow-up period would also be valuable. A prospective multicentre randomised placebo-controlled non-inferiority trial is ongoing, the SAFE-SSPE (NCT04263038)[219] , which may perhaps lead to increasing understanding and knowledge regarding treatment strategies in SSPE patients.

Paper II-IV - Is it safe and efficient to treat selected PE patients with DOAC on an outpatient basis, is it cost-effective, and how is the quality of life in these patients?

Two articles published in the 1990's, one by Koopman et al[220] and the other by Levine et al[221], indicated that outpatient-based treatment was safe and effective in both selected PE and DVT patients. In both these studies, the result could not be translated into practice, however, as many DVT patients had been excluded from outpatient treatment. In the study by Levine et al[221], less than half of the PE patients had actually been randomized. In the end of the 1990's, Wells et al[222] demonstrated that outpatient treatment was possible in selected PE patients, and that self-administered injections of LMWH could be accomplished by 50% of patients. In the early 21st century Aujesky et al[127] derived the PESI score[127] to predict overall 30-day mortality in PE patients, and select those with low 30-day mortality for outpatient treatment or early discharge. Aujesky and other authors intended to show that outpatient treatment potentially resulted in large cost savings without added risk. Subsequently, Jimenez et al[128] published a simplified version of the PESI score, the sPESI score. Not long thereafter, the Hestia criteria[130] were established for the evaluation of safety and efficacy of outpatient treatment. Furthermore, in the beginning of the 21st century DOAC[160] gradually replaced Warfarin and LMWH, and the practicalities regarding monitoring of treatment slowly decreased.

At this stage our patient material for paper II was retrieved by using our regional selection criteria (Figure 4). Our definition of outpatient treatment was similar to the HESTIA study[131], as patients were discharged within 24 hours of diagnosis after assessment of pragmatic criteria like social circumstances, high bleeding risk, and judgment of expected compliance with treatment. In a meta-analysis of outpatient treatment of PE with warfarin and LMWH, Zondag and co-workers[223] identified 13

studies in which the 24-hour limit had been applied, and five other studies defining early discharge (<72 h) after admission. None of these studies included patient on DOAC therapy, however. Similarly, Roy et al[224] published a systematic review, including three meta-analyses and 23 studies, in total 3,671 patients managed at home, whereof only 35 patients received DOAC[225]. In this systematic review all patients had at least three months of follow-up, with <2% overall rate of VTE recurrences and <3% of major bleeding. In our study we report no VTE recurrences and only one case (0.4%) of major bleeding. This might perhaps reflect the fact that DOACs have a significantly reduced rate of major bleeds compared to LMWH in combination with warfarin[160].

HOME-PE[226], a randomized trial triaging acute PE patients for outpatient treatment by either Hestia[130] or sPESI[128] criteria recently showed that approximately one third of patients included in both groups could be treated on an outpatient basis. These results are comparable to our data presented in papers II and III for which patients had been extracted from Auricula from 2013 to 2015. In our study, the decision regarding low-risk PE outpatient treatment in 245 of 881 patients had been based on the judgement of physicians on call using our selection criteria (Figure 4). In the HOME-PE, the proportion of patients discharged within 24 hours were as following; Hestia group 38.4% (378/984) and sPESI group 36.6% (361/986). Notably, the low risk sPESI = 0 had been overruled in 28.5% of patients and the negative Hestia rule had been overruled in only 3.4% of patients. In the former group, the algorithms were mainly overruled based on concomitant illness and social reasons. Similar results obtained with our pragmatic selection criteria, as 112 patients with sPESI 0 in paper III (Figure 6) for some reason had been admitted to inpatient treatment. The use of our selection criteria also resulted in that 50% of patients selected for outpatient treatment had a non-low risk sPESI score. In HOME-PE, adverse events occurred in 1.3% of patients in the Hestia outpatient group and 1.1% in the sPESI group[227]. These results are comparable to ours, but in HOME-PE the incidence of adverse events was slightly higher.

In addition, the HOT-PE trial[227] prospectively reported data regarding the safety and efficacy of outpatient treatment in 525 PE patients receiving rivaroxaban, selected by criteria adapted from the Hestia management study[131]. The definition of outpatient treatment was wider than in our study (within 48 hours versus <24 h). Similar results to ours were reported, however, three non-fatal cases of recurrent VTE and major bleeding in 1.2%.

It is now apparent that outpatient treatment of PE using different selection criteria is safe and efficient in low-risk PE. Nevertheless, PE patients are still often treated in a hospital-based manner, despite LOS of up to 6 days[228]. As previously mentioned, however, national inpatient data from Sweden revealed that LOS for PE patients was 5.7 days in 2011 and 4.3 days in 2021. In our study we observed a LOS of 7.4 days which may perhaps reflect that our selection for inpatient treatment represents a selected group with a high degree of comorbidity. Nevertheless,

hospitalization is the major driver of total cost, any reduction in the number of inpatient days may translate into important cost savings[178]. In paper III we revealed a total cost difference of 6,117 EUR between in and outpatient treated low-risk PE patients. This was mainly driven by the difference in the cost for hospital stay caused by the index acute episode of PE, however, inpatients also spent slightly more time in hospital before and after the acute PE. Furthermore, as both the in- or outpatient treatment variable and the sPESI group variable were associated with costs in multivariate analysis, it was of special interest to evaluate sPESI group 0 and 1 separately, documenting cost savings with outpatient treatment in both groups. Paper III corroborates the results of Dasta et al, who showed that LOS is a major cost driver in PE and that any reduction in LOS may translate into relatively important cost savings[178]. As previously mentioned, DOAC have a more predictable dose response than warfarin and allows fixed dosage without the need for routine laboratory monitoring, DOAC treatment in itself might therefore potentially lead to shorter hospitalization. Dobesh and co-workers reported that such advantages could reduce the costs for the health care system by potentially preventing recurrent VTE and its complications[229]. To determine whether prolonged LOS is always caused by complications, or in itself might lead to complications is not always easy, however. Wang et al recently presented data from 1,918 patients with low-risk PE, whereof 688 with short LOS (≤2 days). Total costs in those with short and long LOS were 9,065 and 12,544 USD, respectively, implying that low-risk PE patients with short LOS had a better net clinical outcome at a lower cost than matched low-risk PE patients with long LOS[230]. Among our patients selected for either out- or inpatient treatment, total costs were 2,176 EUR and 8,293 EUR, respectively. However, it must be kept in mind that our patients had a higher mean age and a more balanced gender distribution compared to previous studies[231]. Furthermore, there were no recurrent VTE or major bleeds in our study reported in paper III, whereas Wang and colleagues reported 14 recurrent DVTs and 5 bleeding episodes[231]. As some of their patients underwent thrombolysis or placement of inferior vena caval filters, one might suspect that these patients had a more complicated course of PE than those in our paper III.

Dasta and co-workers[178] presented data from patients with a slightly lower mean LOS (5.4 days), and mean age (60 years) than in our study. The mean daily cost per patient reported was 1,735 USD, whereof room and board accounted for 38% to 59% of the total cost, and was the main cost driver in our study as well. Furthermore, the use of LMWH injections during institution of warfarin treatment is associated with prolonged hospital stay[231]. Coleman et al showed that rivaroxaban use was associated with a 1.36-day shorter LOS and 2,304 USD reduction in total costs compared to parenteral bridging during institution of warfarin. Similarly, Bookhart and colleagues[188] showed that rivaroxaban use resulted in a 1.7-day mean reduction in LOS compared with enoxaparin and warfarin, enabling a reduction of total hospital cost of 3,000 dollars per patient. Costs incurred by PE in different medical systems cannot be directly compared, however.

By now, the development of validated selection criteria and a more feasible anticoagulation therapy, has resulted in a safe manner reduction of LOS which in turn reduces overall treatment costs. The question whether the development of new drugs and criteria for outpatient treatment has implications for a PE patient´s quality of life still has to be answered, however. We therefore conducted a prospective QoL study using our selection criteria for outpatient treatment of low-risk PE patients in comparison to outpatient treated DVT patients, a group which has already been shown to have a favourable outcome in QoL[232]. Our results reported in paper IV show that PE patients had a HRQoL comparable to DVT patients during the acute and initial phase of treatment which is reassuring for the concept of outpatient treatment. It would of course be interesting to know if results would have been different if patients had been randomised to in- or outpatient treatment, but probably most patient will prefer being at home instead of hospitalized. After six months, however, PE patients had a slightly lower score in the generic tool, which might perhaps be explained by the drop in the domains "pain/discomfort" and "anxiety/depression" in EQ-5D in PE patients at six months. Symptoms of depression, anxiety, and increased utilization of psychotropic drug among VTE patients have been associated with AC therapy and the fear of recurrent VTE[208 233]. One may speculate that termination of AC therapy in more than half of our patients with distally located DVT when apparently considered as "healthy" might perhaps have contributed to our findings. Nevertheless, FOC, ADL, and WRP dimensions of the disease specific questionnaire in PE patients significantly improved from diagnosis to the six month follow up.

Both DVT and PE patients had EQ-VAS scores comparable to the background Danish population after six months follow-up. This is remarkable, but might be explained by the fact that our patients suffered from low-risk PE and in 54% of cases also had a distal DVT. The threshold value reflecting the minimal clinically important difference in the EQ-5D instrument has been debated, and suggestions range between 0.04 and 0.08[234].

Tavloy and colleagues[235] assessed QoL with EQ-5D-3L in PE patients 3.8 years after diagnosis, reporting significantly lower EQ-VAS (67 vs 81) score and EQ-5D index (0.80 vs 0.86) compared to the background Danish population.

In line with our results, Barco and co-workers[212] reported improvements in EQ-5D-5L index from three weeks to three months (0.89 to 0.91), EQ-VAS (76 to 80) and improvements in all dimensions of PEmb-QoL at three months follow-up in outpatient treated PE patients. These results are not directly comparable to ours, as EQ-5D-5L compared with EQ-5D-3L generally underestimates health problems (i.e. the level of index score is higher in EQ-5D-5L). However, Klok et al[211] reported decreased QoL in all subscales of the 36-item Short Form Survey (SF-36) in PE patients 3.6 years after diagnosis compared to the values of the Dutch population norms. Furthermore, the time interval between PE and study inclusion was inversely related to QoL. Chuang and colleagues[209] reinforced this statement by

evaluating EQ-5D-5L and PEmb-QoL in PE patients from seven European countries. In all seven countries, patients with PE had lower QoL compared to the general population. In the studies by both Klok et[211] al and Chuang et al[209], however, the vast majority of PE patients were not highly selected outpatients as in our paper IV. This difference might perhaps explain that EQ-VAS in our patients was similar to in the background population after six months of follow-up.

van Es et al[210] investigated the correlation between thrombus-load as expressed by Qanadli score[236] and the location of the thrombus (central, lobar, segmental, or subsegmental) and QoL. Centrally located PE or higher thrombus load did not appear to affect long-term QoL as reflected by PEmb-QoL and SF-36. Using our selection criteria, a low thrombus load was one of the main criteria for outpatient treatment. As deconditioning might occur during follow-up of PE regardless of its initial severity, this selection criterion may not necessarily affect the generalizability of our results.

These findings might be interpreted as indicating that QoL in PE patients overall is worse than in the background population. Direct comparison of QoL in PE patients between countries is hampered by different standard population indexes and different clinical settings, however, and the PEmb-QoL might perhaps be too complicated to be implemented in clinical practice. Recently, the Post-VTE functional status scale[237] for assessment of functional limitations in VTE patients has been developed, and can be used in both DVT and PE patients, potentially enhancing our understanding of QoL in VTE patients. Its brevity and interpretability will presumably lead to greater utilization of QoL instruments in daily clinical practice.

Conclusions

Withholding of conventional long term AC therapy in patients diagnosed with small PE with V/P SPECT (<20% extension of perfusion defects) was associated with a 4% risk of VTE diagnosis during three months of follow-up. This would not be considered acceptable for the majority of clinicians, and can therefore not be recommended. It remains to be studied whether AC therapy could be withheld in selected groups of young patients with a single isolated SSPE and in patients with high bleeding risk during close monitoring for recurrent VTE.

Outpatient PE treatment with DOAC after selection of low-risk PE patients with our risk stratification tool was safe and efficient, and constitutes a promising strategy to decrease the economic burden to society caused by this disease.

Although costs incurred by PE in different medical systems cannot be directly compared, there is a strong correlation between the economic burden of PE and LOS. Outpatient PE treatment with DOAC after selection with validated risk stratification tools and comorbidities taken into account decreases the economic burden of the disease to the society.

Health related quality of life in low-risk PE patients was similar to DVT patients at diagnosis and after six weeks of follow-up. Furthermore, as their self-rated overall health status was comparable with the background population, low-risk PE patients have an acceptable HRQoL. Direct comparison of QoL in patients with PE across different countries is not possible, however, as this is influenced by various factors such as different healthcare systems, socio-economic factors, and cultural norms. Further investigations are needed to provide truly patient-centered care for VTE patients.

Limitations

Paper I: One of the main limitations is that we conducted a retrospective clinical follow-up study. The study should preferably have been performed in a prospective randomized manner, with pre-specified criteria for withholding AC-therapy and sequential follow-up by for example bilateral ultrasound of lower extremity and CTPA/V/P SPECT if needed. A thorough risk factor assessment regarding both acquired and inherited risk factors for VTE at baseline would be important.

Paper II: The major limitations of the study are its retrospective nature and the lack of randomization. Furthermore, the rationale for selection for out- or inpatient treatment, as well as data concerning comorbidities were not obtained at baseline. It was therefore not possible to calculate Charlson comorbidity index, which would have provided a proxy for disease burden and could have been used as a covariate in a propensity score adjustment of the out- and inpatient groups.

Paper III: Our study is retrospective and not fully matched in terms of other comorbidities, and the selection of patients for in- and outpatient treatment was based upon clinical judgement guided by regional criteria, and not randomized. It is also important to note that our results might not be generalizable to other health care systems. Furthermore, patients were not assessed after six months concerning long-term complications such as chronic thromboembolic pulmonary hypertension, a condition associated with high costs. As this condition rarely occurs in patients with low-risk PE, however, this is probably not an important study limitation. A potentially important limitation, however, is that we did not have the possibility to assess whether the number of sick-leave days or potential outpatient visits outside the hospital differed between groups.

Paper IV: As randomization of low-risk PE patients for in- versus outpatient treatment was not possible, comparisons of PE and DVT patients were performed instead. Furthermore, an EQ-5D index calculator was only available for the Danish standard population and comparison with the Swedish standard population was therefore not possible.

Future perspectives

Artificial intelligence might enhance detection of small PE[238], and telemedicine can provide remote monitoring and support for patients undergoing outpatient treatment for low-risk PE. This can include virtual consultations, remote monitoring of vital signs, and video-based education on self-management of symptoms and medications.

Patient education and self-management programs can empower patients to both take a more active role in their care and prevent complications through education on medication adherence, symptom recognition, and when to seek medical attention.

Patient-centered outcomes: Future research in low-risk PE should focus on patient-centered outcomes reflecting patients experience and preferences. This can include measures of symptom burden, functional status, and psychological well-being.

Collaborative care models involve a multidisciplinary team of healthcare providers might hopefully improve HRQoL outcomes by addressing the complex needs of patients with low-risk PE. This can include coordination of care across different healthcare settings, involvement of specialists such as physical therapists and psychologists, and shared decision-making.

Future research is needed to better understand the optimal duration of anticoagulation therapy in SSPE. The treatment of SSPE may perhaps be individualized based on patients' characteristics such as age, comorbidities, and bleeding risk. As anticoagulation therapy may be contraindicated in specific clinical circumstances, observation or surveillance imaging might be of specific importance for certain patients.

Future research in low-risk PE should focus on patient-centered outcomes, such as QoL and functional status to ensure that the benefits of home-based AC therapy outweigh the potential risks and burdens.

Populärvetenskaplig sammanfattning

Venös blodpropp, så kallad trombos, kan uppstå i alla kroppens vener, men är vanligast i form av djup ventrombos i benet (DVT) och blodpropp i lungan, så kallad lungemboli (LE). Sjukdomen drabbar cirka 5% av befolkningen under livstiden och har ett brett prognostiskt spektrum, inkluderande allt från god prognos till plötslig död. Symptomen av en blodpropp kan variera från svullnad i benet till andfåddhet, bröstsmärta och yrsel. Diagnosen ställs genom ultraljud eller kontrastundersökning av de djupa blodådrorna i benet alternativt datortomografi eller lungscintigrafi av lungkärlen. Modern blodförtunnande behandling vid venös blodproppsjukdom är effektiv och säker. Hembehandling av LE har diskuterats sedan 90-talet. Olika sätt att bedöma patienternas risk kan användas för att identifiera de patienter med låg risk som är lämpliga för hembehandling av LE. Numera rekommenderar både de europeiska och amerikanska riktlinjerna hembehandling av patienter med lågrisk LE. Tidigare har blodförtunnande behandling bestått i subkutana sprutor tillsammans med tabletter (waran) som kräver noggrann uppföljning. Detta kräver mycket sjukhusresurser och upplevs besvärligt av patienterna. Sedan införandet av nya läkemedelstyper, s.k. direktverkande oral antikoagulation (DOAK) har hembehandling underlättats med kvarstående säkerhet.

Denna avhandling har studerat flera aspekter rörande patienter med lågrisk LE.

Studie I: Med förbättrad objektiv diagnostik och ökad medvetenhet om lungembolidiagnosen har antalet och andelen patienter med framför allt små perifera LE ökat. Många internationella riktlinjer föreslår att man kan avstå från blodförtunnande behandling om man samtidigt friar från DVT. Detta vore önskvärt eftersom blodförtunnande behandling är förenad med blödningsrisk på ca 2–4% per år. För att motivera blodförtunnande behandling bör risken med att avstå från behandling vara högre. Vi identifierade 54 patienter med små LE, men som efter klinisk bedömning inte bedömdes ha en behandlingskrävande lungemboli. I denna studie utvärderade vi förekomsten av återfall av venös blodpropp under påföljande tre månader. Det visade sig att 2/54 (4%) patienter diagnostiserades med DVT under uppföljningsperioden. Denna risk ska jämföras med en ca 2% risk efter en normal röntgenundersökning av lungkärlen.

Studie II: Hembehandling av patienter med akut lungemboli har de senaste åren väckt allt större intresse. Hanteringen har underlättats av att DOAK-preparaten till stor del har ersatt waranbehandling. Flera olika modeller har tagits fram för att

identifiera de patienter som kan behandlas på ett säkert sätt i hemmet. Vi har i Region Skåne i många år använt oss av klinisk bedömning av patienten tillsammans med ett antal variabler inkluderande värdering av den anatomiska utbredningen av lungembolierna. I denna studie utvärderade vi vår algoritm avseende säkerhet och effektivitet samt jämförde med en annan beprövad modell (pulmonary embolism severity index, PESI). Vår algoritm fungerade väl i klinisk praxis. Ungefär en tredjedel av patienterna med DOAK behandlades i hemmet, ingen patient drabbades av recidiv, ett allvarligt blödningsfall skedde men ingen patient dog av blodpropp under sex månaders uppföljning. Vi noterade att endast hälften av dessa patienter skulle ha kunnat behandlas i hemmet om vi istället använt PESI-modellen.

Studie III: Efter att ha konstaterat att hembehandling av patienter med lågrisk LE är säker och effektiv ville vi gå vidare och utvärdera dess kostnadseffektivitet. Vårdtiden på sjukhus för LE patienter brukar ligga runt 4 till 6 dagar, men införandet av DOAK-preparaten har sannolikt förkortat vårdtiderna jämfört med tidigare blodförtunnande behandling med injektioner och warantabletter. Förutom att spara sängplatser på sjukhusen var syftet i vår tredje studie att utvärdera om hembehandling av låg risk LE gav hälsoekonomiska vinster. Då det skulle kunna tänkas att vinsten av de sparade vårdplatserna konsumeras av andra kostnader kring hembehandling och ett ökat vårdbehov polikliniskt jämförde vi inneliggande och hembehandlade lågriskpatienter med lungemboli. Resultatet visade att man kunde minska kostnaderna med cirka 60 000 kr per patient vid hembehandling jämfört med patienter med jämförbar lågrisk LE som behandlades inneliggande.

Studie IV: Hembehandling av patienter med lågrisk akut LE är således säkert, effektivt och kostnadsbesparande. En aspekt som däremot inte varit tillfredsställande klarlagd tidigare, är hur patienten själv uppfattar hembehandlingen. Detta resulterade i att vi utförde en hälsorelaterad livskvalitetstudie. Det finns både ett generellt (EQ-5D-3L) och sjukdomsspecifikt (PEmb-QoL) frågeformulär för att mäta livskvalitet. Vi valde patienter som hembehandlats med DVT i stället för inneliggande lungembolipatienter som jämförelsegrupp då vi annars hade fått en orättvis jämförelse, eftersom inneliggande patienter ofta har andra orsaker till slutenvård och en högre samsjuklighet vilket kan påverka deras livskvalitet. Hembehandlade LE patienter utvärderades också med det sjukdomsspecifika PEmb-QoL frågeformuläret. EQ-5D-3L utvärderades i akutskedet, samt cirka 6 veckor och 6 månader därefter hos 63 patienter med DVT och 29 patienter med LE. Vi fann att EQ-5D-3L var likvärdigt hos DVT och LE patienter under akutskedet och efter 6 veckors uppföljning, och att LE patienters sjukdomsspecifika livskvalitet förbättrades under uppföljningsperioden. Båda patientgrupper hade en livskvalitet som var jämförbar med bakgrundsbefolkningen. Detta talar för att hembehandlade lungembolipatienter har en jämförbar livskvalitet med de DVT patienter vilka sedan många år rutinmässigt behandlas i hemmet.

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Last but not least, **my dear family,** my mother **Ozra**, my father **Bagher,** and my sister **Rofida**. I do not know where to start and where to end. My gratitude towards you is limitless and words cannot describe it. Therefore, I dedicate a poem from Hafez as an expression of my love:

این پایان نامه را ضمن تشکر و سپاس و در کمال افتخار و امتنان تقدیم می نمایم به مادر، پدر و خواهرم. آنان که آفتاب مهرشان در آستانه قلبم همچنان پابرجاست و هرگز غروب نخواهد کرد.

مادر مهربانم که زندگیم را مدیون مهر و عطوفت آن می دانم

پدر، مهربانی مشفق، بردبار و حامی

و خواهرم همراه همیشگی و پشتوانه زندگیم

منم که شهره شهرم به عشق ورزیدن
منم که دیده نیالوده ام به بد دیدن
وفا کنیم و ملامت کشیم و خوش باشیم
که در طریقت ما کافریست رنجیدن
به پیر میکده گفتم که چیست راه نجات
بخواست جام می و گفت عیب پوشیدن
مراد دل ز تماشای باغ عالم چیست
به دست مردم چشم از رخ تو گل چیدن
به می پرستی از آن نقش خود زدم بر آب
که تا خراب کنم نقش خود پرستیدن
به رحمت سر زلف تو واثقم ور نه
کشش چو نبود از آن سو چه سود کوشیدن
عنان به میکده خواهیم تافت زین مجلس
که وعظ بی عملان واجب است نشنیدن
ز خط یار بیاموز مهر با رخ خوب
که گرد عارض خوبان خوش است گردیدن
مبوس جز لب ساقی و جام می حافظ
که دست زهدفروشان خطاست بوسیدن

دیوان حافظ

Appendix

Hälsoenkät

Svensk version

(Swedish version)

Markera, genom att kryssa i en ruta i varje nedanstående grupp (så här ☑), vilket påstående som bäst beskriver Ditt hälsotillstånd i dag.

Rörlighet

Jag går utan svårigheter ❑
Jag kan gå men med viss svårighet ❑
Jag är sängliggande ❑

Hygien

Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning ❑
Jag har vissa problem att tvätta eller klä mig själv ❑
Jag kan inte tvätta eller klä mig själv ❑

Huvudsakliga aktiviteter *(t ex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)*

Jag klarar av mina huvudsakliga aktiviteter ❑
Jag har vissa problem med att klara av mina huvudsakliga aktiviteter ❑
Jag klarar inte av mina huvudsakliga aktiviteter ❑

Smärtor/besvär

Jag har varken smärtor eller besvär ❑
Jag har måttliga smärtor eller besvär ❑
Jag har svåra smärtor eller besvär ❑

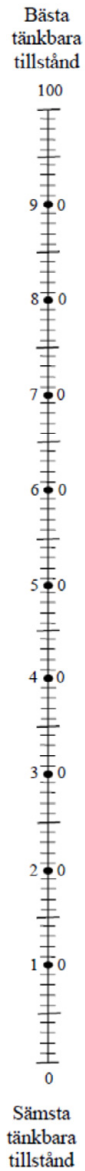
Oro/nedstämdhet

Jag är inte orolig eller nedstämd ❑
Jag är orolig eller nedstämd i viss utsträckning ❑
Jag är i högsta grad orolig eller nedstämd ❑

Till hjälp för att avgöra hur bra eller dåligt ett hälsotillstånd är, finns den termometer-liknande skalan till höger. På denna har Ditt bästa tänkbara hälsotillstånd markerats med 100 och Ditt sämsta tänkbara hälsotillstånd med 0.

Vi vill att Du på denna skala markerar hur bra eller dåligt Ditt hälsotillstånd är, som Du själv bedömer det. Gör detta genom att dra en linje från nedanstående ruta till den punkt på skalan som markerar hur bra eller dåligt Ditt nuvarande hälsotillstånd är.

Ditt nuvarande hälsotillstånd



Enkät om livskvalitet efter att ha drabbats av lungemboli

Instruktioner för ifyllande av enkäten:

Varje fråga besvaras genom att markera det svar som passar bäst. Om du är osäker på hur du skall besvara frågan, vänligen välj det svarsalternativ som stämmer bäst.

Dessa frågor handlar om dina **lungor**. Svaren skall beskriva hur du känner dig. Du kan också ange i vilket utsträckning du kan utföra normala vardagliga aktiviteter.

1. Under de sista 4 veckorna, hur ofta har du haft något av följande symtom från lungorna?

(ringa in ett svar per rad)

	Dagligen	Flera gånger/ vecka	Ungefär 1 gång/vecka	Mindre än 1 gång/vecka	Aldrig
Smärta mellan skulderbladen	1	2	3	4	5
Smärta i bröstet	1	2	3	4	5
Smärta i ryggen	1	2	3	4	5
Tryckkänsla	1	2	3	4	5
Känsla av att det "fortfarande är något fel"	1	2	3	4	5
Brännande känsla i lungorna	1	2	3	4	5
En "irriterande" känsla i lungorna	1	2	3	4	5
Svårigheter att andas eller andfåddhet	1	2	3	4	5

2. Vid vilken tid på dygnet är **symtomen från lungorna** som mest intensiva? (Ringa in ett svar)

1. När du vaknar
2. Mitt på dagen
3. Mot slutet av dagen
4. Under natten
5. Under alla dygnets timmar
6. Aldrig

3. Jämfört med för ett år sedan, hur skulle du beskriva att dina **lungors tillstånd** är nu, generellt sett?

1. Mycket bättre än för ett år sedan
2. Lite bättre än för ett år sedan
3. Ungefär detsamma som för ett år sedan
4. Lite sämre än för ett år sedan
5. Mycket värre än för ett år sedan
6. Jag har inga problem med mina lungor

4. Följande frågor handlar om vardagliga aktiviteter som du kanske utför dagligen.

Begränsar dina nuvarande lungsymtom följande aktiviteter? Om ja, hur mycket?

(Ringa in ett svar per rad)

	Jag jobbar inte	**Ja, begränsar mig mycket**	**Ja, begränsar mig lite**	**Nej, begränsar mig inte alls**
a. Aktiviteter på jobbet	0	1	2	3
b. Aktiviteter i hemmet (t.ex hushållsarbete, stryka kläder, fixa/reparera saker I bostaden osv...)		1	2	3
c. Sociala aktiviteter som att resa, gå på bio, träffa andra, shoppa		1	2	3
d. Ansträngande aktiviteter som att springa, lyfta tunga saker, delta i ansträngande		1	2	3
e. Måttligt ansträngande aktiviteter som att flytta ett bord, dammsuga, simma eller cykla		1	2	3
f. Lyfta eller bära en påse med matvaror		1	2	3
g. Gå **flera** våningar upp för trapporna		1	2	3
h. Gå **en** våning upp för trappan		1	2	3
i. Böja dig ned, knäböja eller sätta dig på huk		1	2	3
j. Gå **mer än en kilometer**		1	2	3
k. Gå **ett par hundra meter**		1	2	3
l. Gå ca. **hundra meter**		1	2	3
m. Tvätta eller klä på dig		1	2	3

5. Under de senaste 4 veckorna, har du haft något av följande problem på jobbet eller i dina andra vardagliga göromål på grund av dina lungsymtom? (ringa in ett svar per rad)

	JA	NEJ
a. Du har fått **dra ned på tiden** för arbete eller andra aktiviteter	1	2
b. Du har **fått mindre gjort** än du hade önskat	1	2
c. Du har upplevt en begränsning i utförandet av **vissa typer** av arbete eller aktiviteter	1	2
d. Du har haft **svårt** att utföra arbete eller andra aktiviteter (t.ex det krävdes extra ansträngning)	1	2

6. Under de sista 4 veckorna, i vilken utsträckning har lungsymtomen påverkat dina normala sociala aktiviteter tillsammans med familj, vänner, grannar eller andra grupper ? (Ringa in ett svar)

1. Inte alls

2. Lite

3. Måttligt

4. Ganska mycket

5. Väldigt mycket

7. Hur mycket smärta har du haft runt skulderbladen eller bröstet de sista 4 veckorna? (Ringa in ett svar)

1. Ingen

2. Mycket lite

3. Måttligt

4. Ganska mycket

5. Svår

6. Mycket svår

8. I vilken omfattning har du upplevt andnöd de sista 4 veckorna? (Ringa in ett svar)

1. Inte alls

2. Mycket lite

3. Lite

4. Ganska mycket

5. Mycket

6. Väldigt mycket

9. Följande frågor handlar om hur du mår och hur du har mått de sista 4 veckorna till följd av dina lungsymtom. För var fråga, vänligen välj det svar som bäst passar med hur du haft det. Hur ofta har du de sista 4 veckorna....(ringa in ett svar per rad)

	Hela tiden	Största delen av tiden	En stor del av tiden	En viss del av tiden	En liten del av tiden	Inte alls
Varit bekymrad över att ha fått en ny lungemboli?	1	2	3	4	5	6
Känt dig irriterad?	1	2	3	4	5	6
Har du oroat dig för att avsluta den blodförtunnande behandlingen?	1	2	3	4	5	6
Känt att dig mer känslosam?	1	2	3	4	5	6
Har det plågat dig att du blir mer känslomässigt påverkad?	1	2	3	4	5	6
Känt dig nedstämd eller på dåligt humör?	1	2	3	4	5	6
Känt att du varit en börda för familj och vänner?	1	2	3	4	5	6
Varit rädd för att anstränga dig?	1	2	3	4	5	6
Känt dig hindrad från att resa?	1	2	3	4	5	6
Varit rädd för att vara ensam?	1	2	3	4	5	6

Tack för samarbetet. Vänligen lägg enkäten i bifogat kuvert

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