Diagnosis, management and prognosis of symptomatic and incidental pulmonary embolism

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The studies described in this thesis were performed at the Department of Thrombosis and Hemostasis of the Leiden University Medical Center, Leiden, the Netherlands.

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Diagnosis, management and prognosis of symptomatic and incidental pulmonary embolism

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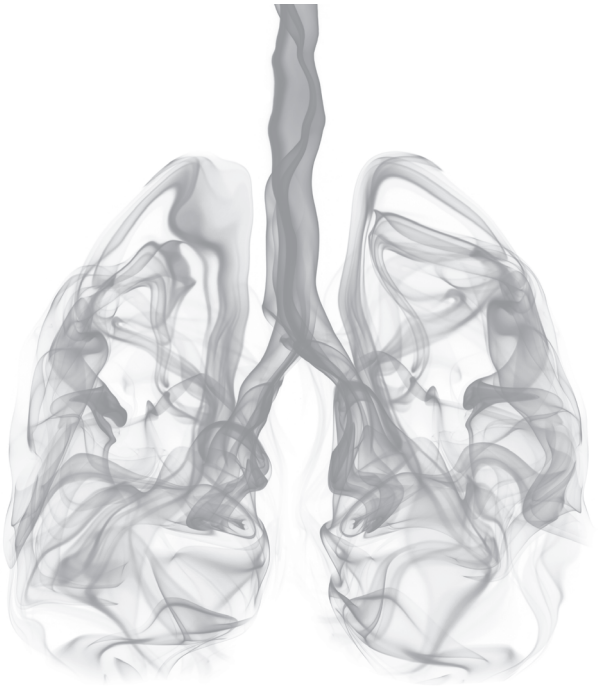
CHAPTER 1

Introduction and outline of this thesis



Although the first recorded case description of deep vein thrombosis (DVT) and pulmonary embolism (PE) goes back to 600-900 BC,[1] it took until the 19th century for Rudolf Virchow to describe the three pillars of venous thrombosis, which still form the fundament of our current understanding of venous thromboembolism (VTE): venous stasis, vessel injury and hypercoagulability.[2] As early as in 1856, Virchow noted that the clinical presentation of PE ranges from silent emboli to sudden death.[3] This heterogeneous clinical presentation with a wide variety of non-specific signs and symptoms, an overview of which is provided in **chapter 2**, still makes establishing a diagnosis of PE challenging today. As a consequence, significant delay may occur before a suspicion of acute PE is raised. **Chapter 3** of this thesis aims to assess the implications of delay in clinical presentation on the diagnostic management and clinical outcome of patients with clinically suspected PE.

Given that the necessary imaging tests for establishing a diagnosis of PE are time-consuming, costly and associated with complications, clinicians are challenged to minimize the number of ordered imaging test without missing any PEs. Therefore, the primary focus of current diagnostic research is to optimize the identification of patients in whom PE can be safely ruled out without the need for invasive testing. The combination of a clinical decision rule with D-dimer testing provides a simple strategy to safely rule out PE without the need for imaging tests.[4] However, although plasma D-dimer levels are typically increased in patients with acute PE, numerous other conditions can influence D-dimer test results. For instance, it has been well established that D-dimer levels increase with age, leading to a lower specificity in the elderly population.[5, 6] To improve the utility of D-dimer testing in elderly patients with suspected PE, an age-dependent cut-off has recently been proposed.[7] In a large sample of patients with clinically suspected PE, an optimal increase in the D-dimer cut-off of 11.2 µg/l per year in patients aged over 50 years was found. To be conservative and to facilitate its use in clinical practice, this new age-dependent D-dimer cut-off in patients aged over 50 years was defined as a patients' age x 10 µg/l. We evaluated the potential of this age-adjusted D-dimer cut-off in a prospective multi-center management study, the so-called ADJUST-PE study, of which the results are described in **chapter 4**.

Now that the majority of hospitals routinely use multi-detector computed tomographic pulmonary angiography (CTPA) in the diagnostic work-up of suspected PE, which allows better visualization of segmental and subsegmental pulmonary arteries, small peripheral emboli isolated to subsegmental branches of the pulmonary artery tree are increasingly being detected.[8] With this increasing incidence of subsegmental PE, a diagnosis that would probably have gone undetected and thus left untreated with former imaging techniques, physicians started to question the clinical significance of these findings. Some evidence suggests that isolated subsegmental PE represents a more benign subset of disease, as compared with PE detected in segmental or larger

branches.[9] To explore this hypothesis, in **chapter 5** we compare the clinical course of patients diagnosed with subsegmental PE to that of patients with PE localized in more proximal pulmonary arteries.

The initial management of acute PE traditionally takes place in hospital. However, recent studies have indicated that selected patients with acute PE may be safely treated on a complete outpatient basis.[10,11] As several serious complications can occur in the initial days to weeks after a diagnosis of PE, it is essential that careful risk stratification takes place before considering early discharge. Two risk models that have been proposed to identify low-risk PE patients suitable for outpatient treatment, the Hestia rule and the simplified Pulmonary Embolism Severity Index (sPESI), are compared in **chapter 6**. To further optimize risk stratification in patients with acute PE, researchers have aimed to identify cardiac biomarkers that may capture early signs of right ventricular distress in patients presenting with stable hemodynamics. N-terminal pro-BNP (NT-proBNP) has been most extensively investigated in this setting; elevated NT-proBNP levels are strongly associated with short-term mortality or adverse clinical outcome.[12,13] Whether this biomarker offers incremental prognostic information on top of clinical criteria remains to be determined. Therefore, in **chapter 7**, we investigate whether selecting PE patients for home treatment on a clinical basis alone, with the use of the Hestia rule, is as safe as combining the Hestia rule with NT-proBNP testing.

Although the duration of anticoagulant treatment and medical follow-up for patients with a first episode of acute PE is generally limited to 3-6 months, it is now increasingly recognized that acute PE has a serious impact on patients' long-term clinical outcome and quality of life.[14,15] To provide more pathophysiologic and perhaps prognostic information on the long-term clinical course of patients who survive an acute pulmonary embolic event, assessment of thromboembolic resolution may be useful. In **chapter 8**, we aimed to systematically assess the course of clot resolution in patients who completed six months of anticoagulant treatment for acute PE, by performing follow-up CTPA examinations. In addition, we aimed to assess the predictive value of residual thrombotic obstruction for the development of recurrent VTE or chronic thromboembolic pulmonary hypertension during long-term follow-up.

Cancer patients form a distinct subset within the spectrum of patients with VTE. Not only do cancer patients display a substantially higher risk of developing VTE, the clinical course of established VTE in cancer patients is far more frequently complicated by recurrent VTE as well as bleeding complications than in VTE patients without cancer.[16] As cancer patients frequently undergo CT-examinations for reasons such as tumour staging and treatment evaluation, these patients are prone to detection of incidental findings. In particular PE, which may be completely clinically asymptomatic, is increasingly detected incidentally in cancer patients now that CT imaging techniques have evolved.[17] An overview of this problem is provided in **chapter 9** of this thesis. **Chapter 10** aims to

assess the accuracy of diagnosing PE on contrast-enhanced CT-examinations that were not conducted for the identification of PE. The current management approach of physicians confronted with a diagnosis of incidental PE is investigated in **chapter 11**. Finally, in **chapter 12**, the clinical outcome of cancer patients with incidental PE is compared to the outcome of cancer patients with symptomatic PE.

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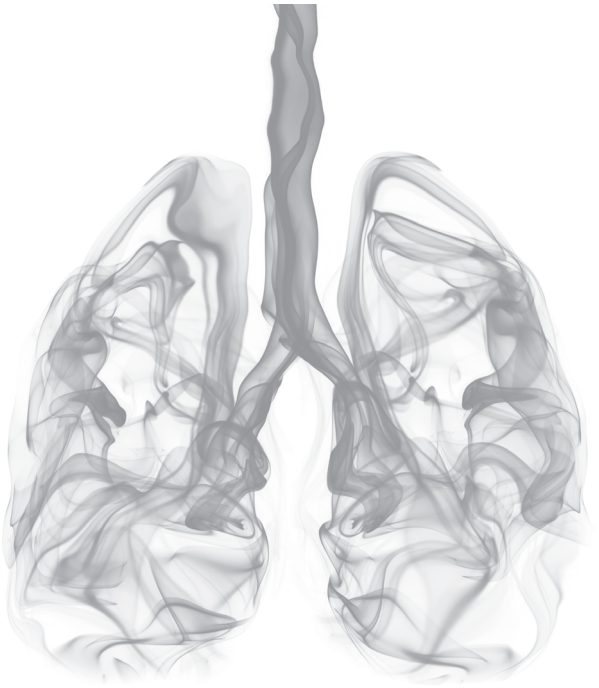
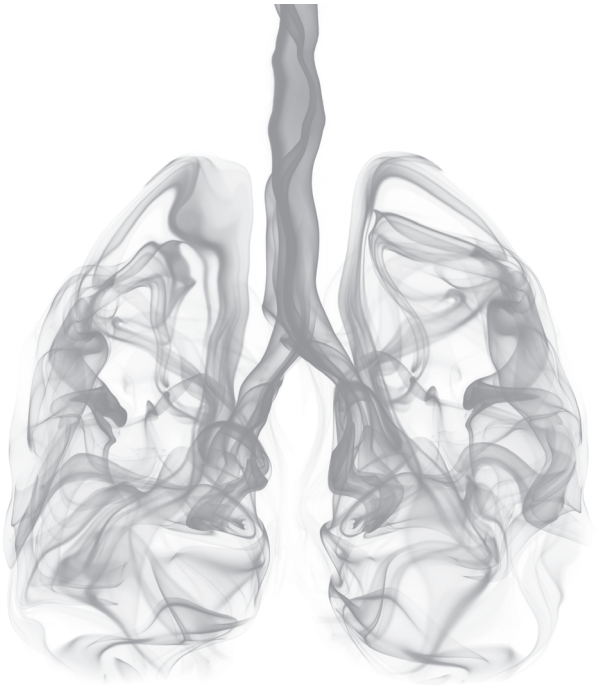
PART I

DIAGNOSIS OF SYMPTOMATIC PULMONARY EMBOLISM



CHAPTER 2

Diagnosis of Pulmonary Embolism: Advances and Pitfalls



P.L. den Exter, F.A. Klok and M.V. Huisman

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ABSTRACT

The signs and symptoms of patients with pulmonary embolism (PE) form a wide spectrum and considerably overlap with other cardiopulmonary diseases. Timely recognizing of this disease therefore remains challenging, but is of vital importance to avoid PE-related morbidity and mortality. To aid and standardize the initial diagnostic approach of patients with suspected PE, clinical probability rules have been developed and simplified for use in clinical practice. It has been demonstrated by clinical outcome studies that it is safe and of high clinical utility to exclude PE on the basis of an unlikely clinical probability and a normal D-dimer test result. For the remaining patients with suspected PE, imaging tests are required. The introduction of multi-detector computed tomographic pulmonary angiography (MD-CTA) has significantly improved the detection of PE, and this test is now regarded as the imaging test of first choice. This review will focus on recent advances and pitfalls that remain in the diagnostic workup of patients with suspected acute PE.

INTRODUCTION

Pulmonary embolism (PE) is a relatively common vascular disease, with an estimated annual incidence of 23 cases per 100.000 persons.[1] This is probably even an underestimation of its true incidence, as PE is thought to be the underlying cause in a significant proportion of patients with sudden death. The clinical presentation of patients with PE forms a wide spectrum, ranging from patients who are completely asymptomatic to those presenting with obstructive shock. The non-specific signs and symptoms suggestive of PE make recognising this disease challenging, even among experienced physicians. It has recently been reported that 16% of the patients with PE are diagnosed after a delay of more than 10 days from the onset of symptoms.[2] As PE can be fatal in up to 30% of the patients when left untreated[3], timely diagnosing is of vital importance. Also, the accuracy of diagnostic methods used to demonstrate PE is of great significance as over diagnosing may expose patients to the risk of bleeding complications associated with anticoagulant therapy. This review will focus on recent advances and remaining pitfalls in the diagnostic workup of patients with suspected acute PE.

CLINICAL DECISION RULES

Most typically, patients with PE present with acute dyspnea, pleuritic chest pain, hemoptysis and/or palpitations. However, signs and symptoms of patients with PE vary widely. Moreover, several cardiopulmonary diseases, including heart failure, pneumonia and COPD exacerbation, are far more prevalent than PE and present with overlapping symptoms.[4] Physicians are thus frequently confronted with patients presenting with symptoms possibly caused by PE, which may be difficult to differentiate from other acute pulmonary diseases. Considering the lack of sensitivity and specificity of individual signs and symptoms, PE cannot reliably be diagnosed nor excluded on a clinical basis alone. To aid clinicians in this complex diagnostic process and to provide a standardized diagnostic algorithm, clinical decision rules (CDRs) have been introduced.[5] These decision rules incorporate clinical signs, symptoms and thrombotic risk factors allowing stratification of patients with suspected PE in different probability categories. Ultimately, a CDR aims to a) select patients in whom PE can be safely ruled out on the basis of a negative D-dimer result without the need for further investigation and b) select patients with a high pre-test probability who require imaging tests and in whom prompt administration of anticoagulant therapy should be considered, in particular if these imaging tests are not readily available.

In the past two decades, several CDRs for PE have been proposed, including the Wells score[6], the original and revised Geneva scores[7,8], the Miniati or Pisa score[9], and the

Table 1. Original and simplified Wells clinical decision rule

Items	Score	Simplified score
Previous history of PE or DVT	1.5	1
Heart rate > 100 beats/min	1.5	1
Recent surgery or immobilization	1.5	1
Hemoptysis	1	1
Active malignancy	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Dichotomized clinical probability:		
PE unlikely	≤4	≤1
PE likely	>4	>1

PE, pulmonary embolism; DVT, deep venous thrombosis.

Charlotte rule.[10] Of these, the Wells score (table 1) and the revised Geneva rule (table 2) are the most extensively validated and, as a result, the most widely used CDRs.[5] Both scores assign different weights (ranging from 1 to 3 points in the Wells score and from 1 to 5 points in the revised Geneva score) to the various variables. Because this may be unpractical to use in busy daily clinical practice and even might lead to miscalculations, the scores have recently been simplified by awarding 1 point for all variables (table 1 and 2).[11,12]

Another recent advance in this field is the proposal of dichotomized CDRs. Whereas the Wells and the revised Geneva score were originally constructed to categorize patients in

Table 2. Revised and simplified revised Geneva score

Items	Score	Simplified score
Age > 65 years	1	1
Previous history of PE or DVT	3	1
Heart rate 75-94 beats/min	3	1
Heart rate ≥ 95 beats/min	5	2
Surgery or fracture within 1 month	2	1
Hemoptysis	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep vein palpation and unilateral edema	4	1
Dichotomized clinical probability:		
PE unlikely	≤ 5	≤ 2
PE likely	> 5	> 2

PE, pulmonary embolism; DVT, deep venous thrombosis.

to three groups of increasing pre-test clinical probability (low, intermediate and high), the modification of these scores in two-level rules (classifying patients as 'PE unlikely' or 'likely') further increases clinical utility and facilitates decision making (table 1 and 2). The effectiveness of the dichotomized Wells score has been demonstrated by the Christopher investigators.[13] In a large cohort including 3306 patients with suspected PE, the combination of an unlikely clinical probability using the dichotomized Wells score and a normal D-dimer test result (<500 ng/ml) safely ruled out PE in 1028 patients (31%), with a 3 month recurrence rate of venous thromboembolism (VTE) of 0.5%.

In an attempt to directly compare the dichotomized versions of the Wells rule, the revised Geneva score, the simplified Wells rule and the simplified revised Geneva score, in their ability to exclude PE with the combination of a D-dimer test, the Prometheus study group recently performed a large prospective management study.[14] By this means, the investigators were also able to prospectively validate the performance of the simplified versions of the Wells and Revised Geneva scores. It was demonstrated that all four CDRs showed similar performance in a) their ability to categorize patients as having an unlikely or likely clinical probability and b) their safety to exclude the presence of acute PE, with the combination of an unlikely clinical probability and a normal D-dimer test result (3-month VTE recurrence rates: 0.5-0.6%). Based on these findings, the authors concluded that the simplified rules can be used in clinical practice and that local hospital experience and preference should determine which CDR is used.

D-DIMER TESTING

D-Dimer is a specific degradation product of cross-linked fibrin that is formed immediately after thrombin-generated fibrin clots are degraded by plasmin, the ultimate enzyme of fibrinolysis. Therefore, elevated D-dimer levels in plasma are indicative for acute thrombus formation. Of the numerous available D-dimer assays, a meta-analysis demonstrated the enzyme-linked immunofluorescence assay (ELFA), the enzyme-linked immunosorbent assay (ELISA) and the latex quantitive assay to have the best sensitivities for PE (respectively 97%, 95% and 95%).[15]

Because of its high sensitivity, D-dimer testing is in particular useful to exclude the presence of acute PE. Several large management outcome studies and meta-analyses of these studies clearly demonstrated that it is safe and of high clinical utility to rule out PE based on a normal D-dimer level and a low or unlikely clinical probability, with reported 3-month VTE risks of 0.0-0.5%.[13,16-20]

In contrast to its high sensitivity, ELISA and second-generation latex agglutination D-dimer assays have a rather poor overall specificity of around 35% to 40%.[21] Therefore, D-dimer tests are of little use in confirming PE. Furthermore, D-dimer testing becomes

less sensitive in patients categorized as having a likely clinical probability. In this subset of patients, VTE could be confirmed in up to 9.3% of the patients with a normal D-dimer test result.[22] Therefore, patients with a high or likely clinical probability should always undergo further testing. The main pitfall of D-dimer testing is to use this essay as a screening test. It is of utmost importance to first examine the patient; D-dimer measurements should not be performed earlier than assessing the pre-test clinical probability.

The low specificity of this test is caused by the increase of D-dimer levels in many other clinical conditions, such as infection, inflammation, cancer, surgery and trauma, extensive burns or bruises, ischemic heart disease, stroke, peripheral artery disease, ruptured aneurysm or aortic dissection or pregnancy.[21] Importantly, it has clearly been shown that that D-dimer levels increase significantly with age.[23-27] This leads to a decreased specificity of the D-dimer test at the usual threshold in the elderly, and thus to a less useful test to exclude thromboembolic disease in older patients. For instance, ELISA D-dimer is able to rule out PE in 60% of patients aged less than 40 years, but in only 5% of patients above the age of 80.[26] As a consequence, older patients with a suspicion of PE, more frequently require imaging tests. Recently, a simple age-adjusted D-dimer cut-off has been proposed in aim to improve the clinical utility of D-dimer essays in the elderly.[28] A retrospective analysis of three large cohorts derived and validated the efficacy and safety of an age-dependent D-dimer cut-off, defined as patients' age $\times$ 10 µg/L in patients older than 50 years with a suspicion of PE. The results of this study indicate that adopting this new age-dependent cut-off point could increases the number of patients in whom PE could be excluded with 20% without further testing, whilst remaining an acceptable safety profile as the three-month VTE rate was very low (0.2 - 0.6%). Since these analyses were performed retrospectively, the safety of this new age-dependent D-dimer cut-off in excluding pulmonary embolism in elderly should be validated prospectively and externally, before adapting this cut-off value in clinical practice.

In some specific situations, including patients with complaints lasting longer than 14 days, patients in whom heparin treatment is initiated before diagnostic testing, and patients already receiving anticoagulant treatment at time of diagnostic evaluation, D-dimer tests may more frequently give false-negative results.[29,30] Since these patients are generally excluded from or underrepresented in outcome studies, little evidence is available to guide their diagnostic management. In these specific scenarios, D-dimer testing should be avoided or at least be used with caution

IMAGING TESTS

Given the low diagnostic accuracy of clinical evaluation and laboratory findings in establishing the diagnosis of PE, imaging is required in a) those patients in whom PE

cannot be ruled out on the basis of a clinical probability and a D-dimer test and b) those patients with a high or likely clinical probability.

For a long time, ventilation-perfusion (V/Q) scanning has been the non-invasive imaging procedure of choice in patients with suspected PE. However, a substantial proportion of patients who undergo V/Q examinations for the detection of PE have a non-diagnostic examination.[31] In these latter patients, the incidence of PE ranges from 10-40%.[32]

To date, computed tomographic pulmonary angiography (CTPA) has become the imaging procedure of choice in patients with suspected PE. Compared with V/Q scans, CTPA has several advantages: 1) a higher diagnostic accuracy; 2) the ability to provide a clear test result, either positive or negative for PE, in most of the cases; 3) a faster acquisition time which provides high-contrast images; 4) its readily availability at most hospitals; and 5) its possibility to demonstrate an alternative diagnoses to explain patient's symptoms.

Although studies assessing the diagnostic accuracy of initially used single-detector CTPA reported sensitivity rates ranging from 53% to 100% and specificity rates from 83% to 100%[33], this inconsistency has likely been overcome with the introduction of multi-detector CT-scanners (MD-CTPA). The PIOPED II investigators reported MD-CTPA to have a sensitivity of 83% and a specificity of 96% for diagnosing PE.[34] Several outcome studies have consistently demonstrated the safety of withholding anticoagulant therapy in patients with a MD-CTPA result negative for PE.[13,35,36] The safety of using MD-CTPA as a single imaging test has been established by a randomized, non-inferiority trial, which could not demonstrate a benefit of performing compression ultrasonography (CUS) in addition to MD-CTPA to exclude PE.[37] In a meta-analysis, the pooled 3-month VTE incidence was 1.2% for patients with a normal CTPA as a sole test, and 1.1% for patients with a normal CTPA and an additional negative CUS examination.[38] Of note, these VTE incidences are even lower than the reported 3-month recurrence rate (1.7%) following normal pulmonary angiography, the traditional reference standard against which all outcome studies in PE are compared.[39]

Still, some pitfalls remain with the use of CTPA as a first-line imaging test to demonstrate PE. First, one must caution for motion artifacts, which are most commonly respiratory related and most prevalent in patients suffering from severe dyspnea.[40,41] These low-attenuation abnormalities, caused by partial volume averaging of vessel and lung, can mimic intraluminal filling defects and are thus prone to be misdiagnosed as PE, in particular in the segmental or smaller pulmonary vessels.

Second, although CTPA clearly performs better than VQ-scans in providing a definitive test-result, a proportion of patients with an intermediate or non-diagnostic scan results still remains. Percentages of inconclusive CTPA examinations of up to 10.8% have been reported.[42] In a single center study, the radiologic reports of 2151 CTPA examinations

were retrospectively evaluated.[43] Examinations were reported to be suboptimal in 8% of the patients, and non-diagnostic in 5%. Limitations in image quality were most frequently attributed to motion artifacts or poor contrast enhancement, the latter being crucial for an adequate CTPA evaluation and largely depending on timing of the contrast bolus. Although the outcome of patients with inconclusive scan results has not been extensively studied, a meta-analysis identified 327 patients out of 16 studies who had either inconclusive, intermediate, non-interpretable, non-diagnostic or suboptimal CTPA results.[44] In 74 of these patients, in whom anticoagulant therapy was not initiated and who did not underwent further diagnostic evaluation, VTE was diagnosed in 16.4% during follow-up. This high VTE risk in this subset of patients underlines the importance of conclusive CTPA examinations and the indication for additional examinations in those patients in whom CTPA is non-diagnostic.

SUBSEGMENTAL AND INCIDENTALLY DIAGNOSED PE

Now that the majority of hospitals routinely use MDCTA in the diagnostic work-up of PE, which allow better visualization of segmental and subsegmental pulmonary arteries, small peripheral emboli isolated to subsegmental branches of the pulmonary artery tree are being increasingly detected.[45] A recent systematic review demonstrated a rate of subsegmental PE (SSPE) of 4.6% with single-detector CTPA, whereas this rate was 9.4% when MD-CTPA was used to diagnose PE.[46] With this increase in incidence, physicians start to question the clinical significance of these findings. Some evidence is suggesting that SSPE represents a more benign subset of disease, as compared with PE detected in segmental or larger branches. The systematic review mentioned above, reported 3-month risks of VTE for patients with suspected PE and a negative CTPA (and thus no anticoagulants prescribed) of 0.9% and 1.0% for single- and multi-detector CTPA respectively.[46] This may be indirect evidence that the additional cases of SSPE detected by MD-CTPA may have a favourable clinical outcome, even when left untreated, and thus clinically of no importance. Further Studies evaluating the risks and benefits of prescribing anticoagulants to patients with SSPE, are urgently needed to improve clinical decision making.

Another topic of recent debate is the increased detection of asymptomatic PE, in patients who undergo contrast-enhanced CT-scanning for reasons other than the suspicion of PE.[47] These so called 'incidental pulmonary emboli', are in particular relatively common identified in patients with malignancy. A recent meta-analysis including 12 studies reported a weighted pooled prevalence of incidental PE of 2.6%.[48] This can be explained by two reasons. First; patients with active malignancy are at increased risk of developing PE because of the prothrombotic state associated with cancer. Second,

oncology patients frequently undergo CT scanning for reasons as diagnosing, staging and follow-up of the malignancy. As for SSPE, physicians confronted with incidental PE question the clinical relevance of these findings and the need for anticoagulant therapy in these patients. In contrast to SSPE, there is currently no evidence suggesting that these incidental findings are harmless, and current guidelines advocate treating these patients in the same manner as patients with symptomatic PE.[49] A recently published cohort study revealed high rates of recurrent VTE (13.3%) in oncology patients with incidental PE, comparable to recurrent rates of cancer patients with symptomatic PE.[50] Further studies assessing the clinical outcome of incidental PE are needed to guide physicians in the management of these patients.

MAGNETIC RESONANCE ANGIOGRAPHY

Gadolinium enhanced magnetic resonance angiography (MRA) is a relative new imaging technique to visualize PE. MRA was introduced as a potentially attractive diagnostic alternative since it bypasses the major drawbacks of CTPA, including radiation exposure and enhancement of iodinated contrast media. However, experience with this technique is limited and up to date there have been few studies addressing its accuracy in detecting PE. A review that strictly included studies on MRA using pulmonary angiography as a reference standard, reported a broad range of sensitivities, from 77% to 100%, whereas the specificity rates of MRA were consistently high, ranging from 95 to 98%.[51] More recently, the PIOPED III investigators performed a large prospective study to evaluate the performance of MRA, with or without magnetic resonance venography, using various accepted diagnostic tests as reference standard, including CTPA and VQ-scan. In those patients in whom MRA was technically adequate, the respective sensitivity and specificity for PE were 78% and 99%. Notably, MRA was technically inadequate, and therefore regarded as non-interpretable, in 92 of the 371 examinations (25%). A retrospective analysis of the data collected in the PIOPED III study revealed that poor arterial opacification of segmental or subsegmental branches (67%) and motion artifacts (36%) were the most prevalent correlates of an non-interpretable MRA.[52] Given this high rate of technically inadequate MRA examinations, its limited sensitivity and longer acquisition time as compared with MDCTA, and its limited direct availability in most hospitals, MRA is at this time far from being implemented in the routine diagnostic work-up of patients with suspected PE.

PATIENTS WITH SUSPECTED RECURRENT PE

Scarce data is available on the diagnostic approach to patients with a suspicion of recurrent PE and therefore, it is currently unclear whether the diagnostic methods discussed earlier are also valid in the specific subset of patients with suspected recurrent PE. The importance of correctly diagnosing recurrent PE lies in the therapeutic consequence that come with this diagnosis: a patient with established recurrent VTE is usually prescribed prolonged or even life-long anticoagulant therapy. Diagnosing recurrent PE is more challenging than diagnosing a first episode of PE for several reasons. First, a decreased specificity of D-dimer tests in patients with recurrent thrombotic disease has been demonstrated.[53] Second, the presence of residual emboli, which may be identified in up to 50% of the patients diagnosed with PE[54], is difficult to differentiate from recurrent pulmonary emboli. It remains to be studied whether a control CTPA after cessation of treatment aids in the clinical decision making in patients under suspicion of recurrent PE.

In a multicenter clinical outcome study, the performance of a diagnostic strategy including the Wells score, D-dimer testing and CTPA, was determined in 516 specific subset of patients with suspected recurrent PE.[55] It was demonstrated that the combination of an unlikely Wells clinical probability and a normal D-dimer level performed well in excluding PE, without recurrent VTE during follow-up (95% CI: 0 - 3.3%). Of note, recurrent VTE was diagnosed during 3 months of follow-up in 3.2% (95% CI: 1.5 – 5.9%) of the patients with a negative CTPA result. This failure rate exceeds the rate of 1.2% that was reported in a meta-analysis which assessed the failure rate of CTPA for the detection of PE, regardless of patients' history of VTE.[38]

SUMMARY

The diagnostic management of patients with a suspicion of PE has significantly evolved over the past few decades. Clinical probability rules have been developed and simplified for use in clinical practice. These probability rules are highly effective in determining the pre-test probability of PE, which is the crucial step in the diagnostic approach before the selection of further diagnostic tests. High level evidence has proofed that it is safe to rule out PE on the basis of an unlikely clinical probability and a normal D-dimer result. However, D-dimer testing is not suitable to be used in patients with a high clinical probability and should not be used as a PE screening test. Also, D-dimer tests should be used with caution in patients with symptoms lasting more than 14 days, and patients receiving therapeutic heparin treatment or oral anticoagulant therapy. In older patients with a suspicion of PE, the specificity of the conventional D-dimer threshold might be

too low to render this approach successful in clinical practice. The development and external validation of age-dependent D-dimer cut-off levels may significantly improve the diagnostic management of PE in elderly.

MD-CTPA has considerably advanced the radiological visualization of PE and its accuracy has been demonstrated to be robust enough to serve as single imaging test for PE. As a result, this technique is now regarded as the imaging test of choice. As a consequence of the routine use of these scanners, isolated subsegmental PE is now increasingly being detected. The clinical relevance of these small peripheral emboli remains to be determined.

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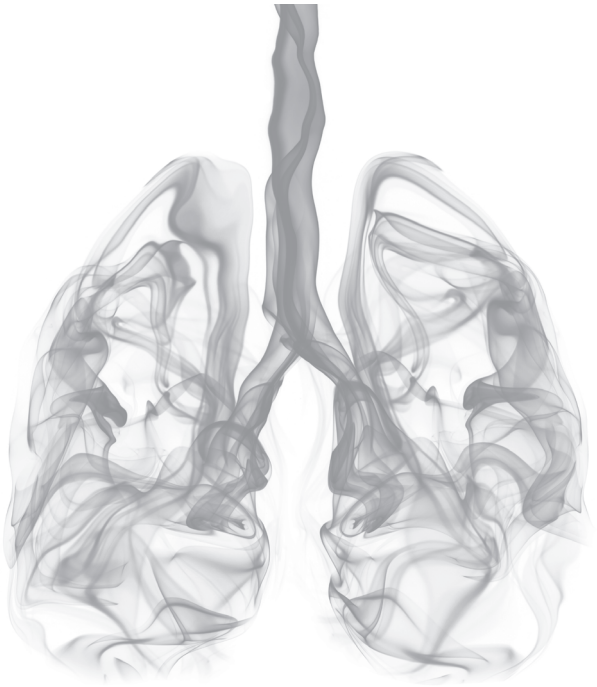
CHAPTER 3

Impact of delay in clinical presentation on the diagnostic management and prognosis of patients with suspected pulmonary embolism



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ABSTRACT

Rationale

The non-specific clinical presentation of pulmonary embolism (PE) frequently leads to delay in its diagnosis. This study aimed to assess the impact of delay in presentation on the diagnostic management and clinical outcome of patients with suspected PE.

Methods

In 4044 consecutive patients with suspected PE, patients presenting >7 days from the onset of symptoms were contrasted to those presenting within 7 days as regards the safety of excluding PE on the basis of a clinical decision rule (CDR) combined with D-dimer testing. Patients were followed for three months to assess the rates of recurrent venous thromboembolism (VTE) and mortality.

Measurements and main results

A delayed presentation (presentation >7 days) was present in 754 (18.6%) of the patients. The failure rate of an unlikely clinical probability and normal D-dimer test was 0.5% (95% CI: 0.01-2.7) for patients with and 0.5% (95% CI: 0.2-1.2) for those without diagnostic delay. D-dimer testing yielded a sensitivity of 99% (95%CI: 96-99%) and 98% (95%CI: 97-99%) in these groups respectively. PE patients with diagnostic delay more frequently had centrally located PE (41% vs 26%, $p<0.001$). The cumulative rates of recurrent VTE (4.6% vs 2.7%, $p=0.14$) and mortality (7.6% vs 6.6%, $p=0.31$) were not different for patients with and without delayed presentation.

Conclusions

PE can be safely excluded based on a CDR and D-dimer testing in patients with a delayed clinical presentation. A delayed presentation for patients who survived acute PE was associated with a more central PE location although this did not affect the clinical outcome at 3 months.

INTRODUCTION

A diagnosis of pulmonary embolism (PE) is typically established in less than 30% of all patients with a clinical suspicion.[1] This is because of the wide range and non-specificity of the clinical signs and symptoms suggestive of PE, which overlaps with several other cardiopulmonary diseases. Timely recognition of acute PE therefore remains challenging. It has been suggested that 16% of the patients with PE are diagnosed after a delay of more than 10 days from the onset of symptoms.[2] Since PE may be fatal when left untreated, a timely and accurate diagnosis is of vital importance.[3]

In the past decade, the diagnostic management of patients with suspected PE has advanced with the introduction of standardized clinical decision rules (CDRs) and high-sensitive D-dimer tests. It has been demonstrated that it is safe and of high clinical utility to exclude PE on the basis of a low clinical probability and a normal D-dimer level, which avoids the need for additional imaging tests in approximately 30% of patients.[4] However, some data suggest that a delay in clinical presentation may decrease the sensitivity of D-dimer testing. For instance, duration of symptoms over 10 days has been shown to be associated with a 3-fold risk in a false negative D-dimer result in patients with either deep vein thrombosis (DVT) or PE.[5] It could therefore be hypothesized that the use of a diagnostic strategy combining a CDR with D-dimer testing may be impaired by a delayed presentation. Furthermore, delays in diagnosing PE results in a postponed initiation of treatment, which may affect the prognosis of these patients.

This study aimed to assess the impact of delay in presentation on the safety of excluding PE with the use of a diagnostic algorithm consisting of a CDR and D-dimer testing. In addition, we investigated whether a delayed presentation was associated with a worse prognosis, in terms of mortality and recurrent venous thromboembolism (VTE), in patients with confirmed PE.

METHODS

Study population

We analysed the combined data of two large prospective outcome trials that studied the diagnostic management of patients with suspected PE. The methods of both studies have been described in detail elsewhere.[6, 7] In short, the first study was a prospective management study including 3306 consecutive hemodynamically stable patients in 12 medical centers, evaluating a diagnostic algorithm consisting of the Wells rule, D-dimer testing, and computerized tomography pulmonary angiogram (CTPA).[7] The second study included 807 consecutive in- and outpatients in 7 hospitals to evaluate 4 different CDRs in the diagnostic management of suspected PE.[6] For the purpose of the present

analysis, we only evaluated the data on the performance of the Wells rule, which was uniformly calculated in all 807 patients in the original study. Both studies were approved by the ethical review boards of all participating hospitals and informed consent was obtained from all included patients.

Diagnostic work-up and management

The pretest clinical probability of PE was considered unlikely in case of a Wells score ≤ 4 and likely in case of a score >4 points.[8] Patients categorized as 'PE unlikely' underwent high-sensitivity D-dimer testing; depending on local practice, either VIDAS D-dimer assay, BioMerieux, Marcy L'Etoile, Tinaquant assay, Roche diagnostica, STA-liatest D-di, Diagnostica Stago or Innovance D-dimer, Siemens. CTPA was performed in all patients with an abnormal D-dimer test result (cut-off ≥500 µg/L) and all patients classified as 'PE likely'. In case of a normal D-dimer test-result or in the absence of PE on CTPA, PE was excluded and patients were left untreated. PE was confirmed in the presence of at least one arterial filling defect on CTPA, and those patients were treated with therapeutic unfractionated or low-molecular weight heparins for at least 5 days, followed by VKA for at least 3 months aiming at a therapeutic INR.

Outcome

All included patients were followed for a period of 3 months. In those patients in whom PE was initially excluded, the diagnostic failure rate was determined, defined as the incidence of symptomatic VTE during 3 months of follow-up. This outcome during follow-up represented the reference standard for the presence of PE at baseline. PE was considered as unprovoked in the absence of at least one risk factor for PE[9]. In those patients in whom PE was confirmed, the 3-month incidences of symptomatic recurrent VTE and all-cause mortality were assessed. VTE during follow-up was defined as the occurrence of objectively documented DVT, PE or death in which PE could not reliably ruled out as primary cause. All suspected VTEs and deaths during follow-up were evaluated by an independent adjudication committee, whose members were unaware of the results of the diagnostic algorithm.

Statistical analysis

The cohort was stratified in two groups: 1) those without a delayed presentation, defined as presentation within 7 days from the onset symptoms, and 2) those with diagnostic delay, defined as presentation >7 days from the onset of symptoms[10,11]. Differences in patient characteristics between these strata were tested for statistical significance with the use of the Chi-square-test or the Fisher's exact test for categorical data and the student-t test or Mann Whitney test for continuous variables. *P*-values < 0.05 were considered to indicate statistically significance. Univariate and multivariate regression

analyses were performed to identify factors associated with a delayed presentation. Any variable achieving a *P*-value of less than 0.05 was included in an unconditional multivariate regression model.

Diagnostic failure rates were calculated both in patients with and without delay in presentation. The diagnostic strategy including clinical probability assessment in combination with D-dimer testing was considered to exclude PE safely if the failure rate was less than 2% and the maximum upper limit of the 95% confidence interval is 2.7% (which is the upper confidence limit of the 3-month rate of VTE in patients in whom PE was suspected but who had normal findings on pulmonary angiography).[12] To estimate the diagnostic accuracy of the D-dimer in each group, we calculated the areas under the Receiver Operating Characteristics curve (AUC), which were compared with the use of the Z-test. Additionally, failure rates and AUCs were calculated using 10 days and 14 days as cut-off for delayed presentation.

The method of Kaplan and Meier was used to estimate the cumulative probability of recurrent VTE and mortality in patients with proven PE, and the log-rank test was used to compare both groups for statistical differences. The patients were censored at time of event, at time of death, or at time of the end of follow-up, whichever came first. A Cox proportional hazard model was used to derive hazard ratios (HR). HRs were adjusted for age, gender, a history of VTE, active malignancy, recent immobilization or surgery, COPD and heart failure. SPSS version 20 (SPSS Inc, Chicago, IL) was used to perform all analysis.

RESULTS

Patient characteristics

Of the 4113 patients with clinically suspected PE, information on the duration of symptoms was missing in 69 patients, who were excluded from further analysis. The median duration of symptoms of the remaining patients was 2 days (interquartile range 2-6 days). Of these 4044 patients, 3290 (81.4%) presented within 7 days from the onset of symptoms, and 754 (18.6%) had symptoms suspicious for PE for more than 7 days. Patients with delayed presentation were older (mean age 56 vs 52 yrs, $p<0.001$) and had more frequently heart failure (6.6% vs 8.8%, $p=0.035$) and COPD (9.2% vs 14.0%, $p<0.001$) compared to patients without delayed presentation (Table 1). The proportion of male patients was equal in both groups (42%).

The prevalence of the following VTE risk factors was lower among patients presenting after 7 days since onset of symptoms: estrogen use (10% vs 14%; $p=0.007$), recent immobilization for more than 3 days or surgery 4 weeks (15% vs 21%, $p<0.001$) and paresis, paralysis or a plaster cast > 4 weeks (1.0% vs 3.1%; $p=0.004$).

Table 1. Baseline characteristics

	Complaints ≤ 7 days (n=3290)	Complaints > 7 days (n=754)	*P*-value
Age (mean ± SD)	52 ± 18	56 ± 18	< 0.001
Male (n, %)	1375 (41.9)	315 (42.0)	0.943
Inpatients (n, %)	622 (18.9)	132 (17.5)	0.372
Duration of complaints, days (median, IQR)	1 (1-3)	14 (14-30)	NA
VTE Risk factors:			
Immobilization or surgery (n, %)	691 (21.0)	111 (14.7)	0.001
Paralysis, pareses or recent leg plaster (n, %)	83 (2.5)	6 (0.8)	0.004
Previous VTE (n, %)	396 (12.0)	108 (14.3)	0.086
Active Malignancy (n, %)	397 (12.1)	84 (11.1)	0.479
Estrogen use, women (n, %)	453 (13.8)	76 (10.1)	0.007
Comorbidities:			
COPD (n, %)	303 (9.2)	105 (13.9)	< 0.001
Heart failure (n, %)	216 (6.6)	66 (8.8)	0.035
D-dimer[a] (all patients; median, IQR)	750 (321-1873)	900 (400-2285)	0.007
D-dimer[a] (if confirmed PE; median, IQR)	2651 (1460-5000)	3339 (1802-5183)	0.059

COPD, chronic obstructive pulmonary disease; N, number; SD, standard deviation; VTE, venous thromboembolism.
[a]D-dimer level in µg/L

Multivariate analyses demonstrated age (OR: 1.01 per year; 95% CI: 1.01-1.02), COPD (OR 1.3; 95% CI: 1.01-1.8), recent immobilization or surgery (OR: 0.67; 95% CI: 0.52-0.87) and paresis, paralysis or plaster cast more than 4 weeks (OR: 0.33; 95% CI: 0.13-0.83) to be independent determinants of a delayed presentation. In an additional analysis, these ORs were adjusted for study cohort and study center. This did not materially influence the result (data not shown).

Performance of the diagnostic algorithm

The proportion of patients in whom PE was excluded based on a Wells score ≤4 combined with a normal D-dimer test result (≤ 500 ng/mL) was similar in patients with and without delayed presentation (31% vs 28%, p=0.13). The duration of symptoms was not found to correlate with a false negative D-dimer test result: OR: 1.00 per day of delay (95% CI: 0.978-1.03; p=0.91). Of the 1184 patients with an unlikely Wells score and a normal D-dimer test result, the failure rate was 0.5% (95% CI: 0.2%-1.2%) in the group without a delayed presentation versus 0.5% (95% CI: 0.01%-2.7%) in the group with delayed presentation ($p = 0.98$). Similar failure rates were observed when extending the definition of delay in presentation to 10 days (failure rate 0.5%; 95% CI: 0.01-2.9%) or 14 days (failure rate 0.58%; 95%CI: 0.01-3.3%).

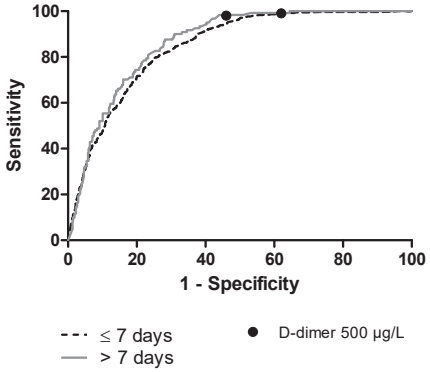

Figure 1. Receiver operating characteristic curves illustrating the diagnostic performance of the D-dimer of patients with ≤ 7 days and with > 7 days complaints. The areas under the curve were 0.85 (95% confidence interval (CI) 0.83-0.86) and 0.86 (95% CI 0.83-0.89) respectively.

In 3538 of 4044 patients a D-dimer test was performed. The AUC of the D-dimer in the group with delay in presentation was 0.86 (95% CI 0.83-0.89), this was not different from the AUC in the subgroup without diagnostic delay (0.85, 95% CI 0.83-0.86; p=0.52) (Figure 1). The sensitivity of the D-dimer test in patients in the group without delay was 99% (95% CI: 96-99%) at a specificity of 38% (95% CI: 34-42%), whereas the sensitivity of the D-dimer in the group without delays in diagnosis was 98% (95% CI: 97-99%) at a

Table 2. Diagnostic test characteristics

	Complaints ≤ 7 days % (95% CI)	**Complaints > 7 days % (95% CI)**	**Complaints < 10 days % (95% CI)**	**Complaints ≥ 10 days % (95% CI)**	**Complaints < 14 days % (95% CI)**	**Complaints ≥ 14 days % (95% CI)**
Clinical probability						
Unlikely (wells score ≤ 4)	67 (65-69)	71 (68-74)	67 (66-69)	71 (67-74)	67 (65-69)	72 (69-76)
Likely (wells score >4)	33 (31-35)	29 (26-32)	33 (31-34)	29 (26-33)	33 (31-35)	28 (24-32)
Test characteristics D-dimer						
Sensitivity	98 (97-99)	99 (96-99)	98 (97-99)	99 (95-100)	98 (97-99)	99 (94-100)
Specificity	44 (42-47)	38 (34-42)	44 (42-46)	39 (35-43)	44 (42-46)	41 (36-46)
Negative predictive value	99 (98-100)	100 (97-100)	99 (98-100)	100 (97-100)	99 (98-100)	100 (97-100)
Positive predictive value	29 (27-31)	27 (23-31)	29 (27-31)	27 (23-31)	28 (27-31)	27 (23-32)
Failure rate[a]	0.51 (0.17-1.2)	0.49 (0.01-2.7)	0.50 (0.16-1.2)	0.52 (0.01-2.9)	0.49 (0.16-1.1)	0.60 (0.01-3.3)

[a] Defined as the incidence of symptomatic venous thromboembolism during 3 months of follow-up in those patients in whom pulmonary embolism was excluded on the basis of an unlikely clinical probability and a normal D-dimer test result.

specificity of 44% (95% CI: 42-47) When assessing a 10-day or 14-day cut-off for delayed presentation, similar D-dimer test characteristics were observed (Table 2).

The sensitivity and specificity of a low clinical probability combined with a normal D-Dimer test result were respectively 98% (95% CI: 96-99%) and 46% (95% CI: 44-49%) for patients without delay, versus 99% (95% CI: 94-100%) and 42% (95% CI: 38-47%) for patients with delay.

Clinical outcome of patients who survived acute PE

PE was confirmed in 849 patients, of whom 689 (81%) were diagnosed within 7 days and 160 (19%) after 7 days from the onset of symptoms. PE patients diagnosed after delay in presentation more frequently had unprovoked PE (62% vs 46%, p<0.001). Furthermore, in PE patients with a delayed presentation, PE was more frequently localized in a central pulmonary artery (41% vs 26%, p<0.001; OR: 2.0, 95% CI: 1.4-2.9).

Follow-up was completed in 832 (98%) of the patients with confirmed PE. During the 3-month follow-up, recurrent VTE was observed in 7 (4.5%) of the patients with delay in presentation and in 16 (2.4%) of the patients without a delayed diagnosis. The respective cumulative recurrent risks were 4.6% and 2.7% (p=0.14 from the log-rank test; adjusted HR: 2.0; 95% CI: 0.80-4.9). Thirteen (8.2%) of the patients with delayed presentation died during follow-up, versus 44 (6.5%) patients without delay in presentation. The respective 3-month cumulative risks for all-cause mortality were 7.6% and 6.6% (p=0.31 from the log-rank-test; adjusted HR: 1.5; 95% CI: 0.81-2.7).

DISCUSSION

This study demonstrates that it is safe to exclude PE with the use of a diagnostic algorithm consisting of the Wells score and D-dimer-testing, in patients with a delayed clinical presentation. Second, although delay in presentation was found to be a predictor for more centrally located PE, in hemodynamically stable PE patients who survived to undergo diagnostic testing, the clinical outcome of those with a delayed diagnosis did not clearly differ from those diagnosed more promptly.

The importance of our findings lies in the facts that 1) a delay presentation is common among patients with suspected PE and 2) uncertainty exists on the validity of diagnostic strategies in patients with delay in presentation. In the present study, 19% of the patients had a delay in diagnosis of more than 7 days. Similar rates, ranging from 16% to 18%, were observed in previous studies.[2,10,11]

Since it has been proposed that the age of a clot, as reflected by the duration of symptoms, could inversely affect the performance of D-dimer testing, it has been doubted whether this test is still valid in patients with a delayed presentation.[13] In a case-control

study including 47 VTE patients with a false negative D-dimer result and 100 controls with a true-positive test result, the presence of symptoms more than 10 days was found to be a predictor for a false-negative D-dimer (OR: 3.2; 95% CI: 1.4-7.4).[5] In a small series of 29 VTE patients, D-dimer testing yielded a false-negative result in two patients, both with symptoms for at least 30 days.[14] Notably, both cases were classified as having a likely clinical probability.

Our results demonstrate, however, that PE can still be excluded safely in patients who present after 7 days from the onset of symptoms, on the basis of an unlikely clinical probability and a normal D-dimer test result. The diagnostic failure rate (0.5%) remained well within acceptable norms, even when extending the definition of a delayed presentation to 10 (0.5%) or 14 days (0.6%). To further explore the impact of delays in presentation on the accuracy of D-dimer testing, we calculated the sensitivity, specificity and negative predictive value, which were all comparable to patients without delay in presentation. Finally, mean D-dimer levels for patients with confirmed PE after delay in presentation, were not lower compared to those diagnosed without delay. Explanations for the absence of a decreased performance of D-dimer testing for patients with delay in presentation in the present study, in contrast to the studies mentioned previously, may include the fact that in the present study, D-dimer testing was used in combination with clinical probability assessment. Second, newer generation D-dimer tests were used, which are known to be of superior sensitivity compared to semi-quantitative latex agglutination and whole-blood agglutination assays.[15]

The high prevalence of delay in presentation among patients diagnosed with PE may reflect the difficulty of recognizing this disease. Known VTE risk factors, such as estrogen use, immobilization, paresis or paralysis, which could trigger physicians to suspect PE, were less frequently present among patients with a delayed presentation. Otherwise, patients who presented after diagnostic delay more frequently had comorbidities such as COPD and heart failure. Given that the symptoms of these diseases considerably overlap with PE, we hypothesize that physicians and patients may have considered these conditions first before suspecting PE, which could contribute to the delay in presentation.

This study also addressed the outcome of PE patients who were diagnosed after a delay. An important and novel finding is that diagnostic delay was associated with a more prevalent central PE location. Theoretically this appears plausible, given that the presence of PE in the absence of anticoagulant therapy allows the clot to extend. This observation may have prognostic implications for PE patients with a delayed presentation, given that central emboli have been associated with a worse clinical outcome. Notably, Vedovati *et al.* reported a negative association between a central pulmonary embolism and adverse clinical outcome, only in hemodynamically stable patients.[16] Furthermore, we found a higher proportion of patients with unprovoked PE among those

diagnosed after delay, and unprovoked PE is known to be associated with a two-fold risk of recurrent VTE on the long-term, compared to those with provoked PE.[17] Yet, in the present study, no significant differences in short-term clinical outcome were seen between PE patients with and without delay in presentation, although a trend towards a higher recurrent VTE risk was noted for those with diagnostic delay. We admit that this observation harbors the risk of underestimation due, to the low number of observed recurrent events. A previous study by Jimenéz *et al.* was also unable to detect an association between a delay in diagnosis and an increased risk of death or VTE recurrence among patients who survived an episode of PE.[11]

The conclusions of this study are strengthened by its large sample of patients, and its multicenter design, which enhance the extrapolation of our findings. Limitations include the fact that these analyses were performed in a post-hoc fashion. Still, all patients were managed according to a consistent diagnostic protocol and all data were collected prospectively. Second, the variable duration of symptoms may be prone to recall bias. For those who present after a time delay, it may be difficult to recall the exact day of onset of symptoms. By stratifying patients in those presenting within one week and those after one week, we believe that this recall bias is minimized. Third, the sample of patients with PE may have been too small and had a too limited follow-up, to draw definite conclusions on the impact of a delayed presentation on their clinical outcome. Furthermore, the fact that patients had to be hemodynamically stable to enter the original studies, forms a potential source of referral bias. It cannot be excluded that delay in presentation has an impact on the hemodynamic outcome, and our results can thus only be extrapolated to hemodynamically stable patients who survived acute PE. Future studies, also including hemodynamically compromised patients, are needed to clarify this issue. Lastly, the D-dimer test characteristics do not reflect our entire study population since D-dimer test results were missing in 13% of the patients.

In conclusion, our results demonstrate that delays in PE diagnosis are common and associated with the absence of VTE risk factors and the presence of cardiopulmonary co-morbidities. This study suggests that excluding PE on the basis of clinical probability estimation and D-dimer testing in patients with a delayed clinical presentation is safe. In hemodynamically stable patients who survived acute PE, a delayed presentation was found to be associated with a central PE location, but does not appear to impact the clinical outcome in terms of recurrent VTE and mortality.

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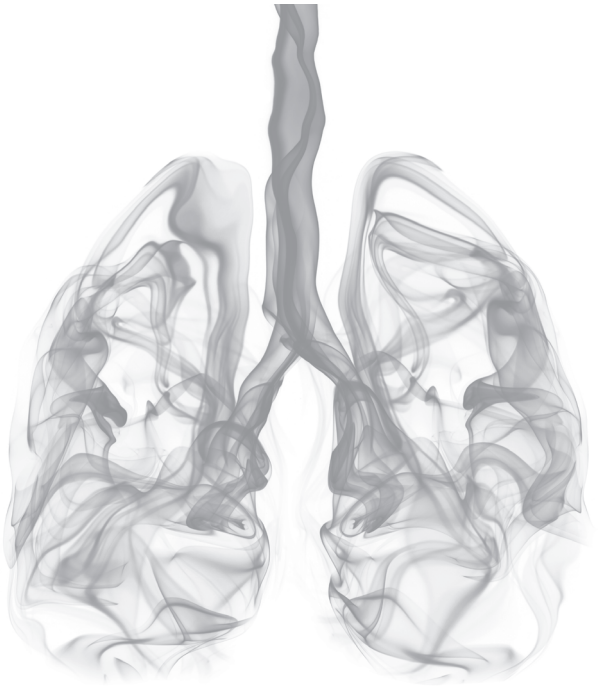
CHAPTER 4

Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study



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ABSTRACT

Importance

D-dimer measurement is an important step in the diagnostic strategy of clinically suspected acute pulmonary embolism (PE) but its clinical usefulness is limited in elderly patients.

Objective

To prospectively validate whether an age-adjusted D-dimer cutoff, defined as age x 10 in patients aged 50 years or older, is associated with an increased diagnostic yield of D-dimer in elderly patients with suspected PE.

Design, Settings and Patients

A multicenter multinational prospective management outcome study in 19 centers in Belgium, France, The Netherlands and Switzerland between January 1, 2010, and February 28, 2013.

Interventions

All consecutive outpatients who presented to the emergency department with clinically suspected PE were assessed by a sequential diagnostic strategy based on the clinical probability assessed using either the simplified, revised Geneva score or the 2-level Wells score for PE; highly sensitive D-dimer measurement; and computed tomography pulmonary angiography (CTPA). Patients with a D-dimer value between the conventional cutoff of 500 µg/L and their age-adjusted cutoff did not undergo CTPA and were left untreated and formally followed-up for a 3-month period.

Main Outcome and Measure

The primary outcome was the failure rate of the diagnostic strategy, defined as adjudicated thromboembolic events during the 3-month follow-up period among patients not treated with anticoagulants on the basis of a negative age-adjusted D-dimer cutoff result.

Results

Of the 3346 patients with suspected PE included, the prevalence of PE was 19%. Among the 2898 patients with a non-high or an unlikely clinical probability, 817 patients (28.2%) had a D-dimer level lower than 500 µg/L (95% CI, 26.6%-29.9%) and 337 patients (11.6%) had a D-dimer between 500 µg/L and their age-adjusted cutoff (95% CI, 10.5%-12.9%). The 3-month failure rate in patients with a D-dimer level higher than 500 µg/L but below the age-adjusted cutoff was 1 of 331 patients (0.3% [95% CI, 0.1%-1.7%]). Among the 766

patients 75 years or older, of whom 673 had a non-high clinical probability, using the age-adjusted cutoff instead of the 500 µg/L cutoff increased the proportion of patients in whom PE could be excluded on the basis of D-dimer from 43 of 673 patients (6.4% [95% CI, 4.8%-8.5%) to 200 of 673 patients (29.7% [95% CI, 26.4%-33.3%), without any additional false-negative findings.

Conclusions and Relevance

Compared with a fixed D-dimer cutoff of 500 µg/L, the combination of pretest clinical probability assessment with age-adjusted D-dimer cutoff was associated with a larger number of patients in whom PE could be considered ruled out with a low likelihood of subsequent clinical venous thromboembolism.

INTRODUCTION

The standard diagnostic approach of patients with clinically suspected acute pulmonary embolism (PE) relies on sequential diagnostic tests, such as clinical probability assessment, plasma D-dimer measurement, compression ultrasonography, computed tomography pulmonary angiography (CTPA), or ventilation-perfusion lung scan.[1,2]

The D-dimer test has been extensively evaluated in the exclusion of PE, particularly among outpatients.[3] The enzyme-linked immunosorbent assay (ELISA) D-dimer test and second-generation latex agglutination tests (immunoturbidimetric tests) have a remarkably high sensitivity and have been proven safe first-line tests in association with clinical probability to rule out PE in outcome studies.[4,5]

Several studies have shown that D-dimer levels increase with age.[6,7] As a result, the clinical usefulness of the test, the proportion of the patients with a D-dimer level lower than the predetermined cutoff value (500 µg/L for most available commercial assays) and in whom the diagnosis of PE may be ruled out by the test, is reduced. In a previous study, the ELISA D-dimer test was able to rule out PE in 60% of patients younger than 40 years, but in only 5% of patients older than 80 years,[8] thus limiting the yield and cost-effectiveness of noninvasive diagnosis in this subgroup of older, often fragile, patients.

We retrospectively derived and validated the value of a progressive D-dimer cutoff adjusted to age in a wide sample of 1712 patients. The optimal age-adjusted cutoff was defined as patient's age multiplied by 10 in patients 50 years or older.[9] In the retrospective validation analysis, the age-adjusted D-dimer cutoff would have increased by about 20% the number of patients in whom the D-dimer test was considered negative without increasing the false-negative rate when compared with the usual 500 µg/L cutoff. The results were particularly appealing in patients older than 80 years—the age-adjusted cutoff allowed an increase in the proportion of patients with a negative D-dimer result from 9% to 21% without any false-negative test.[9]

However, prospective validation of this age-adjusted cutoff was indicated before this strategy could be implemented in clinical practice. Hence, we assessed its failure rate and usefulness in a prospective management outcome study, in which consecutive outpatients with suspected PE were left untreated on the basis of a negative age-adjusted D-dimer test result, in combination with a clinical probability assessment.

METHODS

Study setting

The study was designed as a multicenter, multinational prospective diagnostic management outcome study, involving 19 hospitals in four European countries (Belgium, France,

The Netherlands and Switzerland). The Ethics committees of all participating institutions approved the study. In Belgium, France and Switzerland patients provided written informed consent before enrolment. In The Netherlands, the ethics committee judged than informed consent was not necessary but patients were in all cases informed by the treating physician about the protocol and about the three-month phone call follow-up.

Patients

Consecutive outpatients who presented to the emergency department of the participating hospitals were eligible if they had a clinical suspicion of PE defined as an acute onset or worsening shortness of breath or chest pain without another obvious etiology. Patients were excluded if a PE suspicion was raised more than 24 hours after admission to the hospital, if they were receiving anticoagulant therapy for another indication (e.g. atrial fibrillation), or if they had an allergy to contrast medium, impaired renal function (creatinine clearance less than 30 ml/min as per the Cockcroft-Gault formula), life expectancy of less than 3 months, ongoing pregnancy or inaccessibility for follow-up.

Diagnostic strategy

Clinical probability was assessed using either the simplified revised Geneva score[10,11] or the 2-level Wells' score for PE[2,12] (Table 1). Patients with a high or a 'likely' clinical probability directly proceeded to CTPA. In patients with a low/intermediate or unlikely clinical probability, a D-dimer test was performed. D-dimer result was interpreted according to the age-adjusted cutoff: in patients aged less than 50 years, PE was excluded in those with a D-dimer value below 500 µg/L. In patients aged 50 years or more, the D-dimer test was considered negative in those with a D-dimer value below their age multiplied by 10. Six different quantitative high-sensitivity D-dimer assays were used: the VIDAS D-dimer exclusion test (bioMérieux, Marcy L'Etoile, France), Second generation Tinaquant and Cobas h 232 (Roche Diagnostics, Basel, Switzerland), Liatest D-dimer (Stago, Asnières sur Seine, France), D-dimer HS500 (IL Diagnostics, Bedford, USA) and Innovance D-dimer (Siemens, Munich, Germany). Patients with a negative D-dimer test result did not undergo any further testing and were left without anticoagulant therapy. Patients with positive D-dimer underwent CTPA. Patients with a positive CTPA were started on anticoagulant therapy, while patients with a negative CTPA were left without anticoagulant treatment. Patients with inconclusive CTPA (technical inadequate for interpretation or isolated subsegmental PE) underwent additional testing with compression ultrasonography, ventilation/perfusion scan or pulmonary angiography. Given the uncertainty regarding the clinical relevance and optimal management of isolated subsegmental PE, it was decided to consider CTPA showing isolated subsegmental PE as inconclusive and to recommend further testing. The diagnostic strategy is depicted in the Figure.

Table 1. The Simplified revised Geneva Score and the 2-level Wells' score

Simplified Revised Geneva Score[11]	**Points**
Age > 65 years old	1.0
Previous history of PE or DVT	1.0
Surgery or fracture within 1 month	1.0
Active malignancy	1.0
Unilateral leg pain	1.0
Hemoptysis	1.0
Heart rate (bpm)	
75-94	1.0
≥ 95	2.0
Pain on lower-limb deep venous palpation and unilateral oedema	1.0
Clinical probability	
Low	0-1
Intermediate	2-4
High	≥ 5
Wells Score[12]	**Points**
Clinical signs and symptoms of DVT	3.0
Immobilization or surgery in the previous 4 weeks	1.5
Heart rate greater than 100 beats/min	1.5
Previous history of PE or DVT	1.5
Hemoptysis	1.0
Malignancy	1.0
Alternative diagnosis is less likely than PE	3.0
Clinical probability	
Unlikely	≤4
Likely	>4

DVT, deep vein thrombosis; PE, pulmonary embolism

Follow-up

All patients underwent follow-up for three months. Patients were instructed to return to the clinic or to the emergency room in case of recurrent symptoms of the respiratory system or legs. At the end of follow-up, all patients included in the study were interviewed by telephone by a study coordinator using a structured questionnaire. Patients were asked to disclose all health related events since their hospital discharge: consultations with any physician, admission to hospital, change in medication, diagnostic testing or hemorrhagic complication. The family physician was contacted whenever a possible thromboembolic event was disclosed by the interim history and charts were reviewed if a patient was readmitted to the hospital for any cause.

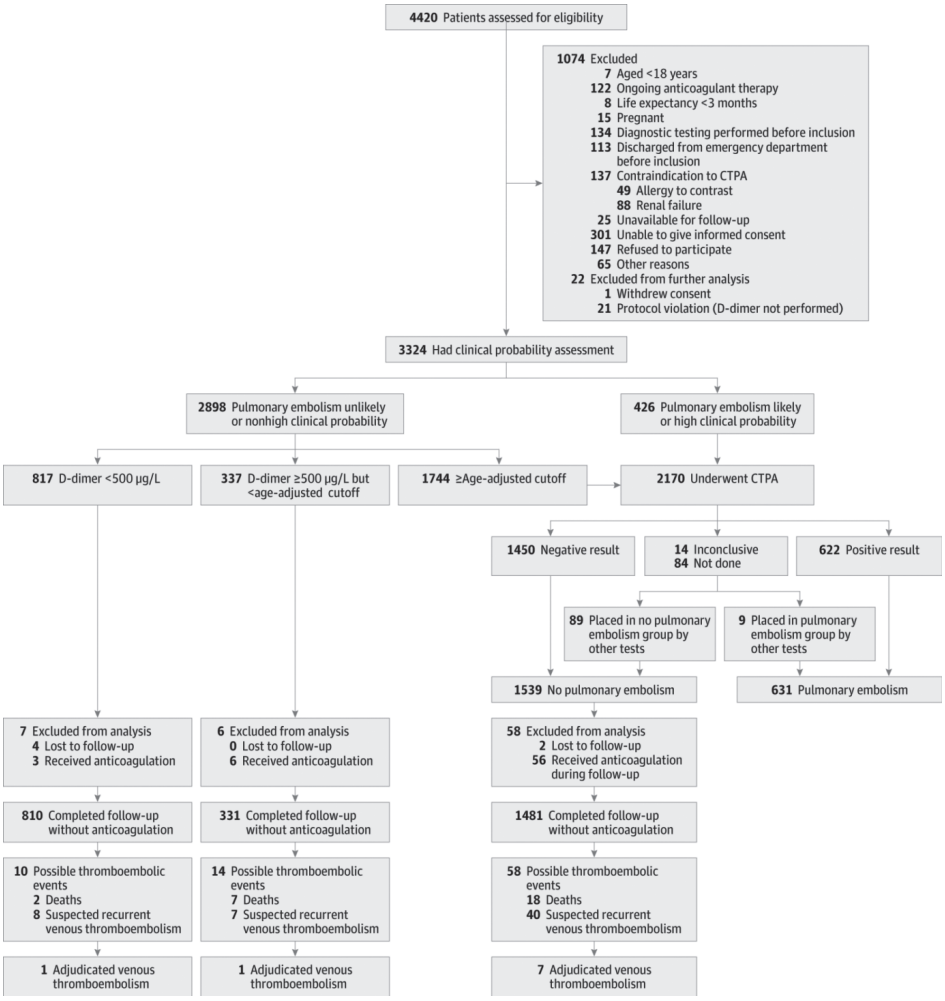

Figure. Flow of patients through the study
CTPA, computed tomographic pulmonary angiography.

All suspected venous thromboembolic events and deaths were adjudicated by three independent experts who were blinded to the criteria used to rule out PE at inclusion.

Outcomes

The primary outcome was the failure rate of the diagnostic strategy, defined as the rate of adjudicated symptomatic thromboembolic events during the 3-month follow-up period among patients not treated with anticoagulants on the basis of a negative D-dimer test result according to the age-adjusted cutoff. It was computed as the number of adjudicated proximal deep vein thrombosis (DVT) or PE (involving a segmental or

more proximal pulmonary artery), divided by the number of patients with a negative D-dimer result that were left without anticoagulant therapy.

Secondary outcomes included the proportion of patients with a low-intermediate or unlikely probability and a D-dimer result between 500 µg/L and their age-adjusted cutoff value. This proportion represents the additional diagnostic yield of the age-adjusted cutoff. We specifically assessed the 3-month thromboembolic risk in this subgroup of patients.

We also defined elderly patients as patients 75 years or older and we analyzed the additional diagnostic yield of the age-adjusted D-dimer cutoff in these patients.

Diagnoses of venous thromboembolic events during follow-up were established with the usual criteria: for DVT, on the basis of abnormal results on proximal compression ultrasonography; and for PE, on the basis of ventilation-perfusion lung scan showing a high-probability pattern or CTPA or angiography showing segmental or more proximal intraluminal defects. Deaths were adjudicated as surely related, probably related, possibly related, or unrelated to PE. Death was judged to be related to PE if it was confirmed by autopsy, or if death followed a clinically severe PE, either initially or after an objectively confirmed recurrent event. Death in a patient who died suddenly or unexpectedly was classified as possibly related to PE. Unrelated deaths were due to an obvious cause other than PE. Three independent experts blinded to D-dimer levels adjudicated the outcome events.

Statistical analysis

General characteristics were assessed using mean and standard deviation or median and interquartile range for continuous variables and proportions for categorical variables. We used the Wilson score method without continuity correction to compute the 95% CI around estimated proportions.[13] Sample size was estimated on the basis of our previous retrospective validation data set. We aimed at including enough patients to provide accurate estimates of our primary and secondary outcomes. To validate the safety of ruling out PE on the basis of a D-dimer level between 500 µg/L and the age-adjusted cutoff, the upper limit of the 95% CI around the 3-month thromboembolic risk (failure rate) in patients left untreated on the basis of such a D-dimer result should not be higher than 3%. This failure rate corresponds to that observed after a negative pulmonary angiography,[14] and is a widely accepted criterion for the validation of diagnostic strategies for PE.[1,2,15-17] This would be obtained if no more than 2 out of 240 patients with such a D-dimer result would experience venous thromboembolism during follow-up. In our previous retrospective study, 10% of patients older than 50 years with an unlikely or a non-high clinical probability had a D-dimer result between 500 µg/L and their age-adjusted cutoff. Hence, to include 240 patients with a D-dimer between 500 µg/L and the age-adjusted cutoff, 2400 patients older than 50 years and with a

non-high or unlikely clinical probability needed to be included. Because these patients represented two-thirds of all patients with suspected PE in our previous study, a total of 3200 patients with suspected PE needed to be included.

RESULTS

Between January 1, 2010, and February 28, 2013, we screened 4420 patients. Among the 4420 screened patients, 1074 were excluded from the study for various reasons, described in the Figure. Hence, 3,346 patients were included in the trial.

Twenty-two patients were excluded from further analysis: the D-dimer test was not performed in 21 patients, and one patient withdrew his consent during the study period. General characteristics of the remaining 3,324 patients are depicted in Table 2.

Table 2. Characteristics of included patients

Characteristics	No. (%) (n=3,324)
Female gender, n, %	1887, 56.8
Age in years, median (IQR)	63 (53-74)
Personal history of VTE, n, %	466, 14.0
Active malignancy, %	429, 12.9
Surgery within one month, %	392, 11.8
Estrogen use, %	183, 5.5
Chest pain, %	1608, 48.3
Dyspnea, %	2092, 62.9
Syncope, %	263, 7.9
Hemoptysis, %	134, 4.1
Heart rate, bpm (mean ± SD)	87.1 (19.6)
Respiratory rate, bpm (mean ± SD)	19.2 (6.2)

IQR, interquartile range; VTE, venous thromboembolism

Diagnostic work-up at initial presentation

The study flow-chart is summarized in the Figure. The clinical probability was non-high (i.e. low or intermediate) using the simplified revised Geneva score, or 'unlikely' using the 2-level Wells' score for PE in 2,898 (87.2%) patients. Among these 2,898 patients with a non-high or 'unlikely' clinical probability, 1,154 (39.8%, 95% CI: 38.1 to 41.6%) patients had a negative D-dimer according to the age-adjusted cutoff: 817 (28.2%, 95% CI: 26.6 to 29.9%) had a D-dimer < 500 µg/L, and 337 additional patients (11.6%, 95% CI: 10.5 to 12.9%) had a D-dimer comprised between 500 µg/L and their age-adjusted cutoff.

Table 3. Study Results According to D-Dimer Assays

D-dimer assay	Low/intermediate or Unlikely Clinical Probability, No of patients	D-dimer < 500 µg/L	3-month VTE risk, n/n,% (95%CI)	D-dimer ≥ 500 µg/L and < age-adjusted cutoff	3-month VTE risk n/n,% (95%CI)
Vidas D-dimer Exclusion (Biomérieux)	1345	423	0/417 0.0 (0.0-0.9)	130	0/127 0.0 (0.0-2.9)
Innovance D-dimer (Siemens)	838	202	1/202 0.5 (0.1-2.8)	103	1/103 1.0 (0.2-5.3)
Liatest D-dimer (Stago)	389	132	0/132 0.0 (0.0-2.8)	49	0/47 0.0 (0.0-7.6)
D-dimer HS 500 (IL Diagnostics)	185	32	0/31 0.0 (0.0-11.0)	23	0/23 0.0 (0.0-14.3)
Second generation Tinaquant D-dimer (Roche)	128	26	0/26 0.0 (0.0-12.9)	32	0/31 0.0 (0.0-11.0)
D-dimer Cobas h232 (Roche)	13	2	0/2 0.0 (0.0-65.8)	0	-
Total	2898	817	1/810 0.1 (0.0-0.7)	337	1/331, 0.3 (0.1-1.7)

VTE, venous thromboembolism

Therefore, the use of the age-adjusted cutoff resulted in an 11.6% (95% CI: 10.5 to 12.9%) absolute increase, or a 41.2% (95% CI: 31.3 to 52.0%) relative increase, in the proportion of negative D-dimer results. The breakdown for the six D-dimer tests used is depicted in Table 3.

Further testing was performed in the remaining 1,744 patients with a D-dimer above the age-adjusted cutoff and in the 426 patients with a 'likely' or a high clinical probability of PE. CTPA was positive in 622 patients. It was negative in 1,450. Finally, it was inconclusive (n=14) or not performed (n=84, protocol violations) in 98 patients. Nine of the 98 patients had PE confirmed on the basis of a high probability V/Q scan (n=2), on a proximal DVT on compression ultrasound (n=7). PE was ruled out in the remaining 89 patients on the basis of a negative pulmonary angiogram (n=1), V/Q scan (n=12), compression ultrasound (n= 26), a negative D-dimer test despite 'likely'/high clinical probability (n=8), or without any further additional testing (n=42). Therefore, PE was diagnosed in 631 patients and the overall prevalence of PE in our study was 19.0 (95% CI: 17.7 to 20.4%).

Three-month follow-up

D-dimer lower than 500 µg/L

During the 3-month follow-up period, out of the 817 patients with D-dimer below < 500 µg/L, 3 patients received anticoagulants for another reason than PE, and 4 (0.5%)

patients were lost to follow-up. Among the 810 remaining patients, there were 2 deaths and 8 suspected VTE during follow-up. Out of these 10 events, one was adjudicated as having a confirmed non-fatal PE. Therefore, the three-month thromboembolic risk was of 1/810 (0.1%, 95% CI: 0.0 to 0.7%).

D-dimer between 500 µg/L and the age-adjusted cutoff

Of the 337 patients with a D-dimer between 500 µg/L and their age-adjusted cutoff, no patient was lost to follow-up and 6 patients received anticoagulation for another indication than PE. Of the remaining 331 patients, 7 died, and 7 underwent testing for suspected VTE. One out of these 14 events was adjudicated as a confirmed non-fatal PE. Adjudicated causes of death were as follows: 3 were due to an end-stage COPD, 1 was from refractory Idiopathic Thrombopenic Purpura (ITP) with severe thrombocytopenia complicated by intestinal hemorrhage, 1 was due to a metastatic melanoma, 1 was due to terminal cachexia in the context of a psychiatric illness, and 1 was due to a hypovolemic shock after a massive hemorrhage associated with over-anticoagulation for atrial fibrillation (anticoagulation was initiated during follow-up).

Therefore, the failure rate of the age-adjusted cutoff was 1 of 331 patients (0.3%, 95% CI: 0.1 to 1.7%).

Patients with D-dimer above the age-adjusted cutoff and patients with a 'likely' or high clinical probability

Of the 1,539 patients with a D-dimer above the age-adjusted cutoff or with a high or 'likely' clinical probability in whom the diagnosis of PE was ruled out, 2 patients were lost to follow-up and 56 patients were given anticoagulants for another reason than PE. Of the remaining 1,481 patients, 18 died and 40 presented with a suspicion of a thromboembolic event. Seven of these 58 suspected events were adjudicated as confirmed or possible events: PE (n=4), DVT (n=1), indeterminate (n=2). Therefore, the failure rate in the patients with a negative CTPA was 7/1,481 (0.5%, 95% CI: 0.2 to 1.0%).

Elderly patients

Overall, 766 patients were aged 75 years or more, of them 673 (87,9%) had a non-high clinical probability. The proportion of patients with D-dimer < 500 µg/L was 43/673 (6.4%). Another 157 patients (23.3%) had a D-dimer below their age-adjusted cutoff. Therefore, the proportion of patients > 75 with a non-high or 'unlikely' clinical probability and a negative D-dimer using the age-adjusted cutoff was 200/673 (29.7%), of them five received anticoagulant therapy for another indication than VTE. None of the remaining 195 had a confirmed VTE during follow-up: 0/195 (0.0%, 95% CI: 0.0 to 1.9%).

DISCUSSION

In this prospective study, using an age-adjusted D-dimer cutoff in emergency department patients with suspected PE increased the diagnostic yield of D-dimer testing. A D-dimer level higher than 500 µg/L but below the age-adjusted cutoff ruled out the diagnosis of PE, with a 3-month risk of venous thromboembolism in line with that observed in patients with a D-dimer level lower than 500 µg/L or after a negative pulmonary angiography result, the gold-standard test for PE. In patients 75 years or older, the age-adjusted cutoff increased 5-fold the proportion of patients in whom PE could be ruled out without further imaging.

These results are in line with those obtained in the initial derivation and retrospective external validation study.[9] After the publication of this initial report, other retrospective validation analyses were published, including more than 10 000 patients with suspected venous thromboembolism, using various D-dimer assays in various clinical settings (suspected DVT, suspected PE) in many different countries, which all indicated a potential clinical usefulness of the age-adjusted cutoff, particularly for elderly patients.[18,19] However, a prospective management outcome study, in which patients with suspected PE would be managed without anticoagulants on the basis of a negative D-dimer test result using the age-adjusted cutoff, was missing. In our study, the diagnostic conclusion and therapeutic management was decided on the basis of the age-adjusted cutoff. Another proposed approach in the literature was to use fixed increased cutoff values in elderly patients (e.g. 750 µg/L in patients 60 years or older).[20] However, this cutoff value was never prospectively validated. Moreover, the strength of the age-adjusted cutoff is that it was derived using receiver operating characteristics (ROC) curve analysis in each age group and linear regression analysis. Another strength is that the age-adjusted cutoff is easy to memorize (patient's age multiplied by 10) and is tailored to each individual patient.

Elderly patients may have the greatest potential benefit of the use of the age-adjusted cutoff. In patients 75 years or older, the proportion of patients with a D-dimer level lower than 500 µg/L was 43 of 673 patients (6.4%). The proportion of patients with negative D-dimer result was 29.7% when using the age-adjusted cutoff. In other words, although only 1 in 16 patients could have the diagnosis of PE ruled out on the basis of the D-dimer as a sole test when using the conventional cutoff, this proportion increased to 1 in 3.4 patients when using the age-adjusted cutoff. Previous studies have shown that in all patients, irrespective of age, the number needed to test with a D-dimer test to rule out 1 PE is approximately 3,[4] but in elderly patients, this number could be as high as 20 after 80 years.[8] Thus, the use of the age-adjusted cutoff allows to "restore" the yield of the D-dimer test in elderly patients. This is particularly important in clinical practice. Indeed, elderly patients are more likely to present with renal impairment and to develop

contrast-induced nephropathy,[21] limiting the use of CTPA in this age group. The use of the ventilation-perfusion lung scan is limited by the higher number of inconclusive results obtained in this age group.[22] The possibility of ruling out PE on the basis of a simple blood test could allow shortening a patient's stay in the emergency department and limiting the unnecessary exposure to radiation, contrast agents of the CTPA, and anticoagulant therapy. On the other hand, it was important to ensure that the increased yield of the D-dimer test would not compromise patient safety, given the risks of untreated PE in this patient population.

This study has several strengths. This was a large international collaboration. All consecutive patients seen at participating centers were approached for inclusion, and all suspected thromboembolic events and deaths during follow-up were adjudicated by an independent committee. Our sample size was calculated to enable assessment of the age-adjusted cutoff failure rate in the subgroup of patients with a D-dimer level higher than 500 µg/L but below the age-adjusted cutoff.

This study also has several limitations. First, 2 different pretest probability assessment tools and 6 different commercial D-dimer assays were used. Therefore, not all included patients were managed using the exact same diagnostic tests. However, the 2 probability assessment tools and the high-sensitive D-dimer tests used have been demonstrated to be equivalent.[23,24] As shown in Table 3, results were homogeneous across the different D-dimer assays. Therefore, this could increase the generalizability of our finding to a wide number of settings with different practices. Second, this study was not designed as a randomized clinical study. Therefore, we could not compare the 3-month thromboembolic risk with that of a control group that would have been managed using the conventional 500 µg/L cutoff. However, the low rate of venous thromboembolic events renders a significant difference between the 2 strategies unlikely. Moreover, the use of the 3-month thromboembolic risk is widely used as the standard reference for the validation of PE diagnostic strategies.[1,2] Third, although all suspected events during follow-up were adjudicated by an independent committee, only 1 of the 7 deceased patients with D-dimer levels higher than 500 µg/L and below the age adjusted D-dimer cutoff had an autopsy (1 of the 3 patients with end-stage chronic obstructive pulmonary disease). Therefore, it is impossible to formally exclude PE as the cause of death in the 6 remaining patients. However, all the 7 deaths were adjudicated as unrelated to PE (obvious cause other than PE). Fourth, in patients with suspected recurrences during follow-up, considering CTPA showing isolated subsegmental pulmonary embolism as inconclusive might be regarded as a potential limitation. However, this scenario did not occur during follow-up of patients with D-dimer levels lower than 500 µg/L or below the age-adjusted cutoff. Therefore, our inferences regarding the failure rate in patients having D-dimer levels between the usual cutoff and the age-adjusted cutoff are likely to be robust. Fifth, the prevalence of PE was somewhat higher than that usually observed

in North American studies.[25-27] However, it is in line with previous studies in Europe.[1,2] Moreover, a lower prevalence would have likely resulted in an even lower failure rate of the age-adjusted D-dimer cutoff.

CONCLUSIONS

In this study, an age-adjusted D-dimer cutoff combined with probability assessment ruled out the diagnosis of PE in emergency department patients with suspected PE and was associated with a low likelihood of subsequent symptomatic VTE, and with an increased proportion of patients in whom the diagnosis could be excluded. This was particularly true in elderly patients, with a 5-fold increase in the proportion of negative D-dimer test results in patients 75 years or older. Future studies should assess the clinical usefulness of the age-adjusted D-dimer cutoff in clinical practice. Whether the age-adjusted cutoff can result in improved cost-effectiveness or quality of care remains to be demonstrated.

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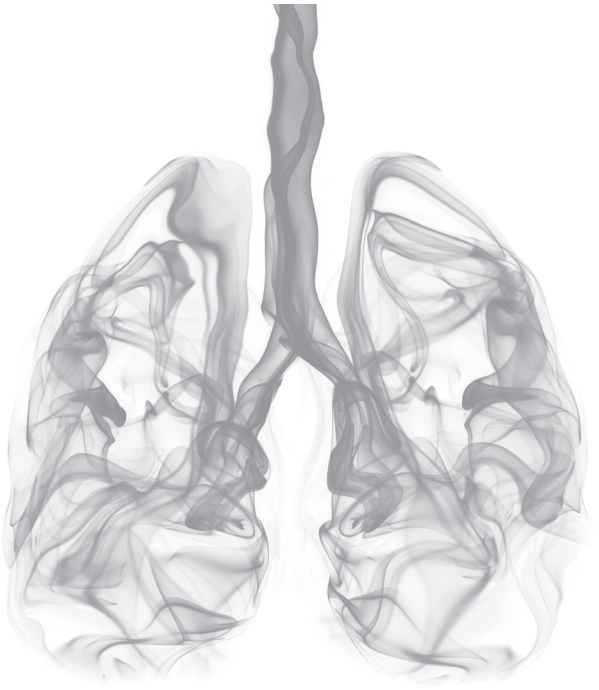
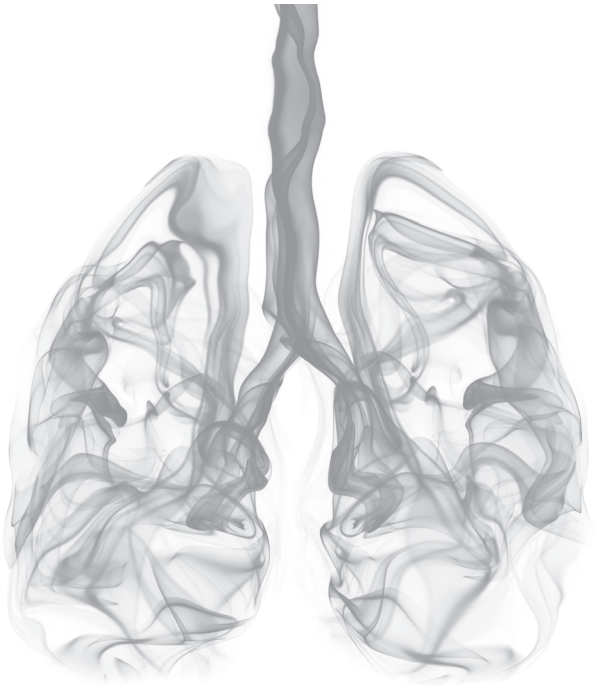
PART II

MANAGEMENT AND PROGNOSIS OF SYMPTOMATIC PULMONARY EMBOLISM



CHAPTER 5

Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism



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ABSTRACT

The clinical significance of subsegmental pulmonary embolism (SSPE) remains to be determined. This study aimed to investigate whether SSPE forms a distinct subset of thromboembolic disease compared to more proximally located pulmonary embolism (PE). We analyzed 3728 consecutive patients with clinically suspected PE. SSPE patients were contrasted to patients with more proximal PE and to patients in who suspected PE was ruled out, as regards the prevalence of thromboembolic risk factors and the 3-month risks of recurrent venous thromboembolism (VTE) and mortality. PE was confirmed in 748 patients, of whom 116 (16%) had SSPE; in 2980 patients PE was ruled out. No differences were seen in the prevalence of VTE risk factors, the 3-month risk of recurrent VTE (3.6% vs 2.5%; p=0.42) and mortality (10.7% vs 6.5%; p=0.17) between patients with SSPE and those with more proximal PE. When compared to patients without PE, age >60 years, recent surgery, estrogen use, and male gender were found to be independent predictors for SSPE, and patients with SSPE were at increased risk of VTE during follow-up (HR: 3.8; 95% CI: 1.3-11.1). This study indicates that patients with SSPE mimic those with more proximally located PE as regards their risk profile and clinical outcome.

INTRODUCTION

The introduction of multi-detector computed tomographic pulmonary angiography (CTPA) has considerably advanced the radiological visualization of pulmonary embolism (PE) and its diagnostic accuracy has been demonstrated to be robust enough to serve as single imaging test in the diagnostic work-up of patients with suspected PE.[1] Compared to previously used imaging techniques to detect PE, multi-detector CTPA allows better visualization of peripheral pulmonary arteries.[2] As a consequence of the widespread use of these scanners as first-line imaging tools to establish or rule out acute PE, small peripheral emboli limited to the subsegmental pulmonary arteries are increasingly being detected. The proportion of this so called isolated subsegmental pulmonary embolism (SSPE) detected on CTPA varies between 4% and 27%.[3-5]

With this increasing incidence of SSPE diagnoses that would probably have gone undetected and thus left untreated with former imaging techniques, physicians started to question the clinical relevance of these findings.[6] The prognostic implications of SSPE are however uncertain, since in few studies the clinical outcome of these patients has been investigated. It remains therefore unclear whether a diagnosis of SSPE deserves the same therapeutic approach as PE located in segmental or more proximal pulmonary arteries.[7] Recently, some evidence suggested that patients with SSPE may have a favourable clinical outcome, even without prescribing anticoagulant therapy.[8;9]

To investigate whether SSPE could be considered as a distinctive subset of venous thromboembolic disease, or even as a prognostically insignificant finding, we compared patients with SSPE to a) patients with PE located in more proximally located pulmonary arteries and b) patients in whom PE was clinically suspected but ruled out, regarding their thromboembolic risk factors, their clinical signs and symptoms, and their short-term clinical outcome in terms of recurrent venous thromboembolism (VTE), bleeding complications and mortality.

METHODS

Study-population

We used the combined data of two prospective outcome studies in which consecutive patients with clinically suspected PE had been included. The first study was a large, prospective management study including 3306 consecutive patients[10], with an aim to evaluate a diagnostic algorithm consisting of the Wells rule[11], D-dimer testing, and CTPA. Exclusion criteria for this study were: treatment with therapeutic doses of unfractionated or low-molecular-weight heparin (LMHW) for > 24 h; life expectancy < 3 months; pregnancy; geographic inaccessibility for follow-up; age < 18 years; allergy to IV contrast

agents; or hemodynamic instability (defined as a systolic BP < 90 mm Hg or clinical signs and symptoms of shock). The institutional review boards of all participating hospitals approved the study protocol, and informed consent was obtained from all participants.

The decision regarding the presence or absence of PE was made by trained attending radiologists who were blinded to any specific patient clinical information. The pulmonary arteries were evaluated down to and including the subsegmental arteries. Embolus localization was classified as central, segmental or subsegmental. Isolated SSPE was defined as a PE that occurred in a subsegmental branch but no larger order of vessels.[12] The subsegmental PE could involve one or more than one subsegmental artery. All patients with confirmed PE were initially treated with subcutaneous body weight-adjusted therapeutic doses of LMWH for a minimum of 5 days or intravenous unfractionated heparin aiming at an activated partial thromboplastin time between 1.5 times and 2 times the baseline value, followed by vitamin K antagonists (VKA), aiming at an international normalized ratio (INR) of 2.0 to 3.0 for a period of 6 months.

The second cohort included 463 consecutive patients with suspected PE, with an aim to identify predictors for the outcome of patients with PE.[13] All patients provided written informed consent. Exclusion criteria for this study were: impossibility for follow-up, age < 18 years, pregnancy, allergy to IV contrast agents or haemodynamic instability at initial presentation. All patients with a likely clinical probability by the Wells rule (>4 points total) and/or an abnormal D-dimer test (>500 ng/mL) underwent multi-detector row CTPA during breath-hold inspiration. The presence of PE was defined as at least one filling defect in the pulmonary artery tree. The method of Qanadli *et al.*[14] was used to quantify the degree of pulmonary arterial obstruction, and the largest pulmonary artery involved, i.e. central, segmental, or subsegmental, was recorded. Isolated SSPE was defined as PE that occurred in a subsegmental branch but no larger order of vessels. All patients in whom PE was confirmed were treated similarly to patients with PE in the first cohort.

Risk factors

We investigated the influence of the following thromboembolic risk factors that were recorded in both studies at baseline: age; sex; hospitalization status; immobilization for at least 3 days within the past four weeks; paralysis, pareses or leg plaster within the past month; major surgery within the past month; a history of VTE; estrogen use; heart failure (defined as New York Heart Association functional class II-IV for which specific therapy was administered); chronic obstructive pulmonary disease (COPD); and active malignancy, defined as any malignancy with ongoing treatment or treatment within the past 6 months, or malignancies in palliative stages.

Outcome

For this comparative analysis, the cohort was stratified into three groups: 1) patients with isolated SSPE, 2) patients with segmental or more proximal PE and 3) patients in whom clinically suspected PE was ruled out. These 3 groups were compared for the incidence of symptomatic (recurrent) VTE, the incidence of major bleeding complications, and the incidence of all-cause mortality during 3 months of follow-up. VTE during follow-up was defined as an objective diagnosis of recurrent PE or deep vein thrombosis (DVT), or death in which PE could not be ruled out as a contributing cause. The objective criterion for the diagnosis of recurrent PE was a new intraluminal filling defect on CTPA or pulmonary angiography; a new high probability perfusion defect on ventilation-perfusion scan; a new non-diagnostic lung scan accompanied by documentation of DVT by ultrasonography or venography; or confirmation of a new PE at autopsy. A diagnosis of (recurrent) DVT had to be confirmed by compression ultrasonography or contrast venography.[15]

Major bleeding was defined as fatal bleeding; symptomatic bleeding in a critical area or organ; clinically overt bleeding causing a fall in hemoglobin level of at least 20 g L^{-1} (1,24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.[16] An independent adjudication committee reviewed and classified all suspected outcome events. Mortality was classified as caused by PE in case of confirmation at autopsy, in case of an objective test demonstrating PE prior to death, or if PE could not be confidently ruled out as the cause of death.

Statistical analysis

Differences in patient characteristics between strata were tested for statistical significance using the Chi-square-test for categorical data and the student-t test for continuous variables. *P*-values < 0.05 were considered statistically significant.

Logistic regression analyses were performed to analyze the association between potential risk factors for VTE and the presence and the location of the PE (ie. odds ratios were calculated for 'no PE' vs SSPE and SSPE vs 'more proximally localized PE'). Any variable achieving a *P*-value of less than 0.10 was included in a multivariate logistic regression model.

The method of Kaplan and Meier was used to estimate the cumulative probability of recurrent VTE and mortality, and the log-rank test was used to compare the groups for statistical differences. The patients were censored at time of event, at time of death, or at time of the end of follow-up year of follow-up, whichever came first. A Cox proportional hazard model was used to derive hazard ratios (HR). HRs for recurrent VTE were adjusted for age, sex, malignant disease and previous VTE. HRs for mortality were adjusted for age, gender, active malignancy, COPD and heart failure. SPSS, version 20 (SPSS Inc, Chicago, IL), was used for all analysis.

RESULTS

Patient characteristics

The combined cohort consisted of a total of 3769 patients with suspected PE. A total of 2688 patients underwent CTPA at baseline, based on either a likely clinical decision rule or abnormal D-dimer test. PE was confirmed in 789 of the 3769 patients (21%). Localization of PE was not determined in 41 (5.2%) patients, and those were excluded from further analysis. Of the remaining 748 patients with PE, 116 (15.5%) had a diagnosis of isolated subsegmental PE, leaving 632 patients who had PE localized in a segmental or more proximal pulmonary artery. In 2980 patients, PE was ruled out either at the basis of an unlikely clinical probability and a normal D-dimer test-result, or on the basis of CTPA.

Table 1. Baseline Characteristics

	SSPE (n=116)	Proximal PE* (n=632)	PE ruled out (n=2980)	*P* Value SSPE vs proximal PE	*P* Value SSPE vs PE ruled out
Age (mean ± SD)	56 ± 17	57 ± 18	52 ± 18	0.46	0.02
Age > 60 (n, %)	50 (43.1)	301 (47.6)	1004 (33.7)	0.37	0.04
Male sex (n, %)	64 (55.2)	309 (48.9)	1212 (40.7)	0.23	0.002
Outpatients (n, %)	87 (75)	496 (78.5)	2431 (81.6)	0.41	0.07
VTE Risk factors:					
Immobilization (n, %)	20 (17.2)	108 (17.1)	273 (9.2)	0.97	0.004
Paralysis, pareses or recent leg plaster (n, %)	5 (4.3%)	37 (5.9%)	63 (2.1)	0.51	0.11
Previous VTE (n, %)	17 (14.7)	128 (20.3)	395 (13.3)	0.16	0.66
Recent Surgery (n, %)	15 (12.9)	72 (11.4)	155 (5.2)	0.64	<0.001
Active Malignancy (n, %)	21 (18.1)	113 (17.9)	347 (11.6)	0.95	0.04
Estrogen use, women (n, %)	15 (30.0)	93 (29.2)	360 (20.7)	0.91	<0.001
Clinical signs and symptoms					
Duration of complaints, days (median, range)	2 (0 - 90)	3 (0 - 90)	2 (0 – 120)	NA	NA
Suspected DVT (n, %)	10 (8.6)	81 (12.8)	90 (3.0)	0.08	0.002
Hemoptysis (n, %)	10 (8.6)	41 (6.5)	100 (3.4)	0.65	0.03
Clinical probability (Wells score)					
Unlikely (n,%)	58 (50)	244 (38.6)	2179 (73.1)	0.02	<0.001
Likely (n,%)	58 (50)	388 (61.4)	800 (26.9)		
Comorbidities					
COPD (n, %)	11 (9.5)	55 (8.7)	337 (11.3)	0.78	0.55
Heart failure (n, %)	10 (8.6)	30 (4.7)	234 (7.9)	0.09	0.75

COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; N, number; PE, pulmonary embolism; SSPE, subsegmental pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

*Defined as pulmonary embolism localized in a segmental or central pulmonary artery.

The mean age of patients with SSPE was 56 years, compared to 57 years for patients with PE localized in segmental or more proximal arteries, and 52 years for patients in whom PE was ruled out (table 1). In these three groups, 55%, 49%, and 41% of the patients, respectively were male. The prevalence of a likely clinical probability (Wells score >4[11]) was lower for SSPE patients than for segmental or more proximal PE patients (50 vs 61%; $p = 0.02$). On the other hand, when compared to patients without PE, patients with SSPE were more frequently classified as having a likely clinical probability (50 vs 27%; $p < 0.001$).

Thromboembolic risk factors

No significant differences were found in the prevalence of thromboembolic risk factors between patients with SSPE and patients with segmental or more proximal PE (table 1 and 2). When compared to patients without PE, the proportions of patients with malignancy (18% vs 12%), immobility (17% vs 9%), recent surgery 13% vs 5%), and estrogen use (30% vs 20%) were higher among patients with SSPE. On multivariate analysis, age >60 years (OR 1.6; 95% CI: 1.07 – 2.42), recent surgery (OR 2.3; 1.23 – 4.20), estrogen use (OR 2.5; 1.34 – 4.81) and male gender (OR 2.1; 1.38 – 3.32) remained significantly associated with SSPE (table 2).

Table 2. Risk Factors for SSPE on multivariate analysis

	SSPE vs PE excluded OR (95% CI)	SSPE vs proximal PE OR (95% CI)
Age > 60	1.6 (1.1 - 2.4)*	0.9 (0.6 - 1.4)
Male sex	2.1 (1.4 - 3.2)*	0.8 (0.5 - 1.2)
Immobilization	1.6 (0.9 - 2.7)	0.9 (0.5 -1.6)
Previous VTE	1.4 (0.8 - 2.4)	0.7 (0.4 - 1.3)
Recent Surgery	2.3 (1.2 - 4.2)*	1.1 (0.6 - 2.0)
Active Malignancy	1.5 (0.9 - 2.4)	1.0 (0.6 - 1.8)
Estrogen use	2.5 (1.3 - 4.8)*	1.0 (0.5 -2.0)

OR, odds ratio; PE, pulmonary embolism; SSPE, subsegmental pulmonary embolism; VTE, venous thromboembolism.
*p<0.05

Risk of VTE during follow-up

Follow-up was completed in 747 (99.9%) of the patients diagnosed with PE at baseline, and in 2974 (99.8%) of the patients in whom PE was ruled out. During 3 months of follow-up, symptomatic recurrent VTE occurred in 4 patients with SSPE (3 patients developed PE, of which 1 case was fatal, and one patient DVT) and in 14 patients with segmental or more proximal PE (10 patients developed PE and 4 patients DVT; in 9 patients, PE was adjudicated either as a direct cause of death or PE could not confidently ruled out as cause

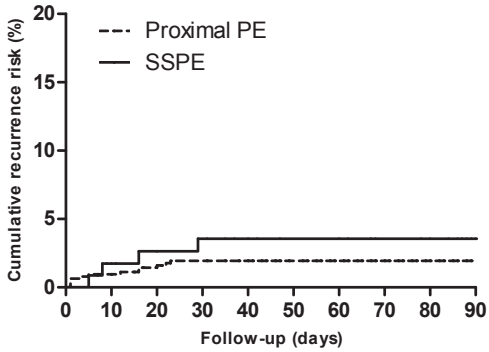

Figure 1. Cumulative risk of recurrent venous thromboembolism for patients with subsegmental pulmonary embolism versus patients with proximal (defined as segmental or central) pulmonary embolism (p = 0.42 from the log-rank test).

of death). The respective cumulative risks for recurrent VTE were 3.6% for subsegmental PE and 2.5% for more proximal PE, respectively (Figure 1; P = 0.42 from the log-rank test). The HR for recurrent VTE was not significantly different for SSPE patients versus patients with more proximal PE (HR: 1.6; 95% CI: 0.5-4.8). Adjustment for age, gender, malignant disease and history of VTE did not materially influence this HR.

One of the patients with SSPE (25%) and 3 of the patients with more proximal PE (21%) had signs or symptoms suggestive of DVT of baseline.

In the group of patients in whom PE was ruled out at baseline, 25 patients (0.8%) developed VTE during follow-up (10 developed DVT, 7 developed PE, and in 8 patients PE was adjudicated either as a direct cause of death or PE could not confidently ruled out as cause of death). The cumulative risk for VTE in this group was 1.1% (Figure 2). The unadjusted HR for the risk of VTE during follow-up for patients with SSPE versus patients with no PE was 4.3 (95% CI: 1.5-12.3). After adjustment for age, gender, malignant dis-

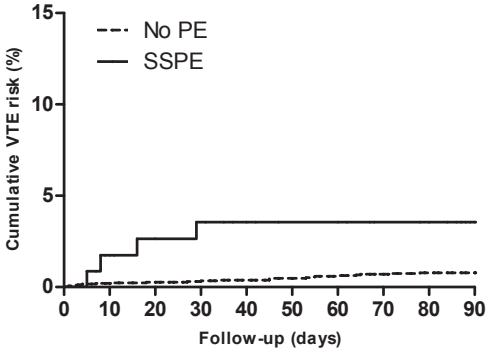

Figure 2. Cumulative risk of venous thromboembolism during follow-up for patients with subsegmental pulmonary embolism versus patients with no pulmonary embolism (p = 0.03 from the log-rank test).

ease and history of VTE, the HR remained statistically significant: 3.8 (95% CI: 1.3-11.1). Malignant disease was independently associated with the occurrence of VTE during follow-up (HR: 3.7; 95% CI: 1.6-8.4).

Bleeding complications in patients with PE

Two patients (1.7%) with SSPE and 10 patients (1.6%) with segmental or more proximal PE experienced major bleeding during follow-up. The age- and sex- adjusted odds ratio for major bleeding in patients with SSPE versus those with larger pulmonary emboli was 1.15 (95% CI: 0.25 – 5.34; *P*= 0.86). Two of these bleeding events were adjudicated as fatal; both events occurred in the group of patients with segmental or central PE.

Risk of mortality

Twelve (10.3%) patients diagnosed with SSPE and 40 (6.3%) patients with segmental or central PE died during follow-up. The respective cumulative mortality risks were 10.7% and 6.5% (adjusted HR: 1.5, 95% CI: 0.8 – 2.8; *P*= 0.17 from the log-rank test).

In the patients in whom PE was excluded, 156 (5.2%) patients died during follow-up. Their cumulative mortality risk (5.4%) was significantly lower compared to patients with SSPE (*P*= 0.01 from the log-rank test). Multivariate analysis identified malignancy (HR 5.6; 95% CI: 4.2 – 7.6), male gender (HR 1.5; 95% CI: 1.1 – 2.1), age (HR 1.04 per year; 95% CI: 1.03 – 1.05), COPD (HR 1.5; 95% CI: 1.1 – 2.2) and heart failure (HR 1.9; 95%: 1.3 – 2.7) as independent predictors for mortality. After adjustment for these covariates, the HR for mortality was 1.4 (95% CI: 0.8 – 2.6) for patients with SSPE compared to those in whom PE was ruled out.

DISCUSSION

To our knowledge, the present study is the largest in patients with SSPE and is the first where patients with more proximally located PE as well as patients without PE as reference groups served for comparison. Two important conclusions can be drawn from our findings. First, with regard to the clinical outcome in terms of recurrent VTE, bleeding complications and mortality, patients with SSPE appear to mimic those with PE localized in more proximal pulmonary arteries. This is supported by the observation of a similar VTE risk profile in both groups. Second, patients with SSPE differ significantly from patients in whom PE was ruled out, both in terms of thromboembolic risk profile and incidences of VTE and mortality during follow-up. The latter appeared to be driven by the presence older age and comorbidities including malignancy, COPD and heart failure.

These findings challenge the hypothesis that a diagnosis of SSPE might be clinically insignificant. Evidence for this latter hypothesis was derived from a recent systematic

review assessing the rates of SSPE diagnoses on multi-detector and single-detector CTPA examinations.[8] Although the proportion of detected SSPE increased from 4.7% to 9.4% for single- compared to multi-detector CTPA, the rate of recurrent VTE in patients in whom PE was ruled out and who were thus left untreated, did not differ between the groups (0.9 versus 1.1%). Based on these results, the authors concluded that the additional SSPE cases detected by multi-detector CTPA may be clinically irrelevant. This however should be regarded as indirect evidence given that the outcome of patients with SSPE was not directly assessed. More indirect evidence supporting the concept that the increased proportion of SSPE detected by CTPA might be clinically insignificant comes from a large population based study.[17] Based on discharge level data, Wiener *et al.* noticed an increased incidence of PE diagnosis following the introduction of CTPA, whilst the mortality risk remained unchanged and the case-fatality rate decreased. The authors referred to these findings as 'evidence of overdiagnosis', defined as the detection of an abnormality, specifically small pulmonary emboli, that will never cause symptoms or death. Again this study does not provide us with direct evidence that the additional PE cases detected by CTPA are harmless. Furthermore, the study does not inform us on the risk of recurrent VTE. Although the decreasing case-fatality rate does suggest that isolated, small pulmonary emboli are less likely to be a direct cause of death, its presence may still reflect a patients' prothrombotic state and therefore be associated with an increased risk of thrombus extension or VTE recurrence in the future.

If SSPE would represent a distinctive subset of thromboembolic disease or even a physiological finding, we postulated that this would translate in a distinct thromboembolic risk profile and clinical outcome, or that the clinical characteristics of these patients would be more comparable to those of patients without PE. However, we found that both the risk profile and outcome of patients with SSPE largely overlapped with those with more proximal PE, suggesting a similar underlying pathophysiology.

Supporting evidence for our findings comes from the recently published Einstein PE study, in which the efficacy and safety of the novel oral anticoagulant rivaroxaban was compared to VKA for the treatment of PE.[18] From that study, separate analyses were performed with respect to the anatomic location of PE. In both treatment arms, similar rates of recurrent VTE were observed for patients with anatomically limited PE (defined as ≤25% of vasculature of a single lobe) versus those with extensive PE (defined as multiple lobes and >25% of entire pulmonary vasculature); respectively 1.6% versus 1.7% in the rivaroxaban group and 1.3% versus 1.4% in the standard-treatment group. Although the definition used for anatomically limited PE may also include segmental PE, one would have expected a lower rate of recurrent VTE in these patients in case SSPE would have had no clinical significance. In line with our findings, these data suggest that the risk of recurrent VTE is not influenced by the anatomic location of PE. It seems more likely that persistent risk factors for recurrent VTE are better risk predictors than the location of the

PE. A recent population-based study demonstrated that active malignancy is by far the strongest predictor for recurrent VTE.[19] Indeed, in the present study, active malignancy was independently associated with the occurrence of VTE during follow-up.

A potential limitation of our study is that an independent radiologist did not confirm the diagnosis of SSPE in the majority of cases. It has recently been demonstrated that significant differences in the interpretation of SSPE among radiologists could occur.[20] Although all CTPAs were assessed according to a pre-specified protocol, it cannot be ruled out that some of our patients were misclassified as having SSPE, this however reflects the diagnostic process of SSPE in daily clinical practice. Second, our definition used for SSPE included both single and multiple SSPE. We were therefore unable to investigate whether the number of emboli and amount of branches affected, influences the prognosis of SSPE patients. Third, the absolute incidences of recurrent VTE, bleeding complications and mortality were small. Although we did not detect a difference in outcome between SSPE patients and those with proximal PE, our study might be underpowered to detect small differences. Our findings should thus be considered hypothesis generating and need to be confirmed in larger studies. Fourth, the presence of DVT at baseline was not systematically assessed; this has recently been identified as an independent predictor for mortality in patients with acute PE.[21] However, the proportions of patients who had signs and symptoms suggestive of DVT did not differ significantly between patients with SSPE and those with more proximal PE. Finally, it should be noted that this study was not designed to answer questions on the benefit of anticoagulant treatment in patients with SSPE; all patients included in this analysis were treated. There is a need for prospective studies assessing the outcome and management of SSPE, before considering distinct management guidelines for this specific group of PE patients. Indeed, a prospective management study assessing the safety of withholding anticoagulation in patients with isolated symptomatic SSPE, without DVT on bilateral lower extremity compression ultrasonography, is currently being conducted (NCT01455818).

In conclusion, in contrast to common believe that SSPE represents a benign subset of VTE, this study shows that patients with symptomatic SSPE appear to mimic those with segmental or more proximal PE as regards their risk profile and short term clinical course. Risk factors for VTE were shown to be associated with SSPE, and the incidences of recurrent VTE and mortality were higher among SSPE patients, compared to those without PE.

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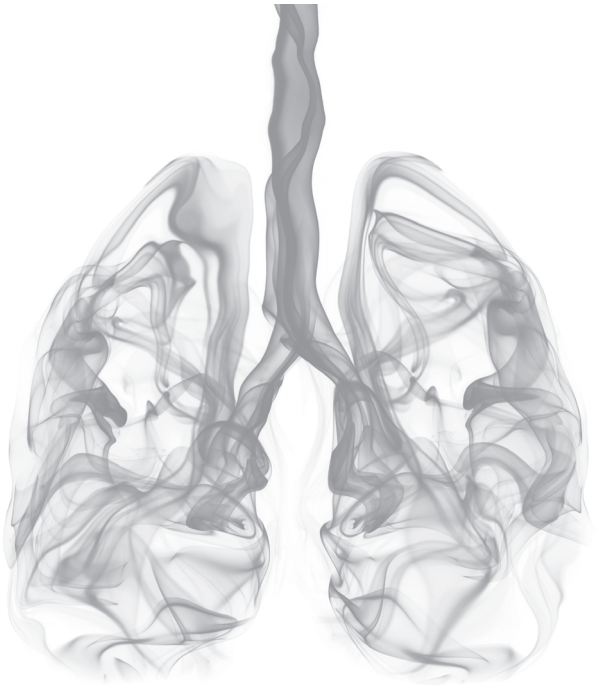
CHAPTER 6

Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism



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ABSTRACT

The aim of this study is to compare the performance of two clinical decision rules to select patients with acute pulmonary embolism (PE) for outpatient treatment: the Hestia criteria and the simplified Pulmonary Embolism Severity Index (sPESI).

From 2008 to 2010, 468 patients with PE were triaged with the Hestia criteria for outpatient treatment: 247 PE patients were treated at home and 221 were treated as inpatients. The outcome of interest was all-cause 30-day mortality. In a post-hoc fashion, the sPESI items were scored and patients were classified according to the sPESI in low and high risk groups. Of the 247 patients treated at home, 189 (77%) patients were classified as low risk according to the sPESI and 58 patients (23%) as high risk. In total, 11 patients died during the first month; two patients treated at home and nine patients treated in-hospital. None of the patients treated at home died of fatal PE. Both the Hestia criteria and sPESI selected >50% of patients as low risk, with good sensitivity and negative predictive values for 30-day mortality: 82% and 99% for the Hestia criteria and 91% and 100% for the sPESI, respectively. The Hestia criteria and the sPESI classified different patients eligible for outpatient treatment, with similar low risks for 30-day mortality. This study suggests that the Hestia criteria may identify a proportion of high risk sPESI patients who can be safely treated at home, this however requires further validation.

INTRODUCTION

Evidence on the safety of outpatient treatment or early discharge of selected low-risk patients with acute pulmonary embolism (PE) is accumulating. The recent American College of Chest Physicians guidelines give a grade 2B recommendation on the safety of early discharge of selected PE patients and the European Society of Cardiology guidelines suggest that low risk PE patients, with negative markers for right ventricular dysfunction or myocardial ischemia, could be treated at home.[1,2]

When considering outpatient treatment for patients with acute PE, the crucial step is to select those patients who are at low risk of adverse outcome. For this purpose, several methods to aid in the selection of low risk patients have been investigated: clinical signs and symptoms[3,4], laboratory values[5], or imaging techniques.[6] The most widely validated method for selection of low-risk patients with PE, is the Pulmonary Embolism Severity Index (PESI)[7,8]; a clinical decision rule, containing 11 items based on signs and symptoms of the patient. The PESI has been prospectively tested in a randomized controlled trial[9], in which low risk patients with <85 points on the PESI, were randomized between home or hospital treatment. Patients treated at home demonstrated equally low rates (<1%) of recurrent venous thromboembolism and all-cause mortality compared to patients treated in-hospital.

Recently, a simplified version of the PESI has been developed.[10] This simple rule, with only six items, is much more useful in the busy emergency department.

Our study group recently published the Hestia Study: a multicenter study on outpatient treatment, which used 11 practical clinical exclusion criteria (Hestia criteria) to select patients for outpatient treatment.[4] The present study is a post-hoc comparison of the data of the Hestia Study, in which we applied the simplified PESI (sPESI) to our patients. In this article we compare the performance of the Hestia criteria and the sPESI in selecting low-risk PE patients eligible for outpatient treatment and the relation of both clinical prediction models to clinical outcome.

METHODS

Design

This is a post-hoc analysis on data from the Hestia Study, which was a multicenter prospective cohort study performed in 12 hospitals in The Netherlands. For this analysis we selected consecutive patients with acute PE treated as in- or outpatients with anticoagulants between 2008 and 2010. Inclusion criteria were: over 18 years of age with proven acute PE presenting to the Emergency Department or outpatient clinic. Patients with asymptomatic or chronic PE, defined as symptoms > 14 days, without acute worsening,

were not included. All patients were treated at home with anticoagulants, unless one of the Hestia criteria was present (Table 1). If one of the Hestia criteria was present, the patient was admitted to the hospital. The complete methods of this study are described elsewhere.[4] The Hestia Study was approved by the Institutional Review Board of all participating hospitals and patients provided written informed consent. The patients treated in-hospital were not included in the original Hestia study, because they were not eligible for the intervention of outpatient treatment. After the study we thoroughly reviewed the medical charts of the patients treated in the hospital to investigate whether they had had predefined adverse clinical outcome within three months following the PE diagnosis, as described below.

Endpoints

All patients were followed for three months for the occurrence of recurrent venous thromboembolism, major bleeding complications and mortality. Follow-up in the patients treated as outpatients was done according to the Hestia Study protocol; patients visited the outpatient clinic at one week, six weeks and twelve weeks after the initial PE. In the patients treated as inpatients, the endpoints were collected by chart review. For this comparative analysis, we used 30-day all-cause mortality as our primary endpoint.

Table 1. Items in the Hestia Criteria and the simplified Pulmonary Embolism Severity Index

Hestia Criteria	Simplified Pulmonary Embolism Severity Index
• Hemodynamically instable?*	• Age > 80 years?
• Thrombolysis or embolectomy necessary?	• Cardiopulmonary co-morbidity?
• High risk for bleeding?**	• History of cancer?
• Oxygen supply to maintain oxygen saturation >90% >24 h.?	• Arterial oxyhemoglobin saturation level <90%?
• Pulmonary embolism diagnosed during anticoagulant treatment?	• Systolic blood pressure <100 mmHg?
• Intravenous pain medication >24 h.?	• 6. Pulse frequency ≥110 beats/min?
• Medical or social reason for treatment in the hospital >24 h.?	
• Creatinine clearance of less than 30 ml/min?***	
• Severe liver impairment****	
• Pregnant?	
• 11. Documented history of heparin induced thrombocytopenia?	
If one of the questions is answered with YES, the patient can not be treated at home	If one of the items is present the patient is regarded as high risk

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

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

*** Calculated creatinine clearance according to the Cockroft-Gault formula

**** Left to the discretion of the physician

An independent adjudication committee adjudicated all outcomes. They also assessed whether death was likely to be PE related based on autopsy reports and clinical reports.

Simplified Pulmonary Embolism Severity Index

In this post-hoc analysis, the sPESI was applied on the data of the Hestia Study.[10] The sPESI consists of six items and if one of the items is present, the patient is considered at high risk for 30-day mortality and cannot be treated at home (Table 1). The age, cardiopulmonary co-morbidity and history of cancer were prospectively registered at time of presentation to the Emergency Department, both for in out- and inpatients, during the Hestia Study. The pulse frequency, blood pressure and oxygen saturation were collected in all patients by chart review, again these items were scored at time of presentation to the Emergency Department. We calculated the proportion of patients who were treated at home according to the Hestia criteria, but could not be treated at home according to the sPESI. Also, we calculated the proportion of patients that were classified as low risk by the sPESI, but as high risk by the Hestia criteria.

Statistics

Differences between categorical variables were studied using the Fisher's Exact test and continuous variables were compared using an independent samples T-test. A two-sided p-value was considered to indicate a significant difference if <0.05. The discriminatory abilities of the Hestia criteria and the sPESI were investigated by measuring the area under the curve (AUC) in receiver operating characteristics (ROC) analyses. SPSS version 17 (SPSS Inc, Chicago, IL) was used for all analysis.

RESULTS

Patient selection and characteristics

From 2008 to 2010 530 patients with an objective diagnosis of acute symptomatic PE were selected; 297 were treated at home in the Hestia Study and 233 were excluded from outpatient treatment by the Hestia criteria and treated in-hospital. In 468 of 530 patients all items of the sPESI score could be collected from the medical charts. This resulted in the inclusion of 247 patients treated at home and 221 patients treated in the hospital according to the Hestia criteria in this post-hoc analysis.

The patients treated in the hospital were excluded from outpatient treatment by the following Hestia criteria: medical or social reasons 82 (37%), hypoxia 67 (30%), hemodynamic instability 28 (13%), high bleeding risk 14 (6%), intravenous pain medication11(5%), use of therapeutic anticoagulants 7 (3%) and indication for thrombolysis 5 (3%). The reason for hospital admission was not specified in 7 patients.

Table 2. sPESI items in patients at home versus patients treated in the hospital

Characteristics of sPESI	All patients N=468	Home treatment N=247*	Hospital treatment N=221**
Age >80	43 (9)	9 (4)	34 (15)
History of cancer	69 (15)	21 (9)	48 (22)
Cardiopulmonary co-morbidity	47 (10)	12 (5)	35 (16)
Heart rate ≥110/min	76 (16)	22 (9)	54 (24)
Systolic blood pressure <100 mmHg	18 (4)	0	18 (8)
Oxygloblin saturation <90%	33 (7)	2 (0.8)	31 (14)
sPESI low risk	275 (59)	189 (77)	86 (39)
sPESI high risk	193 (41)	58 (23)	135 (61)

Data are displayed as N(%).

* 50 patients were excluded because one or more items of the sPESI score were missing

** 12 patients were excluded because one or more items of the sPESI score were missing

Overall, the patients had a mean age of 58 years and 55% were male. Fifteen percent of patients had a history of cancer and 10% had a cardiopulmonary co-morbidity, for example heart failure or chronic obstructive pulmonary disease (Table 2).

Simplified Pulmonary Embolism Severity Index

The distribution of the items of the sPESI in all patients and the patients treated at home or in the hospital is displayed in Table 2. Overall, 275 of 468 patients (59%) were classified as low risk according to the sPESI and 193 of 468 patients (41%) were classified into the high risk sPESI group. Patients with low risk according to sPESI had significantly lower 30-day mortality of 0.4% versus 5.3% in the high risk sPESI patients (P=0.001).

Of the 247 patients treated at home, 189 (77%) of patients would have been in the low-risk sPESI group and 58 patients (23%) would have been in the high-risk sPESI group. Of the 221 patients treated in the hospital, 86 (39%) would have been in the low risk sPESI group and 135 (61%) would have been in the high risk sPESI group.

Patients with cardiopulmonary co-morbidity, malignancy or age >80 years are defined as high risk patients according to the sPESI. In the Hestia study 26% of patients with cardiopulmonary co-morbidities, 21% of patients with malignancies and 30% of patients >80 years could be treated at home, with only one adverse event. One of the patients with pancreatic cancer died of end-stage cancer within 30 days (day 29) and the other patients had uncomplicated clinical courses. Nine patients died within 30 days in the high-risk sPESI patients treated in the hospital (6.8%; 95%CI 3.2-13) versus one in the high-risk sPESI patients treated at home (1.7%; 95%CI 0.04-9.2; Table 3).

Table 3. Distribution of adverse clinical events of low and high risk sPESI groups in the patients treated at home or in the hospital in the Hestia Study

	All patients N=275	Home treatment N=189	Hospital treatment* N=86	p-value
sPESI low risk				
All cause mortality				
7 days	0	0	0	1.0
30 days	1 (0.4)	1 (0.5)	0	1.0
3 months	1 (0.4)	1 (0.5)	0	1.0
Major bleeding	3 (1.1)	1 (0.5)	2 (2.3)	0.231
Recurrent VTE	4 (1.5)	3 (1.6)	1 (1.2)	1.0
sPESI high risk	**N=190**	**N=58**	**N=132**	
All cause mortality				
7 days	4 (2.1)	0	4 (3.0)	0.315
30 days	10 (5.3)	1 (1.7)	9 (6.8)	0.288
3 months	23 (12.1)	2 (3.4)	21 (16)	0.015
Major bleeding	9 (4.7)	0	9 (6.8)	0.059
Recurrent VTE	10 (5.3)	2 (3.4)	8 (6.1)	0.726

* 3 patients lost to follow-up

Risk of recurrent VTE and major bleeding complications Hestia vs sPESI

During the initial 7 days of follow-up, 1 (0.4%) of the patients classified as low-risk by sPESI, versus none of the Hestia low risk patients experienced recurrent VTE. At 30 days, these respective rates were 4 (1.5%) and 4 (1.6%). In the high-risk groups, the rates of recurrent VTE at 7 days and 30 days follow-up were 4 (2.0%) and 6 (3.1%) for sPESI and 5 (2.3%) and 6 (2.7%) for the Hestia criteria.

Major bleeding complications occurred in 3 (1.1%) of the patients classified as low-risk sPESI, as compared with 1 (0.4%) patient in the low-risk Hestia patients within the initial 7 days of follow-up. After 30 days, respectively 3 (1.1%) and 1 (0.4%) patients had experienced bleeding complications. The rates of major bleeding in the high-risk groups were 5 (2.6%) at 7 days and 7 (3.6%) at 30 days for sPESI and 7 (3.2%) at 7 days and 9 (4.1%) at 30 days for Hestia.

Test characteristics Hestia criteria versus sPESI

Eleven patients (2.4%) died within 30 days, nine patients treated in-hospital and two patients treated at home. None of the patients treated at home died of fatal PE. Of the 11 patients that died within 30 days, ten would be classified as high risk according to the sPESI and one would have been classified as sPESI low risk. The Hestia criteria had a sensitivity for 30-day mortality of 82% and a negative predictive value of 99% (Table 4). The sensitivity of the sPESI was 91% and the negative predictive value was almost 100%.

Table 4. Test characteristics Hestia criteria versus sPESI

	Hestia Criteria % (95% CI)	sPESI % (95% CI)
Proportion identified as low risk	53 (48-58)	59 (54-64)
Proportion identified as high risk	47 (42-51)	41 (36-45)
30-day all cause mortality		
Sensitivity	82 (48-97)	91 (57-100)
Specificity	57 (52-61)	60 (56-65)
Negative predictive value	99 (97-100)	100 (98-100)
Positive predictive value	4 (2-8)	5 (3-10)
30-day adverse events*		
Sensitivity	74 (43-52)	74 (51-89)
Specificity	54 (49-58)	60 (56-65)
Negative predictive value	98 (95-99)	98 (95-99)
Positive predictive value	8 (5-12)	9 (5-14)

*All-cause mortality, recurrent venous thromboembolism and major bleeding.

Because of the low incidence of 30-day mortality, the specificity and positive predictive value were low for both clinical decision rules: 54% and 4% for the Hestia criteria and 62% and 5% for the sPESI, respectively (Table 4). The ROC-curve demonstrated an AUC of 0.756 (95% CI 0.642-0.871) for the sPESI and 0.679 (95% CI 0.536-0.822) for the Hestia criteria.

When considering 7 day mortality as an outcome the sensitivity, specificity and negative predictive value of the Hestia criteria were 100%, 53.6% and 100%, as compared with 100%, 59.7% and 100% for the sPESI prognostic model.

Six (2.4%) of the low-risk Hestia patients versus 6 (2.2%) of the low-risk sPESI patients developed an adverse clinical course within 30 days, defined as the occurrence of either recurrent VTE, major bleeding or death. When this combined 30-day outcome was considered, the negative prognostic value was 97.6% for Hestia and 97.8% for sPESI (table 4).

The Hestia criteria identified 53% as low risk and the sPESI would have identified 59% of PE patients as low risk. The Hestia low risk patients were all treated at home. Of the patients identified as low-risk by the sPESI, 86 of 275 (31%) had an indication for hospital admission according to the Hestia criteria. The main reasons for hospital admission were: medical or social reasons in 34 patients (40%), hypoxia in 24 patients (28%), high bleeding risk in 7 patients (8%), intravenous pain medication in 7 patients (8%).

DISCUSSION

We found that both the Hestia criteria and the sPESI safely identified more than half of the PE patients as low risk, with a comparable accuracy of predicting 30-day mortality. However, 39% of patients identified as low risk by sPESI could not be treated at home in the Hestia Study. Although the 30-day outcome of these patients in terms of mortality was favorable (0%), in real clinical practice hospitalization in these patients would still be indicated. In addition, this study demonstrated that a fourth of the patients treated at home safely in the Hestia study would have been classified as high risk by the sPESI and therefore would not have been eligible for outpatient treatment according to the sPESI.

The PESI is currently the best validated method for risk stratification for patients with acute PE. However, only few management studies assessed the safety and clinical utility of this prediction model in managing PE patients either on an in- or an outpatient basis. In contrast to the Hestia criteria, the PESI score and its simplified version were not developed to directly select PE patients eligible for outpatient treatment, but to identify patients with a low 30-day mortality risk. As a consequence, before (s)PESI can be used in clinical practice, some practical exclusion criteria for outpatient treatment have to be added. In the randomized trial by Aujesky *et al.* the 11 items of the PESI were scored after 14 practical exclusion criteria for outpatient treatment were applied, because a part of the PESI low risk patients could not be treated as outpatients, because of medical or social conditions.[9] In this trial, physicians therefore had to check 25 items before the patient could be selected for outpatient treatment. This triaging may be too complicated and time consuming for use in busy emergency departments.[11] The introduction of the simplified PESI, with only six risk items, therefore clearly advanced the field. Still, the current study demonstrates at least four of the Hestia criteria, including medical or social indications for hospitalization, requirement of oxygen therapy or intravenous narcotics, or an anticipated high bleeding risk, are required in addition to the sPESI criteria, in case this model is used as a tool to select candidates for outpatient treatment.

In our study, 59% of PE patients were identified as low risk by the sPESI. This is a high proportion of low-risk patients when compared to the 31-46% reported in the literature.[10,12-14] This is mainly due to the lower proportion of patients with malignancies in our study. Two recent studies have reported low 30-day mortality rates of 0-0.6% of both low risk (s)PESI patients treated at home and low risk patients treated in the hospital.[9,12] This is well comparable to the mortality of 0.5% in low risk patients treated at home and to the 0% mortality in low risk patients treated in the hospital in our study.

Until now, our study and the study of Erkens *et al.*[12], are the only studies that describe clinical outcome in PE patients with high sPESI scores treated at home. The patients with high PESI scores, selected for home treatment, had markedly lower 30-day mortality rates than patients with high sPESI scores treated in the hospital: 0-2% in patients treated

at home versus 7-11% in patients treated in the hospital.[12] In the majority of the patients with high risk sPESI, who were safely treated at home, malignancy was the only sPESI risk item present. This suggests that with the use of the clinical criteria like the Hestia criteria, a selected group of patients with one of the sPESI risk items, mainly patients with cancer, can be safely treated at home. From a clinical perspective this is very important. Patients with malignancy already have many intensive oncology therapies in the hospital and often have a short life expectancy; therefore every day that can be spent at home is of great value to the patient. Moreover, although oncology patients with PE are indeed at increased risk of mortality[15], and therefore assigned high prognostic weight by (s)PESI, most of this mortality may not directly related to the PE event but rather to progression of the underlying malignancy. It is questionable whether this mortality could be prevented by treating these patients as inpatients. However, the safety of treating oncology patients with acute PE, selected as low-risk patients by the Hestia criteria, as outpatients requires further validation.

Our study had strengths and limitations that should be addressed. The inclusion of consecutive patients and the absence of loss to follow-up, as well as the fact that this study was conducted in both academic (n=3) and non-academic (n=9) medical centers, strengthens the generalizability of our findings.

The main limitation of this study lies in the fact that the sPESI score was calculated retrospectively and that management was initially based on the Hestia criteria. To draw definitive conclusions on the accuracy of both scores, a head-to-head comparison would be necessary. Still, the current analysis led us to explore the outcome of a subset of low-risk sPESI patients treated in hospital and a subset treated at home. Another limitation is that in 62 of 530 patients (12%) some of the items of the simplified PESI score were not recorded and therefore these patients were excluded from the analyses. However, follow-up was complete in all of these patients, except for one patient living abroad. During follow-up only one of 62 patients died of a pulmonary infection. This patient would have been in the high risk sPESI group because of preexisting COPD and was admitted to the hospital in the Hestia study because of the need of intravenous antibiotics. The test characteristics of the Hestia criteria and the sPESI in predicting 30-day mortality would not alter significantly by adding this one case in the high risk sPESI group that was treated in-hospital. Third, the incidence of mortality in the current study was low, leading to large confidence intervals. Therefore our results and conclusions should be considered hypothesis generating; external validation of the Hestia criteria and investigating the impact of sPESI on the management of PE patients is required to confirm our findings. Notably, the Hestia criteria are currently being validated externally in a randomized clinical trial (Vesta study; trial number: NTR2603).

In conclusion, our study demonstrated that both the Hestia criteria and the sPESI score were able to identify a large proportion of PE patients with a low risk of adverse clini-

cal outcome. However, when applied in a clinical setting to select PE patients eligible for outpatient treatment, this study demonstrates that at least four Hestia criteria are required in addition to the sPESI. Second, this study suggests that a proportion of patients classified as high risk by sPESI for reasons as malignant disease, cardiopulmonary co-morbidities or high age, can be safely treated at home when the Hestia criteria are applied.

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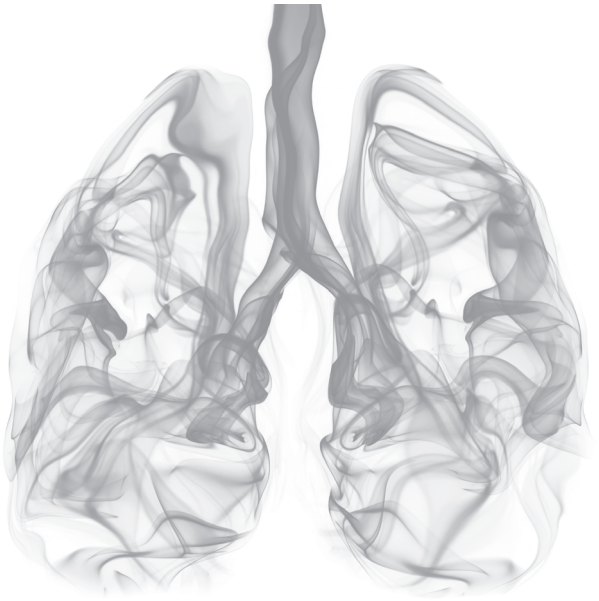
CHAPTER 7

Efficacy and safety of outpatient treatment based on the Hestia clinical decision rule with or without NT-proBNP testing in patients with acute pulmonary embolism: a randomized clinical trial



P.L. den Exter, W. Zondag, F.A. Klok, R.E. Brouwer, J. Dolsma, M. Eijsvogel, L.M. Faber, M. van Gerwen, M.J. Grootenboers, R. Heller-Baan, M.M. Hovens, G.J.P.M. Jonkers, K.W. van Kralingen, C.F. Melissant, H. Peltenburg, J.P. Post, M.A. van de Ree, L.Th. Vlasveld, M.J. de Vreede and M.V. Huisman, *for the Vesta Study Investigators*

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ABSTRACT

Rationale

Outpatient treatment of pulmonary embolism (PE) may lead to improved patient satisfaction and reduced health care costs. However, trials to assess its safety and the optimal method for patient selection are scarce.

Objectives

To validate the utility and safety of selecting PE patients for outpatient treatment by the Hestia criteria, and to compare the safety of the Hestia criteria alone with the Hestia criteria combined with NT-proBNP testing.

Methods

We performed a randomized non-inferiority trial in 17 Dutch hospitals. PE patients without any of the Hestia criteria were randomized to direct discharge or additional NT-proBNP testing. The latter patients were discharged as well if NT-proBNP was ≤500ng/L or admitted if NT-proBNP was >500ng/L. Primary endpoint was 30-day adverse outcome defined as PE- or bleeding-related mortality, cardiopulmonary resuscitation or intensive care admission. The non-inferiority margin for the primary endpoint was 3.4%.

Measurements main results

550 patients were randomized. In the NT-proBNP group, 34/275 (12%) had elevated NT-proBNP values and were managed as inpatients. No patient (0/34) with elevated NT-proBNP level treated in hospital (0%; 95% CI: 0-10.2%), versus no patient (0/23) with a post-hoc determined elevated NT-proBNP from the direct discharge group (0%; 95% CI: 0-14.8%), experienced the primary endpoint. In the total trial cohorts, the primary endpoint occurred in none of the 275 patients (0%; 95%CI: 0-1.3%) subjected to NT-proBNP testing, versus in 3/275 patients (1.1%; 95%CI 0.2-3.2%) in the direct discharge group (p=0.25). During 3-month follow-up, recurrent VTE occurred in 2 patients (0.73%; 95%CI 0.1-2.6%) in the NT-proBNP group versus 3 patients (1.1%; 95%CI: 0.2-3.2%) in the direct discharge group (p=0.65).

Conclusions

Outpatient treatment of PE patients selected by the Hestia criteria alone was associated with a low risk of adverse events. Given the low number of patient with elevated NT-proBNP levels, this trial was unable to draw definite conclusions upon the incremental value of NT-proBNP testing in patients who fulfil the Hestia criteria.

INTRODUCTION

Acute pulmonary embolism (PE) is a relatively common and potentially fatal vascular disease.[1]Traditionally, patients with acute PE are hospitalized for initial treatment with parenteral anticoagulant agents. However, the introduction of low-molecular-weight heparins (LMWH), and more recently non-vitamin K dependent oral anticoagulants (NOACs), has enabled early discharge or even complete out-of-hospital treatment. For deep vein thrombosis (DVT), this strategy has become widely accepted and practiced as a result of high level evidence demonstrating equivalent efficacy and safety compared to inpatient treatment.[2,3] More recently, accumulating evidence has indicated that outpatient treatment is feasible and safe for selected, hemodynamic stable PE patients as well.[4-10] A shift from in-hospital to outpatient care may not only avoid potentially unnecessary admission but also be associated with substantial cost savings and improved patient satisfaction.[6,11]

As the short-term outcome of acute PE is associated with serious, potentially life threatening complications, it is of vital importance that careful risk stratification takes place when considering outpatient treatment.[12] Such stratification can be based on clinical criteria, biochemical measurements or radiological findings. To date, one prospective cohort study and one randomized trial have been conducted that identified low-risk PE patients for outpatient treatment solely on the basis of clinical criteria, i.e. the Hestia clinical decision rule criteria and a combination of a set of clinical criteria and the Pulmonary Embolism Severity Index (PESI) respectively, and both studies yielded promising results.[6,10] Accumulating evidence, however, suggests that adding biomarkers to clinical or radiological assessment of PE severity may improve the risk stratification process.[13,14] N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of myocardial stretch, has been most extensively studied in this setting and is the only biomarker that has been evaluated in an outcome study with outpatient treatment of acute PE. In that study, none of the PE patients selected for outpatient treatment on the basis of a combination of ad hoc defined clinical criteria and a normal NT-proBNP test result (<500ng/L) experienced an adverse clinical course.[5]

Even so, it remains unanswered whether NT-proBNP offers additional safety on top of clinical criteria in the selection of patients for home treatment, since a head-to-head comparison is still lacking to date. The present randomized clinical trial investigated whether selecting patients for home treatment on a clinical basis alone, with the use of the Hestia clinical decision rule, was as safe as combining the Hestia clinical decision rule with NT-proBNP testing. Second, we aimed to prospectively validate the utility and safety of the Hestia clinical decision rule.

METHODS

Study design

We performed an investigator initiated, randomized, non-inferiority open label clinical trial (Netherlands Trial Register identifier NTR2603), in two academic and 15 non-academic hospitals in the Netherlands.

Patients

Patients aged 18 years or older with objectively proven acute PE were screened for eligibility. Diagnostic criteria for acute PE were defined as: 1) (New) intraluminal filling defect on computed tomography pulmonary angiography (CTPA); 2) (New) high probability finding on a ventilation/perfusion (V/Q) scan; 3) (New) constant intraluminal filling defect or an abrupt cutoff of vessels greater than 2.5 mm in diameter on contrast dye pulmonary angiography or 4) Combination of a non-high probability V/Q scintigraphy with objectively documented DVT (compression ultrasonography or venography). Patients with asymptomatic or chronic (symptoms present > 14 days) PE were excluded. Patients with acute PE were eligible for randomization in case none of the items of the previously defined Hestia clinical decision rule were present (table 1).[10] For study reasons, additional exclusion criteria included a life expectancy <3 months or inability to achieve the required 3-month follow-up (e.g. foreign citizen, no fixed address). The

Table 1. Hestia clinical decision rule

Hemodynamically instable?*
Thrombolysis or embolectomy necessary?
High risk for bleeding?**
Oxygen supply to maintain oxygen saturation >90% >24 h.?
Pulmonary embolism diagnosed during anticoagulant treatment?
Severe pain needing intravenous pain medication >24 h.?
Medical or social reason for treatment in the hospital >24 h.?
Creatinine clearance of less than 30 ml/min?***
Severe liver impairment****
Pregnant?
Documented history of heparin induced thrombocytopenia?

If at least one of the above questions is answered with YES, the patient can not be treated at home

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

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

*** Calculated creatinine clearance according to the Cockroft-Gault formula

**** Left to the discretion of the physician

institutional review board of all participating hospitals approved the study protocol and written informed consent was obtained from all patients before randomization.

Randomization

Eligible patients were randomly allocated to undergo NT-proBNP testing or to direct discharge in a 1:1 ratio with the use of a password protected, web-based database management system.

Interventions

In patients randomized to the intervention cohort, NT-proBNP levels were assessed with a quantitative electrochemiluminescence immunoassay (Elecsys or cobas e analyzer, Roche Diagnostics, Mannheim, Germany). The cut-off value for outpatient treatment was predefined at 500 ng/L, consistent with previous studies.[5,15] To put this threshold into perspective, the mean NT-proBNP level is estimated to be 70 pg/L in the general population.[16, 17] Patients with an elevated NT-proBNP were admitted to the hospital and patients with an NT-proBNP level < 500 pg/mL were discharged within 24h of diagnosis. All patients randomized to the direct discharge cohort were discharged within 24h of diagnosis without additional biochemical tests. In these patients, venous plasma and the serum samples preferably taken at arrival on the Emergency Department were obtained and stored immediately at minus 80°C, for post-hoc NT-proBNP measurement. This was performed after a single thaw with use of a quantitative electrochemiluminescence immunoassay (Elecsys/E170, Roche Diagnostics, Mannheim).

All patients were treated with LMWH and vitamin K antagonists (VKA) according to the standard care for patients with PE recommended by international guidelines.[18] This consisted of weight-adjusted doses of LMWH for at least five days and concomitant start of vitamin K antagonists. LMWH was discontinued when the international normalized ratio (INR) was 2.0 or more for two consecutive days. In patients with active cancer, LMWH was continued at therapeutic doses as mono-therapy for at least three months. Patients selected for outpatient treatment received an emergency contact number on a pocket card outlining the symptoms suggestive of a recurrent PE or DVT. Patients were evaluated at the outpatient department after 5-9 days from discharge. For patients selected for inpatient treatment, the duration of in hospital treatment was determined by the local physician. After seven days patients were contacted either in the hospital or by telephone (if they had already been discharged). For all patients, two additional study visits were planned after 4-6 weeks and after three months. The final study visit was allowed to be either at the outpatient clinic or by telephone.

Endpoints

The primary endpoint was a 30-day adverse outcome defined as PE related mortality, major bleeding related mortality, cardiopulmonary resuscitation, admission to an Intensive Care Unit, or requirement of thrombolytic therapy or surgical embolectomy.

Secondary endpoints were symptomatic recurrent venous thromboembolism (VTE), major bleeding and all-cause mortality during three months of follow-up. Recurrent VTE was defined as recurrent PE if demonstrated by new defects on CTPA, perfusion-ventilation lung scan, pulmonary angiography, PE demonstrated at autopsy or a clinical report indicating PE as the (likely) cause of death; recurrent VTE was defined as recurrent DVT if demonstrated by compression ultrasonography or contrast venography showing a thrombus in a new area or in the same area after a normal echo in the past. Bleeding was defined as major if it was clinically overt combined with at least one of the following situations: 1) Critical site involvement e.g. intracranial, retroperitoneal, intraocular, intraspinal, pericardial or non-traumatic intra-articular; 2) Bleeding associated with a decrease in hemoglobin level of 1.3 mmol/L (2.0 gr/dl) or more; 3) Bleeding leading to transfusion of ≥ 2 units of whole blood or packed red cells; 4) Fatal bleeding.[19] The cause of death in patients who died within the study period was assessed by autopsy or a clinical report indicating the -likely- cause of death.

An independent adjudication committee consisting of two experts not involved in the study evaluated all possible endpoints, i.e. adverse outcome, recurrent VTE, major bleeding, or death. Any dispute was resolved by a third opinion.

Monitoring and judging of the plausibility of serious adverse events (death, adverse outcome, recurrent PE, DVT, bleeding, hospitalization) of study patients was carried out by a data safety monitoring board The independent DSMB reviewed safety data at regular intervals. The DSMB assessed the category classification and seriousness of reported adverse events and their possible relation to the study drug. Serious adverse events were also transmitted to the study investigators as well as institutional review boards as per local regulations.

Statistical analysis

The primary and secondary endpoint analyses were based on all events that occurred in the intention-to-treat population.

Our hypothesis was that patients with high NT-proBNP levels treated at home at least did not have a higher rate of adverse outcome than patients with high NT-proBNP who were initially hospitalized. To prove our hypothesis, we aimed to compare the proportion of adverse events between the group with high NT-proBNP treated in the hospital and the group with post-hoc determined high NT-proBNP from the direct discharge group. The non-inferiority margin for our primary endpoint was 3.4%, meaning that the maximum difference in the rate of adverse outcomes between the two study arms is

3.4%. The risk of 30-day adverse outcome in both treatment groups was assumed to be 1%.[5, 10] The test statistic used was the one-sided Z test (pooled). With a targeted significance level of 0.0500 and a power of 80%, 106 patients in each study cohort were needed to prove our hypothesis. Based on previous results, it was estimated that 40% of patients would have elevated NT-proBNP levels.[5, 15] Therefore a total of 530 patients would have to be randomized to achieve the sample size of 106 patients in each high NT-proBNP group.

In a secondary analysis, we aimed to assess whether selecting PE patients for outpatient therapy based on the Hestia clinical decision rule alone would be non-inferior to performing additional NT-proBNP testing, by comparing the two total study arms with respect to the risk of the primary endpoint, again using the non-inferiority margin of 3.4%. In addition, the groups were compared for all secondary endpoints separately, with use of the two-sided chi-square test of proportions, or the Fisher's exact test.

To validate the safety of the Hestia clinical decision rule, the upper limit of the 95% CI interval of the risk of recurrent VTE in patients assigned to the direct discharge group had to be below 7% with a point estimate of 3%, as defined in the original Hestia study, which would require a total of 257 patients in each arm (power 0.91; one-sided binomial test).[10]

SPSS version 20 (SPSS Inc, Chicago, IL) was used to perform all analyses.

RESULTS

Patients

Between December 2010 and February 2014, a total of 1102 patients were screened for eligibility in the participating hospitals. Of those, 544 (49%) were ineligible for randomization according to the reasons specified in figure 1. The most frequent reasons for ineligibility included requirement for oxygen therapy (33.5%) and other medical or social reasons that required inpatient treatment (23.7%). The most frequent medical or social reasons included: Twenty-one patients were admitted because of committed pneumonia. Sixteen patients were admitted because analysis was required for a suspected malignancy or another medical disease. In eleven patients, the attending physician decided to hospitalize the patient because of the extend of the thrombus load at CTPA. Ten patients were found to have elevated troponins, EKG changes or heart rhythm disorders and were admitted to a cardiology department or coronary care unit. Seven patients suffered of delirium or cognitive dysfunction. In nine patients, outpatient treatment was not possible due to complaints caused by malignant disease. In another nine patients, other acute medical conditions required hospitalization (e.g. hyponatremia, COPD exacerbation). In seven patients the home situation was deemed unsafe for outpatient treatment. Finally, six patients were anxious and refused being treated at home.

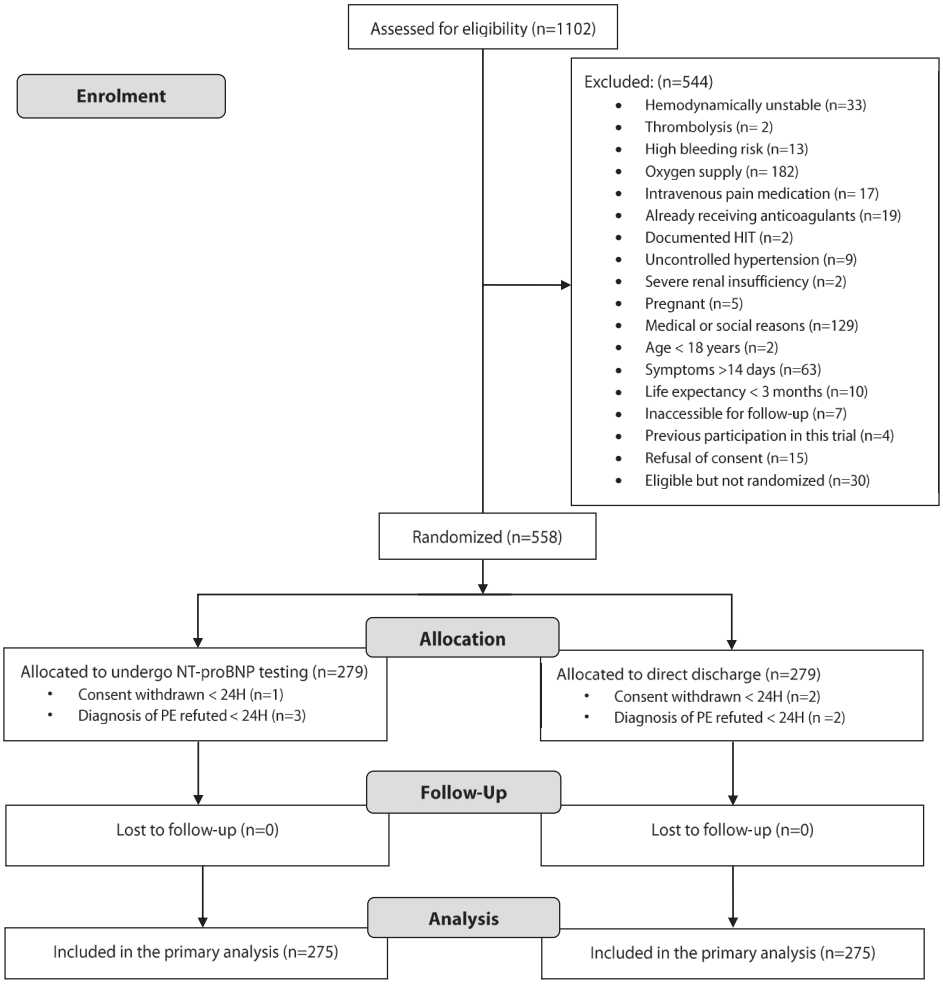

Figure 1. Flow of patients through the study

Of the 558 eligible patients, in both groups four patients were excluded from all analyses because of withdrawal of consent (n=4) or because the diagnosis of PE was rejected at second evaluation of the images (n=4) after randomization.

The demographic criteria, medical history and clinical characteristics of the 550 randomized patients included in the analysis are shown in table 2. A total of 297 male patients were included (54%). Two-hundred-and-seventy-five patients were randomized to be subjected to NT-proBNP testing. Of those patients, 34 (12.4%) had a NT-proBNP level >500ng/L and were treated as inpatients. Mean duration of their hospitalization was 3.5 days. There were three protocol violations: two patients from the NT-proBNP group were hospitalized even though NT-proBNP levels were normal, and one patient

Table 2. Baseline Characteristics

Characteristic	NT-proBNP (N=275)	Direct discharge (N=275)
Age (mean ± SD)	55 (15)	53 (15)
Age > 60 (n, %)	108 (39.3)	99 (36.0)
Male sex (n, %)	145 (52.7)	152 (55.3)
BMI (kg/m2, mean ± SD)	27.0 (4.6)	27.7 (5.2)
VTE Risk factors		
Immobilization or recent surgery (n, %)	33 (12.2)	39 (14.4)
Previous PE (n, %)	41 (15.1)	45 (16.6)
Previous DVT (n, %)	30 (11.0)	28 (10.3)
Active Malignancy (n, %)	23 (8.5)	14 (5.2)
Estrogen use (n, %)	50 (18.4)	45 (16.6)
Clinical signs and symptoms		
Duration of complaints, days (mean ± SD)	4 (3.2)	4 (3.5)
Suspected DVT (n, %)	38 (13.8)	41 (14.9)
Heartrate(mean ± SD)	83 (15.2)	82 (15.7)
Systolic blood pressure mmHg(mean ± SD)	137 (17.1)	139 (19.3)
D-dimer (mean± SD)	2960 (3159)	2878 (4275)
Comorbidities		
COPD with therapy (n, %)	9 (3.3)	14 (5.2)
Heart failure with therapy (n, %)	3 (1.1)	2 (0.7)

N, number; SD, standard deviation; VTE, venous thromboembolism; DVT, deep vein thrombosis; COPD, chronic obstructive pulmonary disease; NT-proBNP, N-terminal pro-brain natriuretic peptide

assigned to the direct discharge group was initially hospitalized for four days. All other patients were discharged within 24 hours of diagnosis. Mean duration of stay in the hospital was 18 hours for patients randomized to undergo NT-proBNP testing, and 10 hours for patients randomized to direct discharge. Of the 275 patients in the direct discharge group, post-hoc NT-proBNP measurement was possible in 240 (87%). Of those patients, 23 (9.6%) had elevated NT-proBNP levels. No patient was lost to follow-up.

Primary endpoint

No patient (0/34) with an elevated NT-proBNP level treated in hospital (0%; 95% CI: 0-10.2%), versus no patient (0/23) with a post-hoc determined elevated NT-proBNP from the direct discharge group (0%; 95% CI: 0-14.8%), experienced the primary endpoint.

Further, in the total study cohorts, no patient assigned to NT-proBNP testing (0%; 95% CI: 0-1.3%) experienced the primary endpoint versus three of the patients assigned to direct discharge (1.1%; 95% CI: 0.2-3.2%) (p=0.25): absolute difference 1.1% (95% CI: -0.46% - 3.2%). All these three patients had an NT-proBNP level below 500ng/L, as

measured post-hoc. A clinical description of these cases is provided in table 3. In all three patients, the adjudication committee concluded that the predefined definitions of the primary endpoint had been fulfilled.

After 10 days of follow-up, the primary endpoint had occurred in no patient assigned to NT-proBNP testing (0/275, 0%) and in one patient assigned to direct discharge (1/275, 0.4%).

Recurrent venous thromboembolism

A total of five patients developed recurrent VTE during follow-up; two patients (0.73%; 95% CI: 0.09 – 2.6%) who were assigned to NT-proBNP testing versus three patients (1.1%; 95% CI: 0.2-3.2%) assigned to direct discharge (p=0.65). In both groups, none of the patients with recurrent VTE had elevated levels of NT-proBNP at baseline. In the NT-proBNP testing group, one patient with lung cancer developed DVT of both the lower and upper extremity during follow-up. Another patient was diagnosed with CTPA proven recurrent PE, whilst the INR was adequate. In the direct discharge group, one patient developed DVT two months after randomization. INR levels were suboptimal at time of the recurrent event and LMWH was re-started. Another patient in the direct discharge group was readmitted during follow-up with new thoracic pain whilst the INR was inadequate. Anticoagulant treatment was intensified. Although no new imaging tests were performed, this patient was adjudicated to have recurrent PE on clinical grounds. Finally, one patient in the direct discharge group experienced sudden death after 15 days, adjudicated as possibly due to recurrent PE (case 1, table 3).

Major bleeding

One patient (0.4%; 95% CI: 0.01-2.0%) in the NT-proBNP group versus three patients (1.1%; 95% CI: 0.2-3.2%) in the direct discharge group experienced major bleeding (p=0.62). In the NT-proBNP group, one patient experienced traumatic bleeding of the lower extremity whilst INR was 7.6, leading to a significant drop in haemoglobin. In the direct discharge group, one patient developed an intra-abdominal bleeding one month after randomization after laparoscopic cystectomy which she had undergone two days before randomization. The second patient developed pericardial bleeding which was likely related to a pacemaker implantation one month before randomization. Finally, the third patient developed gastrointestinal bleeding requiring blood transfusion. All four patients fully recovered.

Mortality

During the 3 months follow-up period, four patients died (1.5%) in the NT-proBNP group versus three (1.1%) in the direct discharge group (p=0.70). In the NT-proBNP group, two patients died because of progressive lung cancer and one patient because of metas-

Table 3. Case descriptions of primary endpoint events

Gender, age	Case description	Vital signs and biochemical markers at initial diagnosis of PE	Conclusion	Outcome
Female, 69yrs	Patient was assigned to the direct discharge group. She was seen at the outpatient clinic 4 days later according to study protocol. At that time she was still using LMWH and VKA. Two weeks later she suddenly felt unwell after dinner and complained of severe flank pain. She went to bed were she collapsed. At time of arrival of the ambulance the patient had already died. She used LMWH as well as VKA until the day she died because INR levels were still inadequate. Permission for autopsy was not obtained.	Heart rate: 76/min RR: 138/89 mmHg D-dimer 2560 ng/mL NT-proBNP: 232 pg/mL	Death because of possible recurrent PE	Death
Female, 47yrs	Patient was assigned to the direct discharge group. One week later the patient was readmitted because of dyspnoea and coughing, which was diagnosed as a respiratory tract infection. Because of progressive dyspnoea, patient was admitted to the IC 5 days later. She responded well to high flow oxygen therapy and returned to the general ward 3 days later. Because of progressive alveolar consolidations, unresponsive to antibiotic treatment, patient was transferred to an academic hospital and admitted to the Intensive Care because of respiratory insufficiency. Bronchoalveolar lavage fluid was positive for Serratia, influenza B virus, and Aspergillus. Although these conditions were all treated, her medical condition worsened. She developed several episodes of pneumothorax due to high pressure ventilation. At last, oxygenation was no longer possible and it was decided to stop treatment after which the patient died.	Heart rate: 80/min RR: 140/84 D-dimer: not determined NT-proBNP: 64 pg/mL	Death because of respiratory insufficiency due to a combination initial PE, pulmonary infection and ARDS with complicated pneumothorax.	Death
Male, 54yrs	Patient was assigned to direct discharge group. Two days later he returned to the emergency department because of progressive dyspnea and thoracic pain. A chest X-ray was suggestive for pneumonia in the right lower lobe. Because of respiratory insufficiency not responding to CPAP, patient was admitted to the IC where he temporary was treated with mechanical ventilation. Eventually the patient responded well to antibiotic treatment after which he was discharged to a general ward.	Heart rate: 92/min RR: 116/98 mmHg D-dimer: 1833 ng/mL NT-proBNP: 390 pg/mL	Respiratory insufficiency due to a combination of initial pulmonary embolism and respiratory tract infection	Fully recovered

PE, pulmonary embolism; LMWH, low-molecular-weight heparins; VKA, vitamin K antagonists; INR, international normalized ratio; CPAP, continuous positive airway pressure.

Table 4. Primary and secondary endpoints

Outcome	NT-proBNP (n=275)	Direct discharge (n=275)
Primary endpoint* at day 30	0	3 (1.1%)
PE related mortality	0	1 (0.36%)
ICU admission	0	2 (0.73%)
Recurrent VTE at 3 months	2 (0.73%)	3 (1.1%)
DVT	1 (0.36%)	1 (0.46%)
Recurrent PE	1 (0.36%)	2 (0.73%)
Major bleeding at 3 months	1 (0.36%)	3 (1.1%)
All-cause mortality at 3 months	4 (1.5%)	3 (1.1%)

N, number; PE, pulmonary embolism; VTE, venous thromboembolism; DVT, deep vein thrombosis; ICU, intensive care unit.
*defined as the occurrence of defined as PE or major bleeding related mortality, cardiopulmonary resuscitation, admission to an Intensive Care Unit, or requirement of thrombolytic therapy or surgical embolectomy.

tasized cholangiocarcinoma. The fourth patient was diagnosed with recurrent B-cell lymphoma at time of PE diagnosis. During follow-up she died in a nursing home because of suspected sepsis of unknown origin. In the direct discharge group, one patient died because of progressive lung cancer. The last two patients who died have been described in table 3 (case 1 and 2).

DISCUSSION

The Hestia clinical decision rule was constructed to provide a simple set of readily available clinical criteria to triage possible candidates for outpatient treatment. The safety of this decision rule has thus far only been assessed in one prospective, single-arm management study.[10] In the present trial, we observed that in patients who were sent home on the basis of the Hestia clinical decision rule alone, the 3-month risk of recurrent VTE was 1.1% with an upper limit of the 95% CI reaching 3.2%. This was well within the predefined safety limit of 7%. Hence, this study serves as an external validation of the Hestia clinical decision rule. Further evidence for the safety of outpatient treatment based on clinical criteria alone comes from the recently published Outpatient Treatment of PE (OTPE) trial.[6] In this trial, a set of clinical criteria combined with the PESI score was used to select outpatient treatment candidates. No difference was observed in the 3-month rate of recurrent VTE for patients with a low PESI score treated at home (0.6%) versus those treated in hospital (0%). These rates of recurrent VTE compare well to the risk observed in both study arms in our trial.

There are several differences between the Hestia clinical decision rule and the PESI rule or its simplified version (sPESI).[20,21] First, the (s) PESI rule was constructed to assess 30-day all-cause mortality instead of providing an estimation of the risk of complications directly related to PE or its treatment. Second, a great practical advantage of the Hestia rule over the (s) PESI score is that the Hestia rule doesn't by definition exclude patients with cancer or patients of older age. The Hestia rule is therefore able to select a larger proportion of outpatient candidates out of the total PE population, underlined by the fact that both in the original Hestia study and the present trial, approximately 50% of all patients screened for eligibility could be treated at home, compared to only 30% in the OTPE trial. Finally and importantly, the (s) PESI score has never been prospectively evaluated to be used as a sole decision tool to treat patients with acute PE at home directly.

NT-proBNP plasma levels, reflecting myocardial stress and thereby the severity of hemodynamic compromise in acute PE, have been extensively studied as a biomarker to optimize risk stratification in PE patients.[15,22,23] Low NT-proBNP levels are associated with a low risk for adverse outcome.[24] This was also observed in a single-arm outcome study in which PE patients selected for outpatient treatment on the basis of clinical criteria and low NT-proBNP levels did not experience any adverse events during follow-up.[5] However, in the most recent guidelines of the European Society of Cardiology (ESC) on the diagnosis and management of acute pulmonary embolism, further risk stratification with cardiac biomarkers is not advocated in patients classified as low-risk with use of the (s)PESI score and those patients could be considered for outpatient therapy.[25] Nevertheless, these guidelines still state that, if NT-proBNP levels are known and are elevated in patients with a low (s)PESI score, patients should be regarded as intermediate-low risk and therefore not suitable for outpatient management. The present trial provides proof for the concept that the assessment of outpatient eligibility could be based on a clinical decision rule alone, irrespective of NT-proBNP levels. This approach based on clinical factors alone would facilitate efficiency and cost-savings in the busy emergency department.

This trial has some aspects that warrant comment. First, the proportion of patients with elevated NT-proBNP levels was considerably lower than anticipated from previous studies. Consequently, we were unable to include the number of patients with elevated NT-proBNP levels as calculated in the power analysis. Increasing the sample size would have led to a vast increase in the number of patients to be included, that was not feasible within our resource capabilities. Therefore, we are unable to definitively conclude whether treating patients selected with the Hestia clinical decision rule with elevated NT-proBNP levels at home is non-inferior to treating them in an inpatient setting. Even so, the most likely explanation for the low number of patients with an elevated NT-proBNP is that the Hestia rule is able to pre-select patients with normal NT-proBNP levels. To further explore this hypothesis, we chose to include an additional

analysis, which compared the total study groups with respect to all primary and secondary endpoints. Although this analysis was not included in the original study protocol, it used identical statistical conditions as was predefined for the primary and secondary endpoints: i.e. a non-inferiority margin difference between the group proportions of 3.4% for the primary endpoint. The very low and non-significant risks of adverse outcome between the two study groups, supports our conclusion that NT-proBNP testing does not clearly provide incremental safety when selecting patients with acute PE for outpatient treatment. Of note, a recent study identified a NT-proBNP cut-off level of 600 pg/mL as the optimal cut-off for distinguishing low-risk from intermediate risk patients with acute PE.[23] This less strict cut-off would have identified even less patients with elevated NT-proBNP levels in our study sample, further supporting the hypothesis that risk stratification can take place on a clinical basis alone. Second, our study had an open-label design, which could have enhanced the risk of bias in the assessment of outcome events. To decrease this risk, all patients were instructed to contact the hospital in case of symptoms suggestive of recurrent VTE and all endpoints were adjudicated by an independent committee unaware of the study intervention assignment. Third, since NOACs were not yet registered for the treatment of VTE during the inclusion period of this trial, we were unable to assess the performance of these agents in the specific setting of outpatient PE treatment. As NOACs do not require laboratory monitoring and continuous dose-adjustment, these agents may further facilitate the management of acute PE on an outpatient basis. Beam et al. reported promising results for the use of the NOAC rivaroxaban in an outpatient setting.[26] In a small observational study including 106 VTE patients, of whom 35 had PE, patients triaged for outpatient treatment based on the Hestia criteria and subsequently treated with rivaroxaban had a favourable outcome without any VTE recurrences or major bleeding complications during treatment. At present, a single-arm management trial aims to confirm these findings, aiming at a total of 1100 PE patients who fulfil the Hestia criteria treated on an outpatient basis with rivaroxaban (EudraCT No.: 2013-001657-28).

This trial confirms that outpatient treatment of patients presenting with acute PE selected by the Hestia clinical decision rule alone is feasible and associated with a very low risk of adverse events. This is important since it reaffirms findings of an earlier study.[10] Given the low number of patient with elevated NT-proBNP levels, this trial was unable to draw definite conclusions upon the incremental value of NT-proBNP testing in patients who fulfil the Hestia criteria. Larger trials will be required to answer this question.

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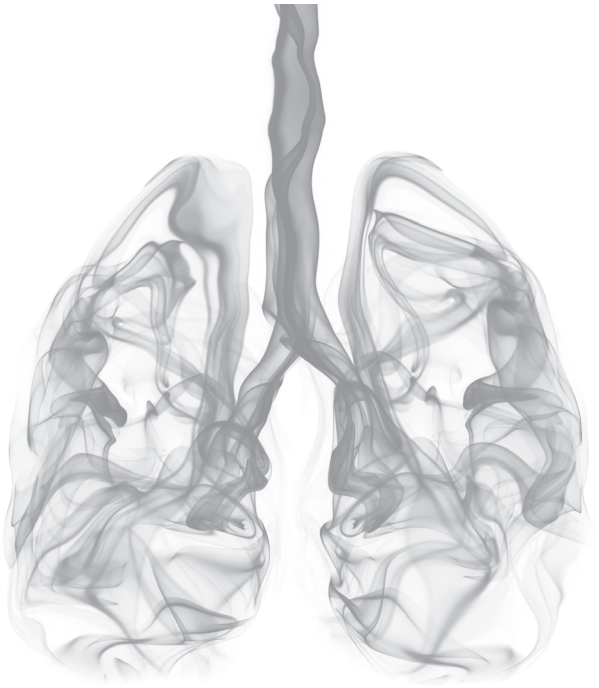
CHAPTER 8

Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism



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ABSTRACT

The systematic assessment of residual thromboembolic obstruction after treatment for acute pulmonary embolism (PE) has been understudied. This assessment is of potential clinical importance, should clinically suspected recurrent PE occur, or as tool for risk stratification of cardiopulmonary complications or recurrent venous thromboembolism (VTE). This study aimed to assess the rate of PE resolution and its implications for clinical outcome. In this prospective, multi-center cohort study, 157 patients with acute PE diagnosed by CT pulmonary angiography (CTPA) underwent follow-up CTPA-imaging after 6 months of anticoagulant treatment. Two expert thoracic radiologists independently assessed the presence of residual thromboembolic obstruction. The degree of obstruction at baseline and follow-up was calculated using the Qanadli obstruction index. All patients were followed-up for 2.5 years. At baseline, the median obstruction index was 27.5%. After six months of treatment, complete PE resolution had occurred in 84.1% of the patients (95% confidence interval (CI): 77.4-89.4%). The median obstruction index of the 25 patients with residual thrombotic obstruction was 5.0%. During follow-up, 16 (10.2%) patients experienced recurrent VTE. The presence of residual thromboembolic obstruction was not associated with recurrent VTE (adjusted hazard ratio: 0.92; 95% CI: 0.2-4.1). This study indicates that the incidence of residual thrombotic obstruction following treatment for PE is considerably lower than currently anticipated. These findings, combined with the absence of a correlation between residual thrombotic obstruction and recurrent VTE, do not support the routine use of follow-up CTPA-imaging in patients treated for acute PE.

INTRODUCTION

Although pulmonary embolism (PE) is traditionally considered to be an acute disease, and its treatment and medical follow-up is generally limited to approximately 3-6 months from diagnosis, it is now increasingly recognized that acute PE has serious impact on patients' long-term clinical outcomes and health status.[1] Not only do recurrent venous thromboembolic events (VTE) occur in over 20% of the patients during the initial five years of follow-up[2], more than half of the patients still report dyspnoea or an impaired physical performance 6 months to 3 years after an successfully treated acute event, for reasons that are as yet unclear.[3,4] Moreover, the quality of life of long-term survivors of acute PE is lower compared to control populations.[5] To provide more pathophysiologic, and perhaps prognostic, insight in the long-term course of acute PE, information on the resolution of PE has become of recent interest. Incomplete thromboembolic clearance has been proposed to be predictive for recurrent thromboembolic episodes, and may ultimately lead to chronic thromboembolic pulmonary hypertension (CTEPH).[6,7] The latter, although rare, may be considered the most severe end of the spectrum of long-term consequences of acute PE. Assessment of the presence of residual thrombotic obstruction after completion of anticoagulant treatment might also facilitate differentiation between residual and new emboli in the diagnostic work-up of patients with suspected recurrent PE.[8] This is of importance given the therapeutic consequences of prolonged or even lifelong anticoagulant treatment resulting from an incorrect diagnosis of recurrent PE, with its high costs, inconvenience and bleeding risk.[9]

Despite these potentially important clinical implications, to date, little is known on the natural resolution of PE following anticoagulant treatment. Although a systematic review suggested that 57% of all patients with PE have incomplete PE resolution 6 months after diagnosis,[10] the studies on which this pooled percentage was based were small and differed largely with respect to the duration of anticoagulant treatment, type of imaging test (i.e. CT-pulmonary angiography (CTPA) or VQ-scanning), and timing of the follow-up scan.[11-13] Moreover, prospective studies assessing residual thromboembolic obstruction with CTPA, which has emerged as the first-line imaging test for the detection of acute PE[14], are lacking.

In this prospective follow-up study we aimed to systematically assess the course of clot resolution, as well as the course of right ventricular dilatation, as assessed with CTPA in patients who completed six months of anticoagulant treatment for acute PE. Secondary objectives were to assess the predictive value of residual thrombotic obstruction for the development of recurrent VTE or CTEPH during 2.5 years of follow-up.

METHODS

Patients

In this prospective multi-center cohort study, patients with acute hemodynamically stable PE, objectively confirmed by CTPA, were included between September 2008 and October 2011 in four academic and two non-academic hospitals. Patients with first or recurrent PE, either provoked or unprovoked, and a planned regular treatment with anticoagulants for at least 6 months were eligible for this study. Exclusion criteria were refusal by patient to undergo a second CT scan, logistic reasons, age below 18 years, pregnancy, life expectancy less than 6 months, impossibility to return for follow-up, inserted vena cava filter, thrombolytic therapy, allergy to intravenous iodinated contrast agent, or severe renal insufficiency (estimated creatinine clearance < 30 ml/min). Institutional ethical review boards of all participating centers approved the study protocol and written informed consent was obtained from all patients.

All patients were treated with LMWH and vitamin K antagonists (VKA) according the standard care for patients with PE recommended by the Dutch CBO guideline. This consisted of dose-adjusted doses of LMWH for a duration of at least 5 days. When the international normalized ratio (INR) was 2.0 or more for two consecutive days, LMWH was discontinued. VKA were administered and dosed according to the national consensus of the Dutch Thrombosis Services with adjustments made using a standardized nomogram, aiming at an INR range of 2.0-3.0. Patients with active malignant disease received LMWH as mono-therapy for at least 3 months. Anti-Xa levels were not routinely monitored.

Procedure

Patients underwent a follow-up CTPA 6 months after the diagnosis of PE. Subsequently, a half yearly follow-up during the following two years was performed by telephone or clinical visits to assess their clinical outcome. Patients were instructed to contact the study center or treating physician in case of any complaints suggestive of recurrent PE or DVT. In case of a clinically suspected recurrent PE or DVT, objective imaging tests were performed, including CTPA or compression ultrasound, respectively. In case of death during follow-up, autopsy or an independent medical report was required to determine the cause of death. Deaths were classified as due to PE in case of confirmation by autopsy, in case of an objective positive test for PE prior to death or if PE could not be confidently excluded as the cause of death.

Patients with otherwise unexplained persistent dyspnea on exertion or at rest during follow-up, as assessed with a standardized questionnaire, were considered to have a suspicion of CTEPH. These patients underwent trans-thoracic echocardiography. If supportive findings were present, patients underwent further diagnostic workup

consisting of VQ-scanning and pulmonary angiography, with direct measurement of the pulmonary-artery pressure. CTEPH was considered to be present if the systolic and mean pulmonary-artery pressures exceeded 40 mm Hg and 25 mmHg, respectively; the pulmonary-capillary wedge pressure was normal; and there was angiographic evidence of pouching, webs, or bands with or without post-stenotic dilatation, intimal irregularities, abrupt narrowing, or total occlusion[7].

CTPA data acquisition and reconstructions

Standard CTPA was performed using a 16-slice, 64-slice or 320-slice CT scanner with acquisition of 0.5 - 1 mm slices (depending on the scanner) in transverse orientation of the entire chest for diagnosing or excluding PE. The tube current was 250-300 mA and the tube voltage 100 kV. Acquisitions were performed during a single breath-hold, lasting 10-12 seconds or less, depending on the type of scanner. 80-100 ml of contrast agent was injected in an antecubital vein with an injection rate of 4.0 ml/sec, with contrast timing for pulmonary artery enhancement. The effective radiation dose varied between 2.8-3.9 mSv.

Diagnosis of PE and residual thrombotic obstruction

Pulmonary embolism was defined as the presence of at least one filling defect in the pulmonary artery tree. Residual thrombotic obstruction at the follow-up CTPA was defined as any of the following: 1) a complete obstruction by thrombus of a pulmonary artery that shows a decrease in diameter as compared to surrounding non-obstructed pulmonary arteries, or 2) an eccentric partial intraluminal filling defect with an obtuse angle to the vessel wall, or 3) an abrupt tapering of a vessel which is usually the consequence of recanalization of a previously completely obstructed pulmonary artery by thrombus, 4) a thickening, sometimes irregularly, of the pulmonary arterial wall, with narrowed lumen if recanalization had occurred, or 5) presence of intraluminal webs or bands, or 6) an intraluminal filling defect with the morphology of an acute PE present for > 3 months[15, 16]. The degree of pulmonary artery obstruction at baseline and at follow-up CTPA was quantified using the scoring system of Qanadli et al[17]. In summary, this index is defined as the number of segmental artery branches that are blocked, corrected by a factor of 1 for partial blockage, or a factor of 2 for complete obstructive PE. Using this scoring system, 40 is the highest possible score (thrombus completely obstructing the pulmonary trunk), corresponding with a 100% obstruction index.

Diagnostic and follow-up CTPA-scans were independently analyzed by two expert thoracic radiologists of different academic medical centers (LJMK and LFMB), who were unaware of clinical information, initial report of the scan and timing of the scan (i.e. diagnostic or follow-up CTPA). The radiologists were allowed to use post processing tools for optimal viewing as is used in clinical practice (e.g., zoom function, slab function,

window-with and window-level adaptations, orthogonal and multiplanar orientations). In case of disagreement, a consensus reading was carried out. Since the inter-observer agreement of the Qanadli score for the diagnosis of PE has previously reported to be excellent (r = 0.944),[17] we performed an interim analysis on the interclass coefficient (ICC) of the scans at baseline. If the ICC after one-third of the scans was >90%, we discontinued the consensus. All follow-up CT images were assessed by the two independent radiologists for the presence and the degree of residual thrombotic obstruction.

Right ventricular / left ventricular ratio

In all patients, parallel to the diagnosis of PE, right ventricular diameter in relation to left ventricular diameter (RV/LV ratio) was measured at CTPA, representing right ventricular function at time of diagnosis and after 6 months of treatment. Right and left ventricular diameters were measured on axial images by identifying the maximal distance between the ventricular endocardium and the intraventricular septum, perpendicular to the long axis. Previous studies have established an association between an RV/LV ratio > 1.0 and an unfavorable short-term clinical outcome.[18] We therefore assessed the proportion of patients with an RV/LV larger than 1.0 at baseline and follow-up.

Statistical analysis

The proportion of patients with residual thrombotic obstruction was calculated, with the corresponding 95% confidence intervals (CI). To assess the inter-observer agreement, the interclass correlation coefficient (ICC) was calculated for the degree of thrombotic obstruction and the multi-reader kappa (κ) coefficient for the presence of residual thrombotic obstruction at follow-up CTPA. Differences in patient demographics, comorbidities and PE characteristics between patients with and without residual thrombotic obstruction were tested for statistical significance with the use of the Chi-square-test or the Fisher's exact test for categorical data and the student-t test or Mann Whitney test for continuous variables. Univariate and multivariate regression analysis were performed for the assessment of significant independent predictors of residual thrombotic obstruction. Any variable achieving a p-value of less than 0.25 was included in an unconditional multivariate regression model.

The method of Kaplan and Meier was used to estimate the cumulative probability of recurrent VTE and mortality during follow-up. The patients were censored at time of recurrent VTE, death, or at the end of follow-up, whichever occurred first. With the use of a Cox proportional hazard model, hazard ratios (HR) were derived for the association between residual thrombotic obstruction and recurrent VTE. HRs were adjusted for age, gender, history of VTE and active malignancy. P-values < 0.05 were considered statistically significant. All analyses were conducted using statistical software SPSS, version 19.0; (SPSS Inc; Chicago, IL).

RESULTS

A total of 166 patients with PE were included during the study period Figure 1. Six patients were excluded from analysis because either the diagnostic or the follow-up CTPA images were considered non-diagnostic for the definite presence of PE by the expert radiologists in consensus. Two patients were excluded because the initial PE diagnosis was refuted on expert reading in consensus, in one patient the filing defect was considered a motion artifact and in the other patient a beam-hardening artifact. One other patient was excluded because on both the baseline and the follow-up images, the filling defects were caused by infiltration of angiosarcoma in the pulmonary artery. The baseline characteristics of the remaining 157 participants are depicted in Table 1. Mean age was 55 years and 54% of the participants were male. Active malignant disease was present in 18% of the patients and 16% had a history of VTE.

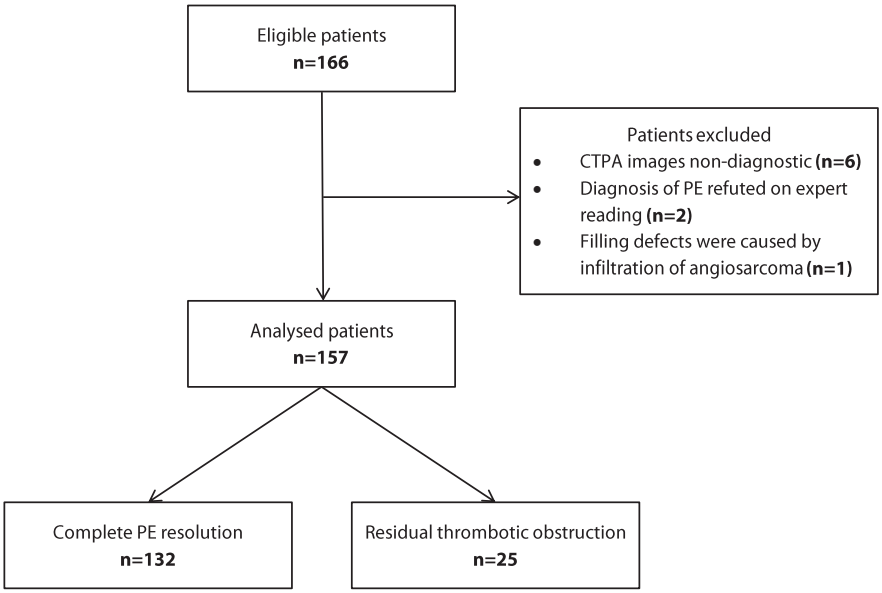

Figure 1. Flow of patients through the study
CTPA computed tomography pulmonary angiography, N, number, PE, pulmonary embolism

In the patients with complete clot resolution, 72.7% were treated for a maximum duration of 6 months. In patients with residual thrombotic obstruction, this rate was 68.0% (p=0.629). The remainder of patients were treated for a duration of one year or longer. Fifteen of the patients (11.3%) with complete clot resolution received long-term LMWH, versus one of the patients (4%) with residual thrombotic obstruction (p=0.264).

Table 1. Patient characteristics

	All patients (n=157)	Residual PE (n=25)	No residual PE (n=132)	*P*-value
Age (mean ± SD)	54.7 (15.7)	54.2 (18.5)	54.8 (15.2)	0.863
Male sex (n, %)	84 (53.5)	12 (48.0)	72 (54.5)	0.547
BMI (mean ± SD)	28.1 (5.9)	28.4 (9.4)	28.1 (5.1)	0.798
DVT at baseline (n, %)	24 (15.3)	6 (24.0)	18 (13.6)	0.211
VTE Risk factors:				
Known thrombophilia (n, %)	14 (8.9)	0 (0.0)	14 (10.6)	0.085
Previous VTE (n, %)	25 (15.9)	8 (32.0)	17 (12.9)	0.017
Active Malignancy (n, %)	28 (17.8)	1 (4.0)	27 (20.5)	0.049
Estrogen use, women (n, %)	14 (19.2)	3 (23.1)	11 (18.3)	0.715
Comorbidities				
COPD (n, %)	7 (4.5)	2 (0.8)	5 (0.4)	0.322
Heart failure (n, %)	1 (0.6)	0 (0.0)	1 (0.8)	1.000
Current smoker	29 (18.5)	5 (20.0)	24 (18.2)	0.722

PE, pulmonary embolism; BMI, body mass index; CHF congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT deep venous thrombosis; N, number; SD, standard deviation; VTE, venous thromboembolism.

Assessment of CTPAs

Contrast delivery was suboptimal but still diagnostic in two diagnostic scans and three follow-up scans. In two other scans, motion artifacts had impaired image quality but were still diagnostic.

The ICC for the degree of thrombotic obstruction at baseline was 0.96, as derived from the first 56 CTPAs that were evaluated. Based on this observation, it was decided that a double reading was not required for the remainder of the baseline CTPAs. For the follow-up scans, which were all assessed by the two expert readers, the interobserver agreement for the dichotomous categories of whether residual thrombotic obstruction was present or not, as expressed by the Kappa, was 0.80.

Residual thromboembolic obstruction

After six months of treatment, consensus reading revealed that complete PE resolution had occurred in 132 patients (84.1%; 95% CI: 77.4-89.4%). Of the 25 patients (15.9%) with residual thrombotic obstruction, nine patients (5.7%; 95% CI: 2.7-10.6%) had residual arterial filling defects, 12 patients (7.6% 95% CI: 4.0-13.0%) had intraluminal webs or bands (Figure 2), three patients (1.9%; 95% CI: 4.0-5.5%) had an abrupt tapering of an artery that was (completely) obstructed at the baseline CTPA and one patient (0.6%; 95% CI: 0.02%-3.5%) had an eccentric partial intraluminal filling defect with an obtuse angle to the vessel wall. When considering only the 143 patients with a first episode of

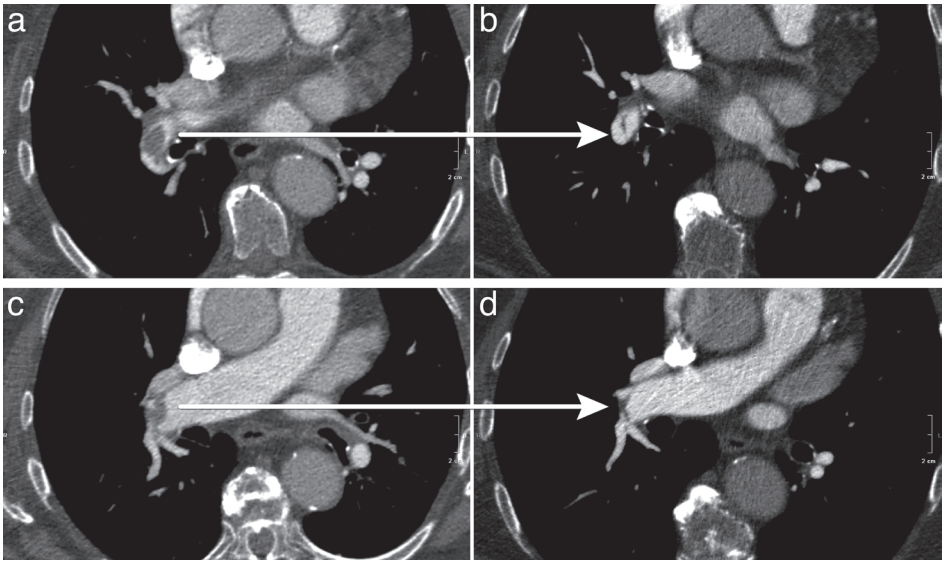

Figure 2. 79-year old female presenting with acute dyspnea on exertion. Computed tomography images, axial orientation. Acute pulmonary embolism in right lung interlobar pulmonary artery (a, c). After six months of anticoagulant treatment (b, d), note presence of band or web in interlobar pulmonary artery, indicating incomplete resolution of the emboli.

PE, complete PE resolution had occurred in 85.3%, compared to 71.4% in the 14 patients with a history of PE (p=0.18).

At time of PE diagnosis, the median obstruction index of the patients was 27.5%. After six months, this had decreased to 0.7% (Table 2). The median obstruction index of the patients with residual thrombotic obstruction was 5.0%. The change in obstruction

Table 2. Assessment of CT-images

	All patients (n=157)	Residual PE (n=25)	No residual PE (n=132)	*P*-value
Median obstruction index at baseline (median, IQR)	27.5 (12.5 - 50.0)	40 (20.0 - 50.0)	25.0 (12.5 - 50.0)	0.186
Obstruction index at baseline >50% (n, %)	41 (26.1)	7 (28.0)	34 (25.8)	0.831
Median obstruction index at follow-up (median, IQR)	0.69 (0.0 - 0.0)	5.0 (2.5 - 5.0)	NA	NA
Decrease in obstruction index	NA	35.0 (13.8 - 46.3)	25.0 (12.5 - 50.0)	0.665
RV/LV ratio at baseline (mean ± SD)	1.02 (0.29)	1.09 (0.27)	1.01 (0.29)	0.179
RV/LV > 1.0 at baseline* (n, %)	64 (40.8)	14 (56.0)	50 (37.9)	0.097
RV/LV ratio at follow-up (mean ± SD)	0.91 (0.13)	0.94 (0.14)	0.90 (0.13)	0.209
RV/LV ratio >1.0 at follow-up* (n, %)	31 (19.7)	7 (28.0)	24 (18.2)	0.258

PE, pulmonary embolism; IQR, inter-quartile range; N, number, SD, standard deviation, RV/LV, right ventricular/left ventricular

*RV/LV ratio >1

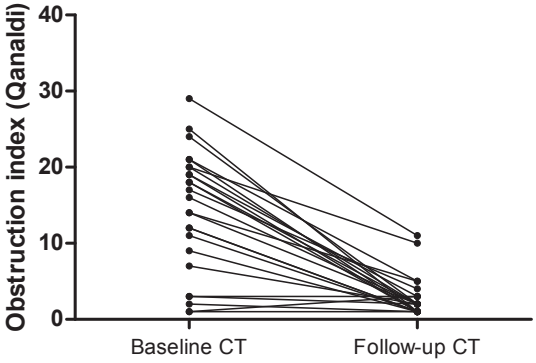

Figure 3. Change in pulmonary thromboembolic obstruction over time for patients with incomplete PE resolution

index over time in each patient with residual PE is depicted in figure 3. There was no difference in the obstruction index at baseline between patients with and without residual thrombotic obstruction. The obstruction index at baseline correlated with BMI (Pearson r=0.199, p=0.02) but with no other patient characteristics.

Predictors of residual thrombotic obstruction

Patients with residual thrombotic obstruction more frequently had a history of VTE compared to those patients with complete PE resolution (32.0% vs. 12.9%, p= 0.017, table 1). In addition, patients with residual thrombotic obstruction less frequently had malignant disease at baseline (4.0% vs 20.5%, p=0.049). No significant differences were observed between these groups for all other baseline characteristics. On multivariate analysis, only previous VTE remained independently associated with the presence of residual thrombotic obstruction: OR: 3.0 (95% CI: 1.1-8.2).

Right ventricular enlargement

The mean RV/LV diameter ratio at baseline was 1.0 (SD 0.29), which significantly reduced to 0.9 (SD 0.13) after 6 months of treatment (P < 0.001). An association was found between RV/LV diameter ratio at baseline and the initial thrombotic obstruction index (Pearson r= 0.44, p<0.001). There was, however, no correlation between the RV/LV ratio and the obstruction index after six months.

At baseline, 64 patients (40.8%) presented with an RV/LV ratio >1.0. After six months of anticoagulant therapy, this number had decreased to 31 patients (19.7%) (P <0.0001). Of the latter patients, 23 (74.2%) already had RV enlargement at baseline. Patients with and without residual thromboembolic obstruction did not differ with regard to the RV/LV ratio and the proportion of patients with an RV/LV ratio > 1.0 (Table 2).

Table 3. Recurrent VTE during follow-up

	Recurrent VTE (n= 16)	No recurrent VTE (n = 141)	*P*-value
Median obstruction index at baseline (median, IQR)	36.25 (13.23 - 52.50)	27.5 (12.5 - 49.38)	0.456
Obstruction index at baseline >50% (n, %)	6 (37.5)	35 (24.8)	0.282
Incomplete PE resolution (n, %)	2 (12.5)	23 (16.3)	0.693
RV/LV ratio at baseline (mean ± SD)	1.08 (0.21)	1.02 (0.29)	0.407
RV/LV > 1.0 at baseline* (n, %)	10 (62.5)	54 (38.3)	0.065
RV/LV ratio at follow-up (mean ± SD)	0.94 (0.18)	0.90 (0.13)	0.354
RV/LV ratio >1.0 at follow-up* (n, %)	5 (31.2)	25 (17.7)	0.223

PE, pulmonary embolism; IQR, inter-quartile range; N, number, SD, standard deviation, RV/LV, right ventricular/left ventricular
*RV/LV ratio >1

Clinical outcome during follow-up

During two years follow-up, 25 patients presented with suspected recurrent PE. Of those, CTPA confirmed recurrent acute PE in 10 patients (6.4%, 95% CI: 3.1 – 11.4%) patients. An additional 6 (3.8%, 95% CI 1.4-8.1%) patients were diagnosed with acute DVT during follow-up. Thus, a total of 16 (10.1%, 95% CI 5.9-16.0%) patients developed recurrent VTE during follow-up, accounting for a cumulative risk of 12.8%. No patients died because of PE during follow-up. The cumulative risk of death was 4.7%.

In 7 patients (4.5%), additional testing was performed for the clinical suspicion of CTEPH during follow-up. In all 7 patients, the presence of CTEPH was considered unlikely based on the results of either echocardiography or VQ-scanning. However, two (29%) of these patients did have intravascular webs on follow-up CT. Only one of these patients had an RV/LV ratio >1.0 on follow-up CT.

Recurrent VTE occurred in 14 (10.6%) of the patients with complete PE resolution and in two patients (8.0%) with residual thrombotic obstruction. The crude HR for recurrent VTE was not significantly different for patients with residual thrombosis versus patients without residual thrombosis (HR: 0.84; 95% CI: 0.19-3.7, p=0.82). After adjustment for age, gender, history of VTE, and malignant disease, this HR was 0.92 (95% CI: 0.2-4.1). In a second analysis, we excluded all patients with a history of VTE, since this may be associated with both the presence of residual PE as the occurrence of recurrent VTE. Taking into account only those patients with a first episode of PE, the crude HR and adjusted HR were 1.1 (95% CI: 0.3-5.1) and 1.1 (95% CI: 0.2 – 4.8), respectively.

Neither recurrent VTE nor death was associated with the obstruction index at baseline or after six months (data not shown). In addition, the RV/LV ratio at baseline or after six months was not significantly different for patients with an uneventful clinical course versus those who experienced recurrent VTE or death.

DISCUSSION

This prospective cohort study, which systematically investigated the natural course of clot resolution in patients treated for acute PE and its impact on their clinical outcome indicates that complete PE resolution occurs in a substantially higher proportion of patients than currently anticipated. Second, the presence of residual thrombotic obstruction did not appear to be of predictive value for the occurrence of recurrent VTE in patients treated for PE.

The rate of residual thrombotic obstruction that we found (16%) is substantially lower and in contrast with previous studies. A systematic review reported residual PE to be present in more than 50% of the patients six months after PE diagnosis.[10] An explanation for this difference may come from the type of imaging test used. Previously, VQ-scanning has been the land-mark tool to assess the presence of residual perfusion defects.[13,19,20] CTPA principally differs from VQ-scanning in detecting PE in that it allows direct embolus visualization, whereas VQ-scans provide an indirect indication for the presence of emboli derived from perfusion defects. Residual perfusion defects detected on VQ-scans may not always reflect the actual presence of residual thrombus, but may be caused by other pulmonary comorbidities.[21] Also, residual perfusion defects may persist even after complete resolution of the emboli. A recently published safety analysis from the EINSTEIN PE study, where 347 patients with acute PE, confirmed by CTPA (n=264) or VQ-scan (n=83) underwent a repeat scan after three weeks of anticoagulant treatment, indeed pointed towards a higher rate of clot resolution assessed with CT-scan (44%) compared to Q-scan (31%).[22] Previous studies that did use CTPA to assess the presence of residual thrombotic obstruction, were designed retrospectively and conducted CTPA after a limited duration of follow-up,[12,23] included a limited sample of patients[12], or only included patients with central PE[11], or did not account for sequelae of chronic PE.[23] The findings of our study are however in line with a recent study by Pesavento et al, who performed follow-up CTPA after 6 months in 113 patients with acute PE and found complete thrombus resolution in 85% of the patients.[24]

To determine the relevance of follow-up CTPA imaging for clinical practice, its benefits should be weighed against its high costs, additional burden for patients, and potential harms, including radiation exposure with its associated lifetime risk of cancer.[25] An important clinical rationale to perform follow-up imaging would be to aid in the differentiation between new and residual PE, in case a patient presents with suspected recurrent PE. Indeed, a recent study suggested that follow-up imaging performed after treatment for either DVT or PE, was associated with an increased diagnostic certainty in patients investigated for suspected recurrent VTE.[8] However, the number of patients with suspected recurrent PE included in this analysis was low (n=38), and in these patients the proportion of diagnostic non-classifiable patients did not differ significantly

between patients with and without baseline imaging. Second, V/Q-scanning was used as follow-up imaging test. In clinical practice CTPA has currently largely replaced VQ-scanning in the diagnostic work-up of patients with suspected (recurrent) PE. The most important advantage of CTPA over VQ-scanning is the low number of inconclusive test results (0.0-3.0% vs. 28-40%).[26] The implementation of CTPA as first-line imaging test for suspected PE makes information on the level of clot resolution using this imaging test relevant, in order to allow valid comparison between images obtained at time of suspected recurrent PE and at time of completion of anticoagulant treatment. The high rate of complete clot resolution that we found may suggest that correctly diagnosing recurrent PE with the use of CTPA is less complicated than currently anticipated.

A second rationale to investigate the presence of residual PE would be its potential prognostic value for subsequent cardiovascular complications. In DVT patients, it has been demonstrated that assessment of residual thrombotic obstruction may aid in the differentiation of patients at risk for recurrent VTE.[27] As the majority of recurrent events included thrombosis in the initially unaffected leg or isolated PE, it has been postulated that residual thrombosis represents a hypercoagulable state. Considering that DVT and PE represent two expressions of a similar clinical pathological process, a similar prothrombotic tendency might be expected in patients with incomplete PE resolution. In the present study, however, no association was found for the presence of residual thrombotic obstruction and the occurrence of recurrent VTE. Given the low number of recurrent events during follow-up and the small proportion of residual PE, it cannot be excluded that our study was underpowered to detect this association. Still, the fact that residual PE was present in a minority of patients and that only two of these patients developed recurrent VTE, does not indicate that implementing follow-up CTPA imaging on a large scale may be useful to identify a subgroup of patients at high risk of recurrences.

Six months after diagnosis, 20% of the patients still had evidence of right ventricular enlargement according to a previously specified margin (RV/LV-ratio > 1.0). The majority of these patients (74%) already had RV enlargement at baseline. A previous study that used serial echocardiograms also indicated that 25% of the hemodynamically stable PE patients still had signs of right ventricular dysfunction six months after diagnosis.[28] Unfortunately, the absence of patients who developed CTEPH during follow-up, does not allow us to draw conclusions on the potential relation between residual PE, persistent or progressive RV enlargement and CTEPH.

The findings of our study are strengthened by its multi-center and prospective design. Furthermore, a pre-specified protocol was used to systematically identify residual thrombotic obstruction with a validated tool after a consistent duration of follow-up, and all scans were analyzed by a central expert adjudication committee. The clinical characteristics of the patients, embolic burden and mean RV/LV ratio at baseline com-

pare well with previous cohorts.[29-31] This may imply that our findings are applicable in a wide range of clinical settings.

This study has some limitations that require comment. Most importantly, its sample size was, although being the largest study up to date in this setting, relatively limited and the incidence of recurrent VTE (12.8%) during follow-up was somewhat lower than reported in previous studies.[32] Although being the largest study in assessing residual thrombotic obstruction with CTPA up to date, the moderate sample size and limited event rate during follow-up do not allow us to draw definite conclusions on the prognostic value of residual thrombotic obstruction. In addition, a larger cohort and longer duration of follow-up are required to assess whether patients with residual thrombotic obstruction are at risk of developing CTEPH. Another limitation that the patients were at a relatively young age at baseline, therefore it is uncertain whether these results also apply to older patients.

In conclusion, this study demonstrates that complete thromboembolic resolution assessed with CTPA following six months of treatment for acute PE, occurs in 84% of the patients. The embolic burden of filling defects that did remain was small and most reflected signs of chronic PE. Follow-up CTPA imaging may therefore be of limited value to improve the diagnostic work-up of patients with suspected recurrent PE. Together with the absence of a clear predictive value for recurrent VTE and the costs and potential harms associated with CTPA, our data do not support routine implementation of follow-up CTPA imaging in clinical practice following treatment of acute PE. Future studies are required to definitely close the gap between incomplete PE resolution and persistent signs of RV enlargement and the development of CTEPH.

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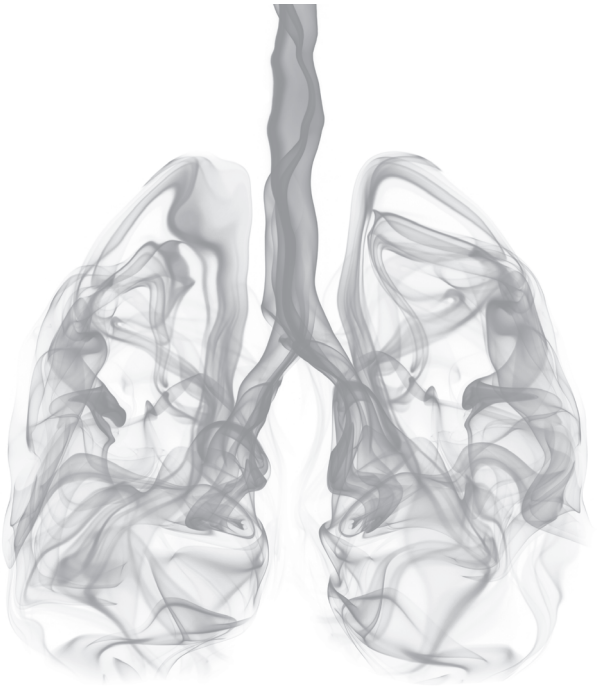
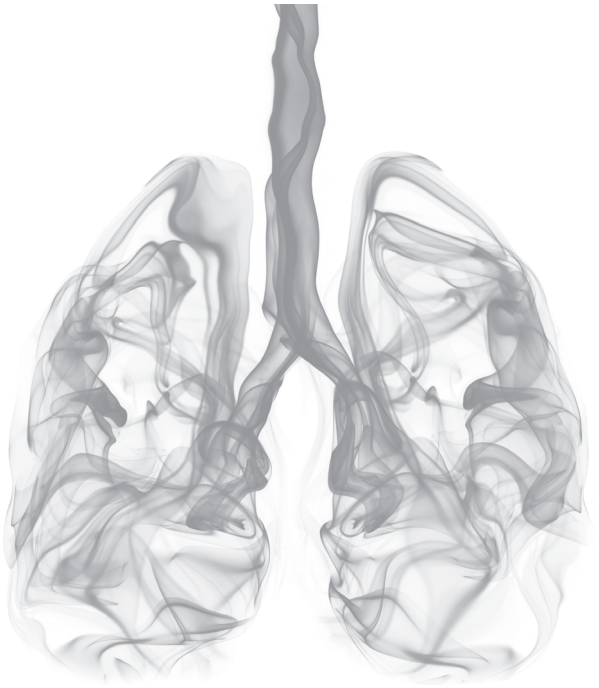
PART III

DIAGNOSIS AND PROGNOSIS OF INCIDENTAL PULMONARY EMBOLISM



CHAPTER 9

Outcome of incidentally diagnosed pulmonary embolism in patients with malignancy



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Curr Opin Pulm Med 2012; 18:399-405

ABSTRACT

Purpose of review

With improvements in the quality of computed tomography (CT) examinations, pulmonary embolism (PE) is increasingly being detected incidentally in oncology patients undergoing routine cancer staging CT scans. The purpose of this review is to update current evidence on the prognosis of cancer patients diagnosed with incidental PE.

Recent findings

Several recent observational studies have shed some light on the prognostic implications of diagnosing incidental PE in cancer patients. In general, anticoagulant treatment is initiated in these patients. Even during treatment, recurrent venous thromboembolic events may occur with a frequency that is comparable to cancer patients who have symptomatic PE. It has been demonstrated that the diagnosis of incidental PE is associated with adverse survival in cancer patients, and long-term mortality rates in incidental PE patients seem to approach that of symptomatic PE patients.

Summary

Overall, the body of literature on patients with incidental PE is sparse and does not allow firm recommendations on the therapeutic approach to these patients. Yet, in the absence of data on the natural clinical course of these patients, and the presence of cohort studies suggesting that incidental PE may impact recurrent venous thromboembolism and mortality, current consensus is to treat these patients in the same manner as symptomatic patients.

INTRODUCTION

Venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), is a frequent complication of cancer and its treatment. Patients with active malignancy carry a 7-fold increased risk of developing VTE.[1] The occurrence of VTE causes significant morbidity and mortality in these patients. In fact, VTE is the second leading cause of death in oncology patients.[2] Furthermore, patients with cancer and established VTE are shown to have more advanced stages of malignancy and, consequently, poorer survival rates compared to cancer patients without VTE.[3] Treatment of VTE in this specific patient group is challenging as the underlying malignancy exposes these patients to a high risk of recurrent VTE, while at the same time cancer patients more frequently experience anticoagulant-related bleeding complications than VTE patients without cancer.[4]

Clinically manifest VTE is diagnosed in approximately 15% of all patients with malignant disease.[5] The actual prevalence of VTE among cancer patients is likely even higher when subclinical or asymptomatic VTE patients are taken into account. It is well-known that patients with PE may commonly present with non-specific symptoms or even remain completely asymptomatic.[6] For instance, silent PE is present in up to 32% of the patients diagnosed with DVT.[7] Also, PE is frequently diagnosed at autopsy while unsuspected ante mortem.[8,9] The overall prevalence of PE identified at autopsies of cancer patients has been reported to be as high as 23%.[10]

Now that computed tomography (CT) imaging techniques have evolved significantly over the past few decades, PE is increasingly being detected incidentally in cancer patients in whom PE was not clinically suspected at the time of the CT examination. To determine the clinical relevance of these incidental findings, data on the prognosis of cancer patients with incidental PE is of great importance. The current review describes the scope of this problem and summarizes recent studies addressing the clinical course and outcome of cancer patients with incidental PE.

PREVALENCE OF INCIDENTAL PULMONARY EMBOLISM IN ONCOLOGY PATIENTS

The introduction of thin-section multidetector row CT scanners with fast acquisition times has resulted in major improvement of visualization of the pulmonary vasculature, while intravenous contrast administration has been optimized. As a result, many routinely performed thoracic contrast-enhanced CT examinations are now of adequate diagnostic value for the identification of PE. This has led to an increasing number of PE diagnoses, incidentally found in patients who had undergone CT-scanning for reasons

other than suspected acute PE (Figure 1 and 2). In the general population, incidental PE has been reported to be diagnosed in 1.5% of all patients undergoing routine helical CT scans.[11] However, this prevalence is significantly higher among high-risk patients, including inpatients and patients with cancer; the vast majority of incidental PE diagnosis are made in the latter group.[12] This is not surprising, since patients with malignant disease are at high risk of developing PE.[13] Furthermore, oncology patients far more frequently undergo CT scanning compared to patients without cancer, for reasons including diagnosing, staging and treatment evaluation of the malignancy. In oncology patients, the reported prevalence of incidental PE ranges from 1.9 to 4.4%.[14-18] The detection of incidental pulmonary emboli may vary upon detector collimation and image reconstruction thickness used. In symptomatic patients, it has been clearly established that the introduction of multidetector computed tomographic pulmonary angiography (CTPA) has significantly improved the detection of PE, in particular those emboli

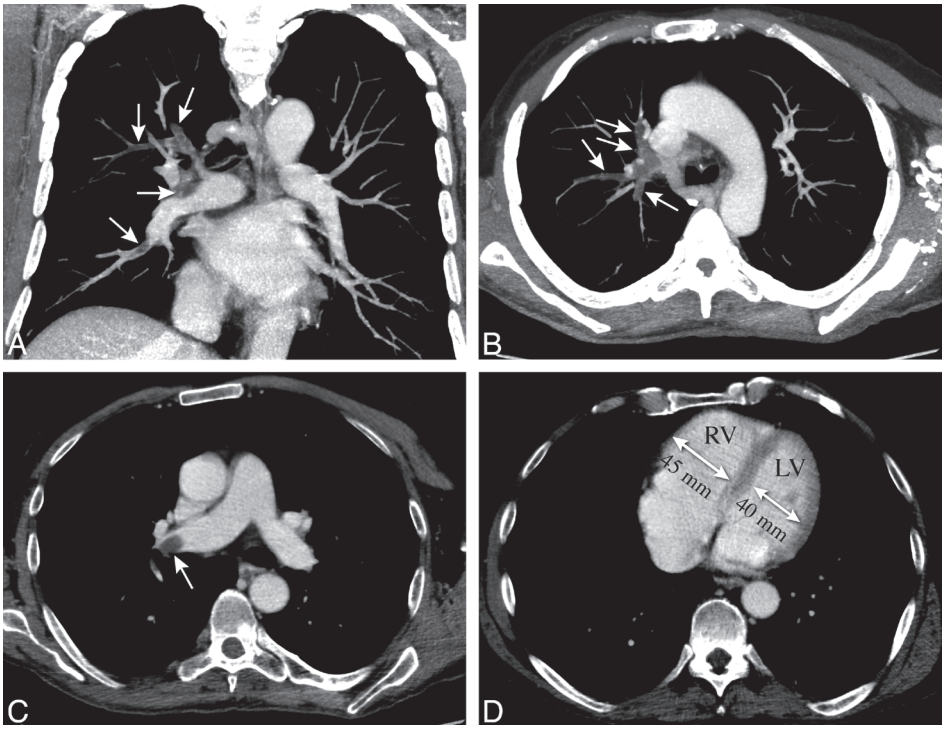

Figure 1. 59-year-old male patient with metastasized melanoma. CT indication was follow-up after partial remission following chemotherapy. CT maximum intensity projections (A, B) and average reconstructions (C, D), in coronal (A) and axial (B-D) view. Progression of disease was found with metastases to liver, peritoneum, mesenterium and mediastinum (not shown). Pulmonary embolism was found as incidental finding (arrows in A-C), with central (C) and segmental (A, B) emboli in the right pulmonary artery. The patient had no symptoms suggestive of pulmonary embolism. Slight enlargement of the right ventricle (RV) as compared to the left ventricle (LV) with RV/LV ratio >1 (normal ratio is <1).

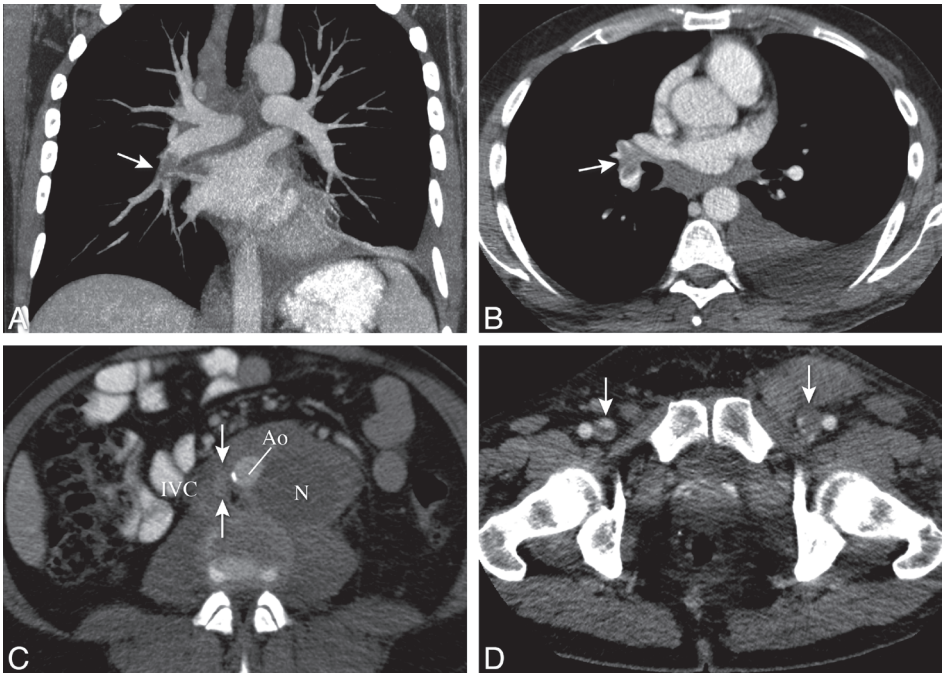

Figure 2. 43-year-old male patient with follicular lymphoma. CT indication was progression of pain in back and lower abdomen. Progression of disease was diagnosed. Incidental segmental pulmonary emboli in right pulmonary artery (arrows in A, B). Cause of pulmonary emboli is shown in C and D. C: large, partly necrotic lymph node tumor (N) with encasement of the aorta (Ao) and inferior vena cava (IVC, between arrows), causing flow obstruction from the lower extremity to the heart. Note deep venous thrombus in the left and right extern iliac veins (arrows in D).

located in the subsegmental branches of the pulmonary arteries.[19] For the detection of incidental PE, a recent systematic review reported a pooled prevalence of 2.0% for studies using CT scans with slice thickness ≥ 5mm and 3.0% for studies in which CT scans with slice thickness < 5mm were used.[20] Brown *et al.*[16] hypothesized that systematically adapting a CTPA imaging protocol, by using 1 – 1.5 mm slices and optimizing the timing of the contrast delivery to the pulmonary vessels, in oncology patients undergoing routine CT examinations, would improve the detection of incidental PE. In the 407 out of 408 enrolled patients in whom CTPA was considered adequate to detect intravascular contrast filling defects, PE was diagnosed in 18 (4.4%) patients. Of note, PE would not have been diagnosed in 39% of these patients if the CT scans were performed without a CTPA protocol.

RISK FACTORS

The increased risk of thrombosis in cancer patients is primarily attributed to the hypercoagulable state associated with malignancies, with the risk being greatest in patients with newly diagnosed malignancy.[21] Several risk factors have been identified that further predispose cancer patients to VTE, these include: older age, obesity, immobility, surgery, comorbid conditions, cancer-associated factors such as primary cancer site and cancer stage, and treatment-associated factors including the use of chemotherapy, hormone therapy and radiation therapy.[22]

Di Nisio *et al.*[23] performed a retrospective cohort study in cancer patients receiving chemotherapy, to characterize these patients' risk factors for incidental VTE. Out of 1921 patients, they identified 62 patients with incidental VTE, of whom 24 had PE. As for symptomatic VTE patients, metastatic disease, high leukocyte count and chemotherapy with platin agents were found to correlate with the occurrence of incidental VTE. Also, the majority of the incidental VTE cases were diagnosed within the first few months following initiation of chemotherapy, which has previously been recognized in patients with symptomatic VTE.[24] Although this study is limited by its small sample of patients and retrospective design, it does assume that cancer patients with incidental and symptomatic VTE share similar risk factors.

PROGNOSIS OF PATIENTS WITH INCIDENTAL PULMONARY EMBOLISM

Knowledge on the short and long-term prognosis of patients with incidental PE, in terms of the risk of recurrent VTE and mortality, is of major importance to guide clinical-decision making for physicians who are now increasingly being confronted with incidentally detected PE.

Incidence of recurrent VTE

As for the development of VTE, the presence of an active malignancy is an important risk factor for VTE recurrences. In cancer patients with established symptomatic VTE, the one-year cumulative incidence of recurrent VTE was reported to be 20.7%, compared to 6.8% for VTE patients without cancer.[4] In the past decade, several trials indicated low-molecular-weight heparin (LMWH) monotherapy to be of superior efficacy compared to conventional treatment with Vitamin K antagonists, for the long-term management of cancer-associated VTE.[25-27] Still, even during LMWH-treatment, recurrent VTE occurs in up to 9% of the patients in the initial six months.[26] It would be important to know whether this strong association between cancer and recurrent VTE disease is also seen in patients with incidental PE. In contrast to symptomatic PE however, the body of literature

Table 1. Studies reporting on the clinical outcome of incidental pulmonary embolism in cancer patients.

Author	Year	Number of patients	Patients treated	Follow-up time	Recurrent VTE	Mortality
Browne *et al.* [16]	2010	18	17 (94%)	6 months	1 (5.6%)	NR
Abdel-Razeq *et al.* [28]	2011	34	29 (85%)	NR	2 (5.9%)	9 (26%)
Douma *et al.* [29]	2010	3	2 (67%)	3 months	0 (0%)	1 (33%)
Font *et al.* [30]	2011	94*	94 (100%)	Mean: 477 days	10 (10.6%)	67 (71.3%)
den Exter *et al.* [31]	2011	51	51 (100%)	12 months	5 (9.8%)	27 (52.9%)
Dentali *et al.* [37]	2011	60*	60 (100%)	6 months	NR	27 (45%)

VTE, venous thromboembolism; NR, not reported

*These studies also included patients with incidental thrombosis at other locations and did not specify the outcome for PE patients seperately

addressing cancer patients with incidental PE is scarce. Only few, small observational studies give some insight of the clinical course and outcome of these patients (table 1).

Browne *et al.*[16] retrospectively followed 18 cancer patients with incidental PE for a period of 6 months. Anticoagulant treatment was initiated in 17 patients and none of these treated patients developed recurrent VTE during follow-up. However, the one patient in whom anticoagulation therapy was withheld, because of a perceived high bleeding risk, was diagnosed with recurrent symptomatic PE 5 weeks later. In another case series of 34 cancer patients with incidental PE, of whom 29 patients received anticoagulant treatment, acute symptomatic recurrent PE was diagnosed in two patients (5.9%).[28] It was not stated at what time these recurrences were diagnosed and whether or not they occurred whilst on treatment. In a smaller study including 3 cancer patients with incidentally detected PE, no recurrent events occurred during 3 months of follow-up.[29]

Gladish *et al.*[18] identified 16 patients with incidental PE by re-assessing contrast-enhanced thoracic CT-scans of oncology patients. In 12 of those patients, PE was not detected at the initial clinical CT image interpretation and those patients thus did not receive anticoagulation. During a variable follow-up period (range: 2 days to 24 months; average: 13 months), symptomatic DVT was diagnosed in one patient, whilst two patients developed asymptomatic recurrent embolic disease (DVT in one patient, PE and DVT in the other patient). Of the four patients in whom PE was initially reported, treatment was initiated in 3 patients. None of these patients developed recurrent events during a short follow-up period (ranging from 1 day to 3 months).

Font *et al.*[30] prospectively followed a cohort of 340 cancer patients with VTE. In 94 patients, VTE was detected incidentally, and the majority (60%) of them had PE. All patients were treated with LMWH; in most of the patients indefinitely. Recurrent VTE was observed in 10 (11%) of the patients with incidental VTE and 44 (18%) of the symptomatic VTE patients (mean follow-up time: 477 days). Recurrent rates were not specified for PE patients separately. The one year cumulative risk of recurrent VTE was significantly lower

for incidental (7%) than for symptomatic (18%) patients ($P = 0.043$). In a retrospective cohort study including 51 cancer patients with incidental and 144 with symptomatic PE, den Exter *et al.*[31] did not find a difference in the one year cumulative risk of symptomatic recurrent VTE in the incidental PE group compared to the symptomatic PE patients (13.3% and 16.9% respectively, $P = 0.77$). All patients included in this study received anticoagulant therapy with LMWH or vitamin K antagonists. The recurrent events in the incidental PE group comprised two cases of PE and three cases of DVT.

To summarize, these observational studies suggest that the risk of recurrent VTE for cancer patients with incidental PE is at least non-negligible, or may even be as high as for those with symptomatic PE; even while receiving anticoagulant treatment. The natural clinical course of incidental PE, without anticoagulant treatment being prescribed, has too rarely been investigated to draw any meaningful conclusions.

Impact on survival

Symptomatic VTE has clearly been established as a poor prognostic marker in cancer patients, as it is associated with both short- and long-term overall mortality.[3,21] With an aim to assess the impact of incidental PE on the survival of cancer patients, O'connell *et al.*[32] performed a matched cohort study. Seventy patients with incidental PE were matched to 137 patients without VTE, in terms of age, cancer type and cancer stage. Compared to the matched control patients, patients with incidental PE had a hazard ratio for death of 1.51 (95% CI: 1.01-1.27). Notably, the increased risk of death appeared to be driven by proximally located PE, as cancer patients with isolated subsegmental PE did not have poorer outcomes than control patients. The fact that the negative impact on survival was not significant at two months but became and was sustained significant at 6 months, suggests that most mortality was not directly related to the initial PE event. This is not surprising as PE-related death is predominately caused by impaired right ventricular function[33], which is unlikely to be present in patients without symptoms. The adverse impact on long-term survival in these patients is most likely caused by progression of the underlying malignancy. Given that the PE patients were matched to the control patients for cancer type and stage, mortality could not directly be attributed to more aggressive types of cancer or more advanced disease stages at baseline in the PE group. However, for patients with symptomatic VTE, it has previously been demonstrated that the occurrence of VTE was a predictor of mortality in specific types of cancer (namely, breast and lung cancer) even after adjusting for cancer stage and other variables associated with death.[34,35] A possible explanation for this finding might be that the occurrence of VTE, reflecting the cancer-associated hypercoagulable state, is a surrogate for adverse tumor biology, which in turn increases the risk of tumor progression and adversely impacts survival.[36]

In line with the findings of the matched cohort study mentioned above, Dentali *et al.*[37] found the 6-month mortality rate in cancer patients with asymptomatic VTE to be significantly higher compared to cancer patients in whom VTE was clinically suspected but ruled out (45% versus 27%, $P = 0.036$). Furthermore, the mortality rate among incidental VTE patients did not differ from the rate found in cancer patients with symptomatic VTE (45% and 47.5% respectively, $P = 0.75$). This is in agreement with the cohort study of den Exter *et al.*[31], who did not find a difference in the one-year mortality risk of incidental PE patients (52.9%) compared to symptomatic PE patients (53.3%; $P = 0.7$). The majority of the deaths (77.8%) in the incidental PE group were a related to progressive cancer and none of the patients died of fatal (recurrent) PE. Consistently, Font *et al.* reported similar long-term mortality rates for incidental (71%) and symptomatic VTE patients (71%). Three patients (3.2%) in the incidental group and 13 (5.3%) in the symptomatic group died of fatal VTE. Finally, in a cohort of pancreatic cancer patients, both the occurrence of incidental and symptomatic VTE appeared to adversely affect three-month survival (survival rates not specified).[38] Of note, the majority of the incidental patients had asymptomatic visceral vein thrombosis (82%) and only a small proportion (7%) had PE.

ANTICOAGULANT TREATMENT

The central question for clinicians confronted with incidental PE, is whether the initiation of anticoagulant therapy improves the prognosis of these patients. Until now, no randomized trials have evaluated anticoagulant therapy in patients with incidental PE. Furthermore, patients with incidental PE are routinely excluded from trials evaluating treatment strategies for patients with acute PE. Therefore, management of incidental PE is mainly extrapolated from clinical trials of symptomatic PE patients. Observational studies reveal that anticoagulant therapy is generally instituted once incidental PE is diagnosed.[16,30,31,39]

Given that the occurrence of incidental PE by definition does not give symptoms, the primary objective of initiating anticoagulant therapy would be the prevention of recurrent, potentially fatal, VTE events. In this respect, the risk reduction in recurrent VTE must be carefully balanced to the risk of anticoagulant-related bleeding complications, in order to determine their clinical benefit. The risk of bleeding complications among cancer patients receiving anticoagulant therapy has well been recognized.[4] It has however been hypothesized, and some of the previously discussed studies may support this hypothesis, that incidental PE could be a harbinger of symptomatic VTE, and this may justify initiating anticoagulant treatment.[40] There is a clear need for further research addressing the risk benefit ratio of anticoagulant therapy in patients with incidentally diagnosed PE. Until then, and in the absence of any data suggesting that the occurrence of

incidental PE is harmless, the general consensus is that these patients should be treated. This has also been recommended in the latest edition of the American College of Chest Physicians guidelines, which suggests the same initial and long-term anticoagulation for incidental PE patients as for those with symptomatic PE, in particular if these patients are not at high risk of bleeding (Grade 2B).[41]

CONCLUSION

The increased prevalence of incidental PE diagnoses has made this a significant issue among cancer patients. With little knowledge on the prognosis of these patients, the greatest challenge for clinicians is to determine the best therapeutic approach. The lack of clinical trials and the limited number of observational studies do not allow firm treatment recommendations. However, some recent cohort studies suggest that the occurrence of incidental PE in cancer patients mirrors the pro-thrombotic state of these patients, which may be associated with both recurrent VTE and mortality. Further studies are needed to clarify the risk-benefit ratio of anticoagulant therapy in these patients. Currently, it is recommended to treat cancer patients with incidental PE in the same manner as those with symptomatic PE.

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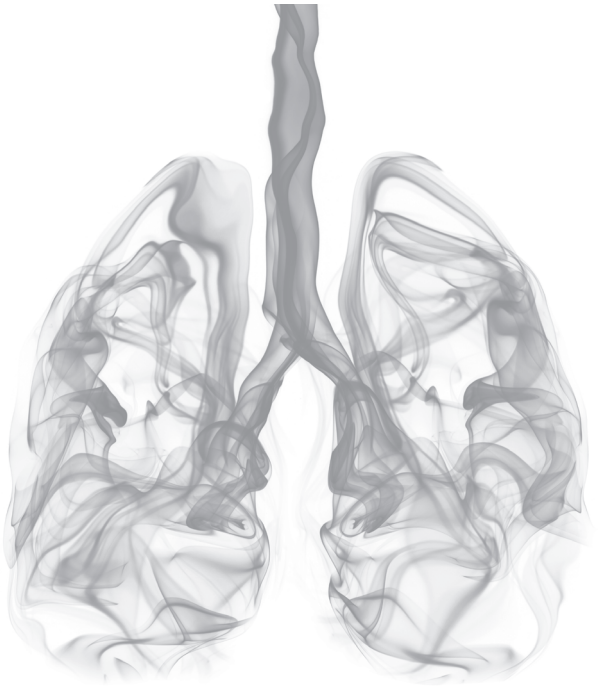
CHAPTER 10

Reliability of diagnosing incidental pulmonary embolism in cancer patients



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ABSTRACT

Background

With the routine use of advanced multi-slice CT scanners, pulmonary embolism (PE) is increasingly detected as an incidental finding among cancer patients. Although this generally leads to therapeutic interventions, the accuracy of diagnosing PE on routinely performed contrast enhanced CT scans is unknown.

Methods

Consecutive cancer patients diagnosed with incidental PE were eligible for inclusion. Their CT images were reassessed in a blinded fashion by two thoracic radiologists. To ensure blindness, a total of 19 cancer staging CT images without PE were included. The inter-observer reliability for the presence of PE was calculated with use of Kappa statistics.

Results

A total of 62 incidental PE patients (mean age 64 years, 60% male) were included. All patients received anticoagulant treatment upon diagnosis. Level of agreement between the two expert readers was high: they disagreed on the presence of PE in only two patients (3.2%), resulting in a Kappa statistic of 0.93. After final consensus reading, it was concluded that the CT images of all 62 patients initially diagnosed with incidental PE were indeed positive for PE.

Conclusions

This study indicates that an incidental PE diagnosis is reliable and highly reproducible, despite the suboptimal reading conditions of a non-dedicated scan protocol.

INTRODUCTION

As a consequence the increased use of more advanced CT imaging techniques, radiologists now increasingly report pulmonary embolism (PE) to be present on routinely performed contrast-enhanced CT examinations. This is in particular true for cancer patients, who display a high risk of developing venous thromboembolism (VTE), and frequently undergo CT scanning for reasons as tumor staging and treatment evaluation. Increased awareness among radiologists of incidental PE may also have contributed to the growing number of their reports. In recent literature, the reported prevalence of incidental PE diagnosed on routine cancer staging CT scans ranges from 1.9 to 4.4%.[1,2]

By definition, these incidental findings are diagnosed on CT scans that are not primarily conducted to establish or rule out acute PE. The accuracy of diagnosing incidental PE on CT scans that were not performed according to a standardized CT pulmonary angiography (CTPA) imaging protocol is as yet unknown. Since a false positive diagnosis of PE, whether symptomatic or incidental, comes with the consequence of unnecessary exposure to anticoagulant therapy with its associated risk of bleeding complications, establishing this diagnostic accuracy is highly relevant. The present study therefore aimed to assess the reproducibility and inter-observer agreement of diagnosing incidental PE on cancer staging CT scans.

METHODS

Study population

Consecutive adult patients with active malignant disease who were diagnosed with incidental PE between January 2003 and July 2012 in the Leiden University Medical Center were eligible for this study. The design and characteristics of this cohort study have, in part, been described previously.[3] Patients were identified using International Classification of Diseases (ICD) 9 codes for diagnosis of PE and a diagnosis of cancer. These included hospital discharge diagnoses as well as outpatient and emergency department encounters. Active malignancy was defined as cancer (either solid or hematologic) diagnosed within six months before the CT examination, recently recurrent or progressive cancer or any malignancy that deserved curative or palliative treatment within the previous six months. Incidental PE was defined as a diagnosis of PE detected on CT scans ordered for reasons other than the suspicion of acute PE (e.g. CT scans performed for cancer staging, treatment evaluation or cancer recurrence detection).[4] This does not imply that all patients were asymptomatic from PE, however, any complaints did not result in a clinical suspicion of PE. The presence of (asymptomatic) DVT was not systematically investigated and no differentiation was made between possible in-situ

thrombosis and true pulmonary emboli. Follow-up CT scans in order to assess pulmonary reperfusion were not performed. Institutional review board approval was waived for this observational and retrospective study.

Image acquisition and interpretation

Multi-detector CT scanners (4, 16-, 64-, and 320-slice CT scanners, Toshiba, Otawara, Japan) were used in all patients. Images were reconstructed with 1.0 mm slice thickness, if possible. For two patients, scanned with a 4-slice CT scanner, the slice thickness was 2mm images and for one other patient only images with a slice thickness of 5 mm were available. The images were reassessed by two thoracic radiologists independently (LK and IH), who were blinded to the original CT report, location of the filling defect and clinical information of the patients. The radiologists were allowed to optimize reading by using post-processing tools such as stacking, adapting window-settings, and use of zoom-function, as is used in clinical practice. PE was defined as the presence of at least one filling defect in the pulmonary artery tree. The reviewers' findings were reported on a pre-specified and standardized form, on which the following information was recorded: 1) the image quality of the CT examination regarding the level of confidence in PE diagnosis, i.e.: good confidence, uncertain, or not confident; and 2) contrast phase, i.e. late arterial (contrast delay approximately 30 sec.) or portal-venous (contrast delay approximately 70 sec.).

To ensure control and blindness of the expert readers, a number of 19 cancer staging CT examinations without reported PE were included, originating from the same inclusion period as the CT scans with incidental PE, with a similar distribution of late arterial and portal-venous contrast phase.

Statistical analysis

The proportion of cases, with its corresponding 95% confidence interval (CI), in whom the expert readers' interpretations were concordant was calculated. The kappa-coefficient was calculated to assess the rate of agreement upon PE diagnosis in the total sample of CT scans. SPSS version 20 (SPSS Inc, Chicago, IL), was used for all analysis.

RESULTS

A total of 65 consecutive patients diagnosed with incidental PE were identified during the study period. We were unable to retrieve the original CT images in three patients, and those were excluded from the present analyses. Mean age of the remaining 62 patients was 64 years, and 60% of the patients were male (Table 1). The most prevalent malignancies were lung cancer (18%) and colorectal cancer (11%). The main indications for the

Table 1. Patient characteristics

Age in years (mean ± SD)	64 ± 15
Male sex (n, %)	37 (59.7)
BMI (mean ± SD)	25.5 ± 3.9
Inpatient (n, %)	21 (33.9)
Recent immobilization (n,%)	26 (41.9)
Recent surgery (n,%)	9 (14.5)
Previous VTE (n, %)	3 (4.8)
Primary tumor site (n, %)	
Lung	11 (17.7)
Breast	6 (9.7)
Colorectal	7 (11.3)
Other GI	12 (19.4)
Gynecological	6 (9.7)
Other solid	13 (21.0)
Hematologic	7 (11.3)
Thrombus localization (n, %)	
Central	20 (32)
Segmental	41 (66)
Subsegmental	1 (1.6)

BMI, body mass index; VTE, venous thromboembolism; GI, gastro-intestinal

CT examinations were primary diagnosis (24%), staging (27%), or treatment evaluation (32%) of the malignant disease. In 20 patients (32%) expert reading identified central PE, in 41 patients (66%) segmental PE and in 1 patient (1.6%) subsegmental PE.

All patients were treated with anticoagulant agents following the diagnosis of incidental PE. In three patients (4.8%), a CTPA was conducted following the identification of PE on the staging CT, which confirmed the presence of PE in all three cases (Figure 1). The expert radiologists only evaluated the initial CT scans on which PE was found, and were unaware of these CTPAs.

The contrast phase was late arterial in 14 patients and portal-venous in 48 patients. In 13 patients (21%), incidental PE was diagnosed on an abdominal CT without a complete chest CT examination. In 60 of the 62 patients diagnosed with incidental PE, the expert readers agreed on the presence of PE. In two patients (3.2%), either one of the observers refuted the presence of PE whereas the other observer confirmed the presence of PE. Of these 2 patients, 1 patient was diagnosed with incidental PE with the most proximal PE in the central pulmonary artery on a 64-slice CT-scanner with contrast in the portal-venous phase. The second patient was diagnosed with incidental PE with the most proximal PE in a subsegmental pulmonary artery on a 16-slice CT-scanner with contrast in the portal-venous phase. Thus, the proportion of agreement on the presence of PE between the

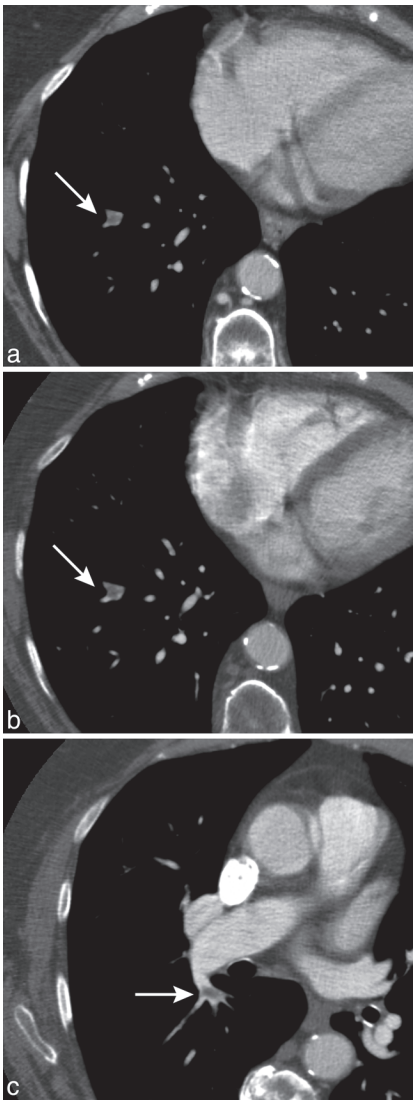

Figure 1. 79-year female patient with non-Hodgkin lymphoma underwent abdominal CT for staging malignancy. Incidental finding of pulmonary embolism in segmental pulmonary artery of right lower lobe was found in basal lung fields at upper slides of CT (arrow in a). Dedicated CT pulmonary angiography confirmed diagnosis pulmonary embolism (arrow in b). Also, additional segmental emboli were found at higher levels (arrow in c).

initial report and expert reading was 96.7% (60/62; 95% CI: 88.8-99.6%). Regarding the level of confidence of diagnosis, one reader classified 61 of the incidental PE diagnoses as good confidence for PE and one as non-confident, whereas the other reader classified 60 as good confident, one as non-confident, and one as uncertain/non-confident. After consensus reading, it was concluded that PE was present in all 62 patients. Both readers did not identify PE in any of the 19 control scans. In the total sample of 81 patients with and without PE, Kappa analysis revealed a Kappa statistic of 0.93 ($p < 0.001$) for the dichotomous categories 'PE present' versus 'PE absent' after first reading by the expert readers.

DISCUSSION

The results of this study indicate that diagnosing incidental PE on CT scans that were conducted for other reasons than a clinical suspicion of PE, is reliable with excellent inter-observer agreement. None of the incidental PE diagnoses were found false positive according to the final consensus evaluation of two experts.

Our observed Kappa level compares well to the level of inter-observer agreement found for diagnosing PE with the use of dedicated CTPA, which has repeatedly been reported to be good.[5-7] Of note, CTPA is currently widely considered the imaging test of choice for the diagnosis of acute PE.[8]

The importance of accurately diagnosing PE, including incidental episodes, lies in the therapeutic consequences that come with this diagnosis. The current consensus is that cancer patients with established VTE should continue anticoagulation as long as the cancer is active.[9] For incidental PE, a similar therapeutic approach as towards symptomatic PE patients has been proposed.[10] Indeed, a recent international survey among physicians revealed that the vast majority would initiate treatment in a cancer patient with incidental PE[11]. A false positive diagnosis of incidental PE would thus unnecessarily expose patients to the potential harms of long-term anticoagulant treatment. Particularly in cancer patients, anticoagulant treatment comes with a substantial bleeding risk, which has been reported to be more than two-fold higher compared to non-cancer patients.[12] In cancer patients with incidental PE, we previously observed a one-year cumulative major bleeding risk of 12.5%.[3]

Notably, in only three patients an additional CTPA was performed to confirm the diagnosis of PE. This reveals that in routine practice, most physicians rely and act upon the diagnosis made on staging CT scans. Our data strongly suggest the validity of the PE diagnosis based on the cancer staging CT's without the need for performing CTPA.

Limitations of this study include the limited sample size and its single center design, which may impair the extrapolation of our findings. Also, the high prevalence of PE in our study may have resulted in an overestimation of the kappa level. Nonetheless, the study group is relatively large regarding its specific study topic and the first addressing this research question. Second, for a definite confirmation of the presence of PE, a CTPA may ideally have been performed in all patients following the incidental PE detection. However, our study was retrospective in design. Also, in the patients evaluated, the confidence of PE diagnosis was good in most patients and performing an extra CTPA would not have added to the diagnosis. Also, in only 3 patients, the original staging CT scan was followed by CTPA for confirming PE diagnosis. Therefore, for reproducibility measures, independent reading performed by two expert thoracic radiologists from different hospitals was used as standard for the presence of PE. In selected cases, in which

uncertainty may exist after reading the images, additional dedicated CTPA investigations may be considered in order to guide clinical decision making.

In conclusion, in this sample of CT examinations that were not intended for pulmonary artery evaluation, the diagnosis PE was found confident with high reproducibility. This information is relevant given that in clinical practice, a diagnosis of incidental PE on routinely performed CT scans generally leads to instant initiation of anticoagulant treatment without additional diagnostic tests being performed.

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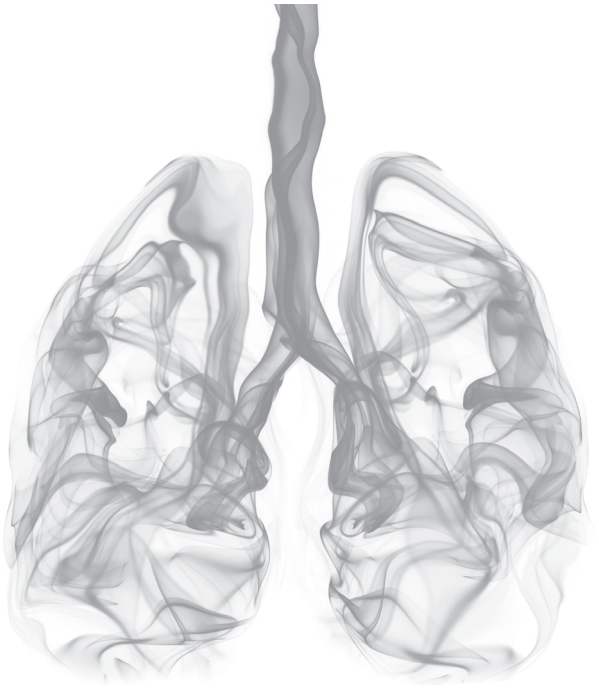
CHAPTER 11

Physicians' management approach to an incidental pulmonary embolism: an international survey



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J Thromb Haemost 2013; 11:208-13

ABSTRACT

Background

Pulmonary embolism (PE) is increasingly detected incidentally as a result of improved CT technology. However, little evidence on the prognostic implications of these unsuspected findings is available to guide clinical decision-making. This study aimed to investigate current management patterns for clinicians confronted with incidental PE.

Methods

A survey was distributed among 585 physicians worldwide. Two patients with incidentally diagnosed PE, one with and one without malignancy, were presented to assess the clinicians' management approach in terms of initiation, duration and type of anticoagulant therapy, and the need for hospitalization.

Results

183 completed surveys were available for analysis. Every respondent decided to treat a patient with central incidental PE. In case of segmental PE, 98% would initiate treatment, regardless the presence of malignancy. When a patient with subsegmental PE (SSPE) was presented, 11% (95%CI: 6-15%) and 28% (95%CI: 21-35%) opted not to treat in the presence and the absence of malignancy respectively. Of those who withheld treatment, 90% would initiate treatment once deep vein thrombosis (DVT) was diagnosed concurrently. Irrespective of the presence of malignancy, two thirds of the respondents choose to treat a patient with SSPE on an outpatient basis, as compared to 62% for segmental and 36% for central PE.

Conclusions

This study reveals that most physicians would treat a patient with incidental PE. However, uncertainty exists about the need for anticoagulants in patients with incidental SSPE, particularly in the absence of cancer and DVT. The majority of physicians would manage patients with small incidental PE on an outpatient basis.

INTRODUCTION

Now that the quality of computed tomography (CT) imaging techniques has greatly improved with the introduction of thin section multi-detector row CT scanners, pulmonary embolism (PE) is increasingly diagnosed on routine CT examinations in the absence of a clinical suspicion. This phenomenon is often referred to as 'incidental PE'. This increased detection has made incidental PE the topic of recent debate. In particular, physicians have questioned the prognostic relevance of these incidental findings.[1,2] However, scarce data are available to guide clinical decision-making for physicians who are now increasingly being confronted with a diagnosis of incidental PE.[3] Given the absence of any clinical trial assessing the management of incidental PE and the paucity of prognostic studies addressing the outcome of these patients, recommendations on the treatment of incidental PE are almost solely based on expert opinion. To investigate current management practice patterns for incidental PE, in terms of the initiation and duration of anticoagulant administration, and the need for hospitalization, we undertook a worldwide survey among physicians.

METHODS

A questionnaire, consisting of two patient cases, was designed and pretested by the investigators. The first case described a patient in whom incidental PE was diagnosed on a CT-scan conducted for the follow-up of a malignant disease. In the second case, incidental PE was detected on a CT-scan performed for follow-up of non-malignant disease. The patients did not have any symptoms suggestive of PE. Multiple-choice questions were used to investigate a) whether the respondent would initiate anticoagulant treatment and if so, for what duration of time, b) the type of anticoagulant prescribed, and c) whether the respondent would treat the patient on an out- or inpatient basis. Also, the participants were asked whether a concurrent diagnosis of deep venous thrombosis (DVT) would influence their management strategy. To assess the impact of the location of PE on the participants' management approach, both cases were subdivided in a case with subsegmental PE (SSPE), segmental PE, and central PE. The questionnaire was published online using Thesis Tools (http://www.thesistools.com).

We intended to reach a large number of physicians practicing in various disciplines and in various countries. For this purpose, the memberships list of the International Society on Thrombosis and Haemostasis (ISTH) was used to randomly select a total of 127 physicians practicing in 31 different countries. Criteria used for selection were both being registered as a physician and practicing in a field that potentially encounters patients with PE. Second, 177 members of the Registro Informatizado de Pacientes con

Enfermedad TromboEmbólica (RIETE) registry[4], a multidisciplinary project which aims to register the management and outcome of patients with venous thromboembolism (VTE) were surveyed. Third, 131 members of the Dutch society of Vascular Medicine were asked to participate. Last, the survey was distributed among 150 members of the Spanish society of Medical Oncology.

Data were analyzed using descriptive statistics. Since not all participants fully completed the survey, proportions were calculated based on the number of respondents per question.

RESULTS

Out of the 585 invitations, a total of 183 (31%) questionnaires were returned and available for analysis. The majority of the group of respondents practiced in the field of internal medicine (45.8%), oncology (14.8%), hematology (14.8%), and pulmonary medicine (13.5%). Of the respondents, 61% practiced in an academic medical center versus 39% in a non-academic hospital (table 1).

When a patient was presented with incidental subsegmental PE, 72% (95% CI: 64.4 – 78.8%) of the participants would initiate anticoagulant treatment in case the patient did not have malignant disease, whilst in the presence of a malignancy 89.1% (95% CI: 83.6 – 93.2%) opted to treat (table 2). In case incidental PE was located in a segmental pulmonary artery, 98% (95% CI: 96.4 – 100%) of the respondents decided to initiate treatment when it concerned a cancer patient, and 97.5% (95% CI: 95.1 – 99.9%) if the patient did

Table 1. Respondents' practice characteristics

Area of Work, n (%)	*(n=155)*
Internal medicine	71 (45.8%)
Oncology	23 (14.8%)
Hematology	23 (14.8%)
Pulmonary medicine	21 (13.5%)
Cardiology	8 (5.2%)
Vascular surgery	2 (1.3%)
Vascular medicine	2 (1.3%)
Thrombosis center	2 (1.3%)
Angiology	2 (1.3%)
Internal medicine and Oncology	1 (0.6%)
Academic or non-academic, n (%)	*(n=156)*
Academic	95 (60.9%)
Non-academic	61 (39.1%)

Table 2. Management patterns of physicians confronted with incidental, asymptomatic PE

Location of PE	Case 1 - Cancer patient			Case 2 - Non-cancer patient		
	Sub-segmental	Segmental	Central	Sub-segmental	Segmental	Central
Initiation of treatment, n (%)	*(n=183)*	*(n=175)*	*(n=169)*	*(n=161)*	*(n=157)*	*(n=156)*
No treatment	20 (10.9%)	3 (1.7%)	0 (0.0%)	45 (28.0%)	4 (2.5%)	0 (0.0%)
Anticoagulation 3 months	24 (13.1%)	18 (10.3%)	9 (5.3%)	37 (23.0%)	43 (27.4%)	24 (15.4%)
Anticoagulation 6 months	61 (33.3%)	63 (36.0%)	54 (32.0%)	70 (43.5%)	102 (65.0%)	118 (75.6%)
Anticoagulation for indefinite period	78 (42.6%)	91 (52.0%)	106 (62.7%)	9 (5.6%)	8 (5.1%)	14 (9.0%)
Type of treatment*, n (%)	*(n=161)*	*(n=172)*	*(n=167)*	*(n=115)*	*(n=151)*	*(n=153)*
VKA	14 (8.7%)	13(7.6%)	13 (7.8%)	50 (43.5%)	79 (52.3%)	86 (56.2%)
LMWH - therapeutic dose	99 (61.5%)	114(66.3%)	116 (69.5%)	50 (43.5%)	55 (36.4%)	52 (34.0%)
LMWH - therapeutic dose followed by prophylactic dose	45 (28.0%)	41 (23.8%)	36 (21.6%)	13 (11.3%)	15 (9.9%)	12 (7.8%)
LMWH - prophylactic dose	3 (1.9%)	4 (2.3%)	2 (1.2%)	2 (1.7%)	2 (1.3%)	3 (2.0%)
Treatment location*, n (%)	*(n=163)*	*(n=174)*	*(n=168)*	*(n=115)*	*(n=151)*	*(n=154)*
Outpatient basis	114 (69.9%)	107 (61.5%)	61 (36.3%)	77 (67.0%)	94 (62.3%)	54 (35.1%)
Hospitalized	10 (6.1%)	17 (9.8%)	66 (39.3%)	10 (8.7%)	21 (13.9%)	66 (42.9%)
Depends on patient preferences	2 (1.2%)	2 (1.1%)	1 (0.6%)	2 (1.7%)	3 (2.0%)	2 (1.3%)
Decide on a case-by-case basis	37 (22.7%)	48 (27.6%)	40 (23.8%)	26 (22.6%)	33 (21.9%)	32 (20.8%)
Change treatment if proven DVT, n (%)	*(n=181)*	*(n=177)*	*(n=168)*	*(=160)*	*(n=153)*	*(n=156)*
Yes	49 (27.1%)	22 (12.4%)	12 (7.1%)	55 (34.4%)	20 (13.1%)	14 (9.0%)
No	132 (72.9%)	155 (87.6%)	156 (92.9%)	105 (65.6%)	133 (86.9%)	142 (91.0%)

PE, pulmonary embolism; DVT, deep vein thrombosis; VKA, vitamin K antagonists; LMWH, low-molecular-weight heparin

*In case treatment was initiated

not have malignant disease. Every respondent choose to initiate anticoagulant therapy in case PE was localized centrally, irrespective of the presence of malignant disease.

With respect to the duration of treatment, in case incidental PE was diagnosed in a patient with malignant disease, indefinite treatment was opted by 42.6%, 52% and 62.7% of the respondents if PE was respectively localized in a subsegmental, segmental, or central pulmonary artery. Most of the remaining respondents choose to treat the patient for six months (33.3%, 36% and 32% for subsgemental, segmental and central PE respectively). In the absence of malignant disease, a treatment-period of 6 months was preferred by 43.5% of the respondents in case of SSPE, 65% in case of segmental PE, and 75.6% for a patient with central PE.

A large group of participants decided to treat a patient with incidental SSPE on an outpatient basis: 69.9% (95% CI: 62.9 – 76.9%) in the presence and 67% (95% CI: 58.4 – 75.6%) in the absence of malignant disease. These proportions slightly decreased in the case of segmental PE: 61.5% (95% CI: 54.3 – 68.7%) for a patient with and 62.3% (95% CI: 54.6 – 70%) for a patient without malignancy. When it concerned a patient with central PE, hospitalization became the most prevalent treatment option chosen by the respondents: 39.3% (95% CI: 31.9 – 46.7%) in case of a cancer patient and 42.9 (95% CI: 35.1% - 50.7%) in case of a patient without cancer.

In the case of a cancer patient with SSPE, 16 of the 18 (89%) respondents who initially choose to withhold treatment, decided to initiate treatment once DVT was proven concurrently. When a non-cancer patient with SSPE was presented, 37 of the 41 (90%) of the respondents who initially opted not to treat, choose to start anticoagulant therapy following a diagnosis of DVT.

DISCUSSION

This study demonstrates that the majority of physicians would initiate anticoagulant therapy once incidental PE is diagnosed, in particular if PE is localized proximally. Of importance, least consensus appears to exist regarding the need for anticoagulant therapy in patients with incidental SSPE. In particular in the absence of malignant disease, a large proportion of participants (28%) opted not to treat. Also, there seemed to be a tendency to treat more centrally located incidental PE for a longer period of time. These findings may reflect the uncertainty in recent literature about the clinical relevance of small, subsegmental emboli.[5,6] A survey specifically addressing the management of symptomatic SSPE found similar high rates of respondents who would not initiate treatment in such patients, or at least not before performing additional diagnostic tests.[7] The issue concerning the clinical significance of SSPE is of particular relevance for patients with incidental PE, as incidentally detected PE are likely to be smaller emboli, with a reported rate of SSPE in 27% of the cases.[8]

Our survey also addressed the issue of outpatient management. Three recent cohort studies have demonstrated that selecting PE patients for outpatient treatment solely on a clinical basis, primarily focusing on hemodynamic stable PE patients who do not require oxygen supply, yields safe results in terms of low risks of recurrent VTE and mortality.[9-11] Given that patients with asymptomatic PE are clearly able to compensate for the hemodynamic and respiratory consequences of the PE and unlikely to have decreased right ventricular function, these patients may be deemed good candidates for outpatient management, in particular if PE is detected on elective CT scans in an

outpatient setting. Indeed, the present study indicates that the majority of physicians would feel comfortable to treat patients with incidental PE on an outpatient basis.

It should be stated that this survey specifically addressed the management of incidental PE patients in whom symptoms suggestive of PE were absent. It has previously been demonstrated that 75% of the cancer patients diagnosed with incidental PE, actually were symptomatic at time of diagnosis.[12] In fact, the presence of symptoms in patients with incidental PE may be associated with a worse outcome.[13]

The results of this survey may be compromised by the relatively low response rate (31%). However, it was our intention to reflect the practice patterns of a wide variety of randomly selected clinicians. Distributing the survey among a selected group of experts would possibly have yielded a higher response rate; however, this would have made the results less generalizable to clinical practice. A second limitation is that the survey did not assess the respondents' country of practice. We were therefore unable to investigate inter-country differences in the management approach to incidental PE. For instance, the choice whether to manage patients on an outpatient basis may well be influenced by local health care systems.

In summary, this study reveals most physicians decide to treat a patient with incidental PE. Uncertainty exists about the need for anticoagulant treatment in patients with incidental SSPE, particularly in the absence of cancer and DVT. The majority of physicians would manage patients with small, asymptomatic incidental PE on an outpatient basis. Further studies are needed to clarify the risk-benefit ratio of anticoagulant therapy in incidental PE, with a particular focus on the safety of withholding treatment in patients with incidental SSPE and the safety of treating incidental PE patients as outpatients.

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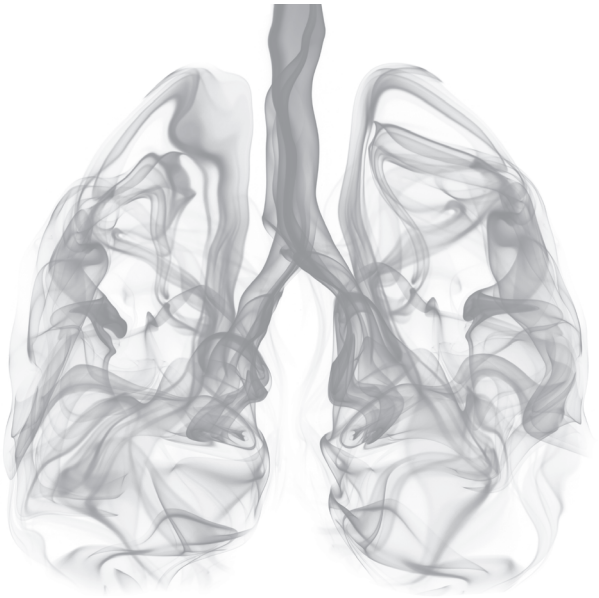
CHAPTER 12

Risk of recurrent venous thromboembolism and mortality in cancer patients incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients



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ABSTRACT

Purpose

The routine use of modern CT-scanners has led to an increased detection of incidental pulmonary embolism (PE), in particular in patients with cancer. The clinical relevance of these incidental findings is unknown.

Patients and methods

In this retrospective cohort study, oncology patients in whom PE was objectively proven between 2004 and 2010 and anticoagulant treatment was started, were included. Fifty-one patients with incidental PE and 144 with symptomatic PE were followed for one year to compare the risks of recurrent venous thromboembolism (VTE), bleeding complications and mortality. Kaplan-Meier and Cox survival analyses were performed.

Results

Incidental and symptomatic patients did not differ with respect to mean age, gender, cancer type and stage, and risk factors for VTE. As a result from evolving treatment guidelines, approximately half of the patients in both groups received long-term treatment with vitamin K antagonists in stead of currently recommended low-molecular-weight heparin. The 12-month cumulative incidence of recurrent VTE was 13.3% in the incidental group versus 16.9% in the symptomatic group ($p = 0.77$). Notably, 20% VTE events recurred after premature termination of anticoagulant therapy. The risk of major bleeding complications was also comparable in the two groups (12.5% for incidental patients and 8.6% for symptomatic patients; $p = 0.5$). The respective 12-month mortality risks were 52.9% and 53.3% ($p = 0.7$).

Conclusion

Our findings suggest that oncology patients diagnosed with and treated for incidental PE, have similar high rates of recurrent VTE, bleeding complications and mortality, as compared with oncology patients who develop symptomatic PE.

INTRODUCTION

With recent advances in the quality of computed tomography (CT) examinations, in particular with the introduction of multidetector CT scanners, the detection of incidental, asymptomatic pulmonary embolism (PE) has become relatively common, particularly in patients with malignancy.[1] A recent meta-analysis reported a weighted pooled prevalence of 2.6% of incidental PE in oncology patients.[2] To guide medical decision making for clinicians confronted with these incidental findings, knowledge on the prognosis of oncology patients with incidental PE is relevant. However, whereas it has been clearly established that symptomatic PE in cancer patients causes significant morbidity and mortality[3], there is a lack of knowledge on the outcome of incidental PE in cancer patients.

Therefore, this study was performed in aim to investigate the follow-up of cancer patients incidentally diagnosed with PE. In a cohort of oncology patients diagnosed with and treated for PE, we compared incidental with symptomatic PE cases regarding the rate of recurrent venous thromboembolism (VTE), the frequency of major hemorrhage and survival.

METHODS

Patients

A single-center, retrospective cohort study was conducted in a university hospital (Leiden University Medical Center). Patients with a diagnosis of PE between January 2004 and January 2010 were identified using ICD-9 codes. These included hospital discharge diagnoses as well as outpatient and emergency department encounters. Adult patients (age ≥ 18 years) with objectively proven PE and a concomitant active malignancy were eligible. Active malignancy was defined as cancer diagnosed within six months before the index PE, recently recurrent or progressive cancer or any malignancy that deserved curative or palliative treatment within the previous six months. Both solid and hematologic malignancies were eligible. PE had to be confirmed by pulmonary angiography, contrast-enhanced computed tomography or V/Q scanning showing a high probability of PE. PE was classified as 'incidental' if PE was detected on CT scans ordered for reasons other than suspected PE (e.g. CT scans performed for cancer staging, treatment evaluation or cancer recurrence detection).

Patients were treated with anticoagulation therapy according to local clinical practice. Before 2007, patients initially received low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) followed by vitamin K antagonists (VKA). From 2007, patients received long-term therapy with LMWH. To minimize potential bias because of diverse

treatment regimes, patients in whom anticoagulation treatment was withheld and patients treated with thrombolytic therapy, were excluded.

Institutional review board approval was not required for this observational and retrospective study.

Clinical data

The medical charts of all eligible patients were comprehensively reviewed for the following data: patient demographics; diagnosis, localization and management of the index PE; type and duration of anti-coagulation therapy; cancer type, stage and treatment; date of diagnosis, localization and management of recurrent VTE events; the occurrence of major bleeding incidents; and date and cause of death. In addition, the following risk factors for VTE were recorded at baseline: immobilization (complete bed rest for 3 or more days in the 4 weeks before PE); major surgery in the 4 weeks before PE; prior history of VTE; obesity (BMI > 30 kg/m^2); and active chemotherapy, hormonal therapy or anti-angiogenic therapy (these therapies were defined as active if they were ongoing or if PE occurred < 30 days after cessation).

Outcome

All patients were retrospectively followed during one year after initial PE. Endpoints of this study were the occurrence of recurrent symptomatic VTE, major bleeding events and all-cause mortality.

Recurrent PE was defined as a new intraluminal filling defect on pulmonary angiography or spiral CT pulmonary angiography, a new high probability perfusion defect on VQ-scan or any new defects after earlier normalizing of the scan, or confirmation of a new PE at autopsy. Recurrent deep vein thrombosis (DVT) was confirmed by compression duplex ultrasonography or contrast venography.

Major bleeding was defined as fatal bleeding; symptomatic bleeding in a critical area or organ; clinically overt bleeding causing a fall in hemoglobin level of at least 20 g L^{-1} (1,24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.[4]

Cause of death was verified by reviewing the pathology report. If autopsy was not performed, the likely cause of death was verified with the treating physician by reviewing the medical records and death certificates. For patients who were lost to follow-up, general practitioners (GP) were contacted to determine whether endpoints had occurred. In case of death, the likely cause of death was verified with the GP.

Statistical analysis

Differences in baseline characteristics between patients with incidental and symptomatic PE were tested for statistical significance using the Chi-square-test or the Fishers

exact test for categorical data and the student-t test for continuous variables. According to the method of Kaplan and Meier[5], the cumulative incidence of recurrent VTE, major bleeding and all cause mortality were estimated and the groups were compared for statistical differences with the log-rank test. Patients were censored at time of event, at time of death, at date of last medical chart documentation, or after one year of follow-up, whichever came first. A Cox proportional hazard model was used to estimate hazard ratios (HR) for recurrent VTE and mortality. The HRs were adjusted for age and sex. In a second analysis the model was additionally adjusted for treatment type, mean duration of treatment and variables that were previously described as risk factors for VTE. The proportional hazards assumption was tested with inspection of log-log survival curves. SPSS, version 17.0.1 (SPSS Inc, Chicago, IL), was used for all analysis.

The reporting of this study conforms to the STROBE guidelines for reporting of observational studies.[6]

RESULTS

Patient selection

Between January 2004 and January 2010, 201 patients with established PE and active malignancy were identified. Two patients incidentally diagnosed with PE were excluded from analysis because the PE was interpreted by the radiologist to be long-standing and anticoagulation therapy was not initiated. All other incidental PE cases discovered in the study period received anticoagulation therapy. Four symptomatic patients with massive PE requiring thrombolytic therapy or surgical intervention were excluded. Follow-up was limited to four weeks in one patient, because of geographical inaccessibility.

The accuracy of case ascertainment was cross-checked with a database from the Radiology department in which consecutive patients with a diagnosis of PE were registered. From November 2008, the reports of thoracic CT scans, performed for any indication, were daily reviewed for the presence of PE. In the 15 months that this database overlapped with our study period, one patient with incidental PE and three patients with symptomatic were found that were undetected by using ICD-coding.

Patient characteristics

Of the 195 included patients, 51 (26%) were classified as incidental PE and 144 (74%) as symptomatic PE. The majority (n = 39, 77%) of the incidentally diagnosed PE was detected on CT-scans performed for the diagnoses, staging, or treatment evaluation of the malignancy. The other 12 were diagnosed during CT examinations performed for the evaluation of other (acute) medical illnesses, including abscess detection in postoperative patients.

The demographic and clinical characteristics of the study population at baseline are presented in table 1. Mean age was 64 years in the incidental group versus 60 years in the symptomatic group. In the incidental and symptomatic group respectively, 59% versus 49% were male patients, 63% versus 66% were outpatients, 8% versus 13% had isolated subsegmental PE, 12% versus 17% had hematologic malignancies, and of the patients with solid tumors, 69% versus 67% had metastatic disease. None of these differences reached statistical significance.

Lung tumors most frequently accounted for the concomitant malignancy in both groups, followed by breast cancer and colorectal cancer. No clear differences were seen in the proportion of patients with obesity or previous VTE, and similar proportions of patients were recently exposed to immobilization, major surgery, hormonal therapy, anti-angiogenic therapy, or chemotherapy.

Table 1. Baseline characteristics of the patients

	Incidental PE (n = 51)	Symptomatic PE (n = 144)	*P*-value
Mean age ± SD (years)	64 ± 15	60 ± 14	0.079
Male sex, No. (%)	30 (58.8)	71 (49.3)	0.242
VTE site, No. (%)			0.987
Isolated PE	46 (90.2)	130 (90.3)	
Combined PE and DVT	5 (9.8)	14 (9.7)	
Largest artery involved, No. (%)			0.421
Main or lobar	11 (21.6)	34 (23.6)	
Segmental	30 (58.8)	84 (58.3)	
Subsegmental	4 (7.8)	18 (12.5)	
Unknown	6 (11.8)	8 (5.6)	
Hospitalization status, No. (%)			0.678
Inpatient	19 (37.3)	49 (34.0)	
Outpatient	32 (62.7)	95 (66.0)	
Hematologic cancer, No. (%)	6 (11.8)	25 (17.4)	0.348
Cancer type			
NHL	4 (7.8)	5 (3.5)	
Multiple myeloma	0 (0)	8 (5.6)	
Other hematologic	2 (3.9)	12 (8.3)	
Solid cancer, No. (%)	45 (88.2)	119 (82.6)	0.348
Cancer type			
Lung	8 (15.7)	20 (13.9)	
Colorectal	5 (9.8)	8 (5.6)	
Other GI	10 (19.6)	16 (11.1)	
Breast	4 (7.8)	12 (8.3)	

Table 1 (continued)

	Incidental PE (n = 51)	Symptomatic PE (n = 144)	*P*-value
Brain	2 (3.9)	9 (6.3)	
Gynaecological	5 (9.8)	10 (6.9)	
Testicular	2 (3.9)	8 (5.6)	
Other solid	9 (17.6)	36 (25.0)	
Solid cancer stage			0.839
Localized disease	14 (31.1)	39 (32.7)	
Metastatic disease	31 (68.9)	80 (67.2)	
Risk factors for VTE, No. (%)			
Immobilization	23 (45.1)	68 (47.2)	0.794
Recent major surgery	9 (17.6)	31 (21.5)	0.555
Prior history of VTE	2 (3.9)	8 (5.6)	0.649
BMI* > 30 kg/m^2	6 (11.8)	17 (11.8)	0.994
Active chemotherapy	11 (21.6)	29 (20.1)	0.828
Active anti-angiogenic therapy	2 (3.9)	6 (4.2)	1.000
Active hormonal therapy	1 (2.0)	6 (4.2)	0.679

VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep venous thrombosis; NHL, Non-Hodgkin lymphoma; GI, gastrointestinal tract; BMI, body mass index.

* Data on BMI was missing in 5 patients with incidental and 15 patients with symptomatic PE.

Anticoagulation therapy

Details on the type and duration of anticoagulation therapy are provided in table 2. VKA was prescribed as long-term therapy to 45% of patients in the incidental group and 51% of the patients of symptomatic group (p= 0.23).

Considering those patients who survived the first six months after the index PE, in 30% of the incidental patients and 35% of the symptomatic patients, treatment was terminated after six months or earlier. The main reasons for discontinuing therapy were bleeding complications and definitive treatment of the malignancy. In 10% of the incidental patients and 13% of the symptomatic patients, treatment was discontinued after 6 months whilst there was still active malignancy. This was primary a result of evolving institutional treatment guidelines during the inclusion period.

Recurrent VTE

During one year of follow-up, symptomatic recurrent VTE was diagnosed in 5 (9.8%) patients with incidental PE and in 15 (10.4%) patients with symptomatic PE. None of these events were fatal.

The 12-month cumulative recurrent VTE incidence was 13.3% for patients with incidental and 16.9% for patients with symptomatic PE (Figure 1; $p = 0.77$ from the log-rank test).

Table 2. Treatment Pulmonary Embolism

	Incidental PE (n = 51)	Symptomatic PE (n = 144)	*P*-value
Initial treatment, No. (%)			0.06
LMWH	42 (82.4)	87 (60.4)	
UFH	9 (17.6)	55 (38.2)	
VCF	0 (0)	2 (1.4)	
Long-term treatment*, No. (%)			0.225
LMWH	27 (52.9)	58 (40.3)	
VKA	23 (45.1)	74 (51.4)	
Duration of treatment, No. (%)			0.547
3 months or shorter	16 (31.4)	53 † (36.8)	
Death	14 (27.5)	46 (31.9)	
Bleeding complications	2 (3.9)	4 (7.5)	
Physician's judgment to stop treatment	0 (0)	2 (1.4)	
3 – 6 months	17 (33.3)	58 (40.3)	
Death	4 (7.8)	13 (9.0)	
Bleeding complications	1 (2.0)	2 (1.4)	
Malignancy cured	7 (13.8)	20 (13.9)	
Physician's judgment to stop treatment	0 (0)	5 (4.4)	
Reasons for discontinuing treatment not specified	5 (9.8)	18 (12.5)	
6 – 9 months	4 (7.8)	6 (4.2)	
Death	3 (5.9)	5 (3.5)	
Malignancy cured	1 (2.0)	1 (0.7)	
9 – 12 months	1 (2.0)	3 (2.1)	
Death	0 (0)	3 (2.1)	
Physician's judgment to stop treatment	1 (2.0)	0 (0)	
At least 12 months	13 (25.5)	24 (16.7)	

LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VCF, vena cava filter; VKA, vitamin K antagonist.

* 13 patients died before long-term therapy was initiated.

† Information on total treatment duration was missing in 1 patient because of geographical inaccessibility after 4 weeks of follow-up.

After adjustment for age, sex and treatment duration, the HR for recurrent VTE was not statistically significant for symptomatic versus incidental patients (HR: 1.0; 95% CI: 0.4–2.9). Adjustment for the additional risk factors did not materially influence the study results.

Two patients in the group of incidental PE patients had recurrent PE, two patients developed lower-extremity DVT and one patient experienced upper-extremity DVT. In the symptomatic group, eight patients had recurrent PE and seven patients developed lower-extremity DVT.

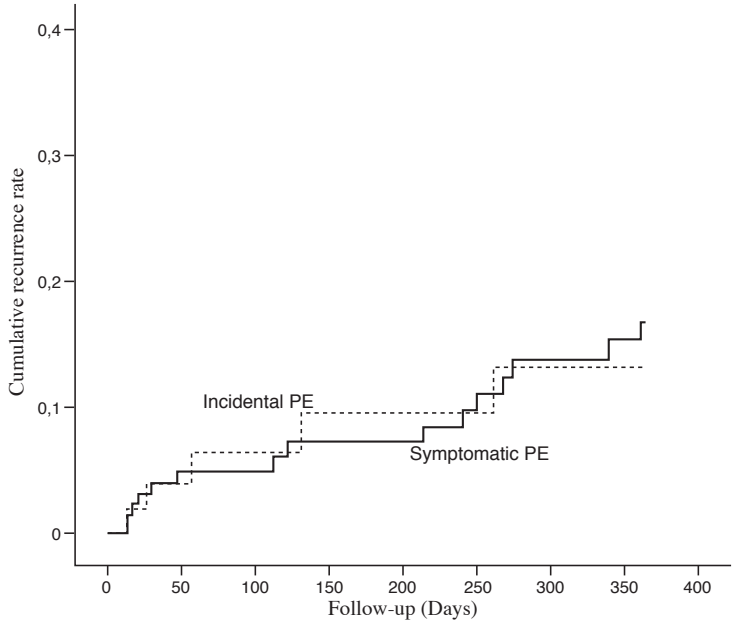

Figure 1. Cumulative risk of recurrent venous thromboembolism for cancer patients with incidental versus symptomatic pulmonary embolism ($p = 0.77$).

In one patient with incidentally detected subsegmental pulmonary embolism, a follow-up CT-scan 8 months later revealed recurrent asymptomatic PE localized in a lobar pulmonary artery. No other recurrent asymptomatic emboli were detected during follow-up of both asymptomatic and symptomatic patients.

In the incidental group, one recurrent VTE event occurred after temporary cessation of anticoagulation therapy and insertion of an inferior vena cava filter because of a surgical intervention. Of the 15 recurrent VTE events in the symptomatic group, two recurred whilst receiving prophylactic LMWH doses. One event (20%) in the incidental group and three (20%) in the symptomatic group occurred while anticoagulation was discontinued after six months whilst there was still active malignancy. All other recurrent events in both groups occurred under adequate anticoagulation therapy.

Bleeding complications

Nine patients with symptomatic and five patients with incidental PE had major bleeding; the respective 12-month cumulative incidences were 12.5% and 8.6% ($p = 0.50$ from the log-rank test; adjusted HR 0.75, 95% CI: 0.2-2.3).

In the incidental group, three patients had intracranial bleeding of whom two patients died, and two patients had gastrointestinal tract bleeding leading to blood transfusion. At time of bleeding, three patients were treated with VKA, one with LMWH and one with UFH. In the symptomatic group, two patients had bleeding at a critical site: one

patient died of fatal intracranial bleeding and one patient had retroperitoneal bleeding. The other bleeding complications caused a significant fall in hemoglobin level or led to blood transfusion; including one hematothorax, one case of severe epistaxis, two intra-abdominal and two gastro-intestinal bleeding, and one post-operative bleeding nine days after a neck surgery. At time of bleeding, three patients received UFH, four patients were treated with VKA and two with LMWH.

Mortality

During follow-up, 27 (52.9%) patients with incidental PE and 76 (52.8%) patients diagnosed with symptomatic PE died. In both groups, the majority of the deaths were a result of progressive cancer (77.8% and 78.5% for patients with incidental and symptomatic PE respectively). In the symptomatic group, the index PE was fatal in six patients.

The respective 12-month mortality risks for patients with incidental and symptomatic PE were 52.9% and 53.3% (Figure 2; $p = 0.70$). The adjusted HR for mortality was not statistically significant for patients with symptomatic versus patients with incidental PE (HR: 1.1; 95% CI: 0.7-1.8).

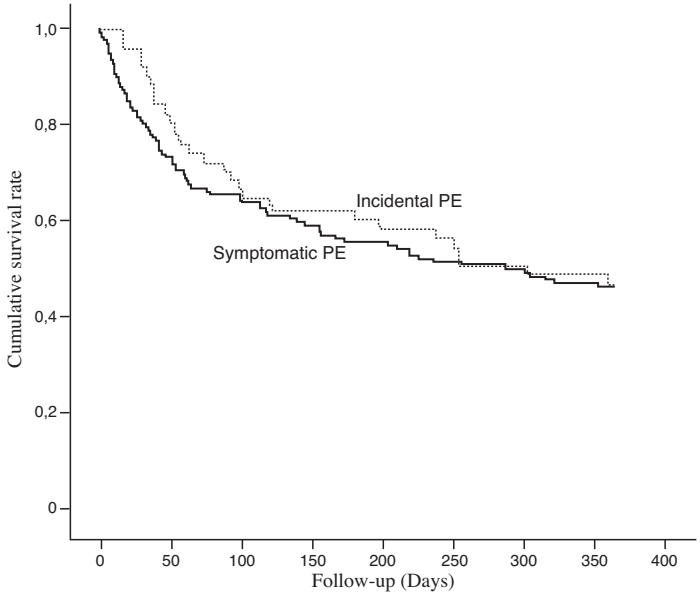

Figure 2. Kaplan-Meier survival curve until overall death for cancer patients with incidental versus symptomatic pulmonary embolism ($p = 0.70$).

DISCUSSION

This study aimed to evaluate the clinical outcome of oncology patients who were incidentally diagnosed with and treated for PE. We found that the one-year recurrence risk for VTE, the risk of major bleeding complications and overall survival in incidental patients were similar to those diagnosed with symptomatic PE.

So far, only few studies addressed the outcome of cancer patients with incidental PE, and those were small, uncontrolled series with limited follow-up. In a retrospective case series, incidental PE was detected in 16 out of 403 oncology patients by reassessing CT scans. Of the 12 patients who did not receive anticoagulant treatment, four developed further thromboembolic disease during an average follow-up of 13 months.[7] In a prospective study, unsuspected PE was detected in 18 out of 407 oncology patients on routine CT-scanning. During six months of follow-up, one patient developed recurrent symptomatic PE.[8] Remarkably, this was the only patient in whom treatment was withheld. Douma and colleagues reported no further thromboembolic events during three months of follow up of three patients with incidental PE; one of these patients was not treated.[9] Compared with these studies, our cohort was larger and our follow-up was longer. Furthermore, our study is the first to directly compare the VTE recurrence rate in cancer patients with incidental PE to those with symptomatic PE.

In the absence of convincing evidence that anticoagulation therapy can be safely withheld, current ACCP guidelines recommended treating patients who are unexpectedly diagnosed with asymptomatic PE exactly as comparable patients with symptomatic PE (Grade 1C).[10] We found that cancer patients with incidental PE, despite receiving anticoagulant treatment, display a high recurrence rate, which was even comparable to those with symptomatic PE. In our view, these results provide indirect evidence for a comparable treatment effect in both groups. However, our study was not designed to definitively determine whether anticoagulation therapy is indicated for these patients. Of note, as international guidelines now recommend treating these patients, performing a randomized controlled trial would probably be very difficult to perform or even regarded unethical.

To date, LMWH has become the agent of choice for the long-term treatment of patients with cancer-associated thrombosis.[11] Resulting from evolving treatment guidelines, a substantial number of patients in both groups received VKA in stead of LMWH. It might therefore be that the found incidence in our study is an overestimation of the incidence if all patients would have been treated according to current guidelines. Still, the patients with symptomatic PE were selected within the same study period and type and duration of anticoagulation treatment did not differ significantly between the groups.

We found that the one-year mortality rates of incidental and symptomatic PE patients were well comparable. These findings are consistent with Dentali et al[12], who found

similar 6-month mortality rates for cancer patients with asymptomatic and symptomatic VTE (51% and 48.6% respectively), which were both significantly higher compared to the mortality rate of cancer patients without VTE (27.1%). Another recent study indicated that the detection of unsuspected PE had a negative impact on survival of cancer patients, compared with matched cancer patients without VTE (HR: 1.5; 95% CI: 1.01-2.27).[13]

Our study has several limitations. First, its retrospective design may enhance information bias. In an attempt to minimize this bias, we used a pre-specified and standardized protocol to thoroughly review all medical charts of included patients and GPs were contacted in case data was incomplete. As our primary outcomes are clearly defined and serious medical events, we assumed that these would be accurately recorded in the medical charts. Second, although we used broad inclusion criteria, the exclusion of untreated incidental patients may restrict the generalisibility of our findings.[14] However, treatment was initiated in the vast majority (96%) of the incidental patients identified in the study period, which is in line with earlier reports.[8] Although we cannot claim complete case ascertainment by relying on ICD-9 codes for the identification of patients diagnosed with PE, a cross-check with the Radiology department for a period of 15 months revealed only one additional patient with incidental PE, and treatment was initiated in this patient. Third, the incidental PE cohort included a relatively limited number of patients in a single-center. Although we did not detect a difference in outcome between the symptomatic and asymptomatic group, our study might be underpowered to detect small differences.

In conclusion, we found similar rates of recurrent VTE, bleeding complications and mortality in cancer patients diagnosed with and treated for incidental PE compared with cancer patients with symptomatic PE. Given the limitations of this retrospective analysis, these findings should be considered hypothesis generating and need to be confirmed prospectively in larger studies.

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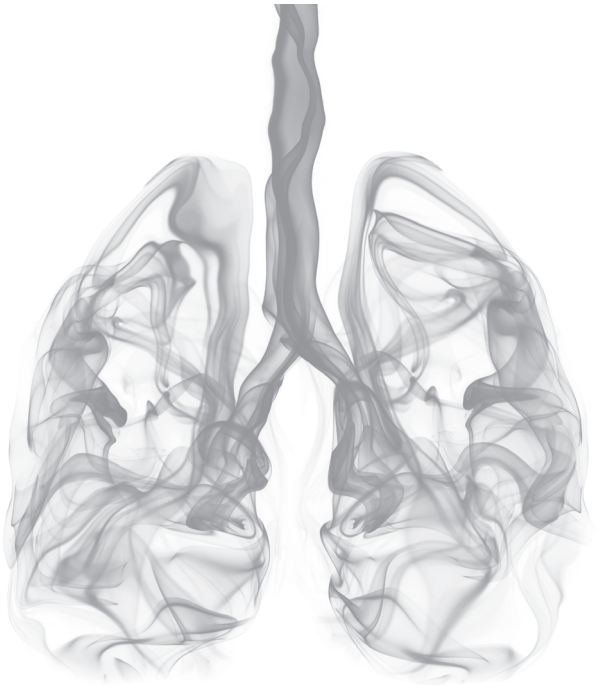
CHAPTER 13

General discussion and summary



This thesis aimed to evaluate and improve the diagnostic work-up of suspected acute pulmonary embolism (PE). Furthermore, this thesis aimed to assess the short- and long-term prognosis of patients diagnosed with acute PE and to investigate the possibility of outpatient treatment in selected low-risk patients. Finally, this thesis aimed to assess the clinical implications of incidentally diagnosed PE. **Chapter 1** provides a general introduction of the diagnosis and management of PE and addresses the topics that require further research.

PART I: DIAGNOSIS OF SYMPTOMATIC PULMONARY EMBOLISM

Chapter 2 reviews the recent advances and remaining pitfalls in the diagnostic workup of patients with suspected acute PE. Establishing a prompt diagnosis of acute PE is challenging due to its non-specific signs and symptoms. To streamline the diagnostic work-up, several clinical decision rules have been proposed in recent years. Of those, the Wells rule is the best validated and therefore most widely practised clinical decision rule. Combined with a normal D-dimer test result, a low pre-test clinical probability, as assessed with the Wells rule, safely rules out acute PE. For patients with a high pre-test probability or elevated D-dimer levels, contrast-enhanced computed tomographic pulmonary angiography (CTPA) is required to either establish or rule out acute PE. It has been postulated that D-dimer testing more frequently yields false negative results in patients with a delay in clinical presentation. Therefore, in **chapter 3**, we aimed to assess the impact of delay in clinical presentation on the safety of excluding PE on the basis of a low clinical probability score and a normal D-dimer test result. In addition we aimed to assess the impact of a delayed presentation on the clinical outcome of patients with PE. In a large cohort of 4044 consecutive patients with clinically suspected PE, delay in clinical presentation was found to be common: 19% of the patients presented with symptoms lasting more than seven days. As the diagnostic failure rate was 0.5% for patients both with and without a delay in presentation, we concluded that PE can still safely be excluded in patients with a delayed presentation on the basis of a clinical decision rule and a normal D-dimer test result. A delayed presentation was associated with a more central location of the PE, although this did not appear to affect the 3-month clinical outcome.

The main drawback of D-dimer testing is its low specificity at its conventional threshold of 500 µg/l, which is approximately 35-40% for high sensitivity assays. As D-dimer levels increase with age, regardless of the presence of PE, the clinical usefulness of D-dimer testing is particularly limited in elderly patients, leading to high numbers of CTPA examinations. In **chapter 4**, we aimed to prospectively validate the efficiency and safety of applying an age-adjusted D-dimer cut-off, defined as a patient's age times 10

in patients aged 50 years or older with clinically suspected PE. For this purpose, a large multicenter, multinational, prospective management outcome study was performed. A total of 3346 patients with suspected PE were included. Among the 2898 patients with a low pre-test probability, 337 patients (11.6%) had a D-dimer between 500 µg/L and their age-adjusted cut-off (95% CI, 10.5%-12.9%). During three months of follow-up, the incidence of venous thromboembolism (VTE) was low: 0.3% (95% CI: 0.1%-1.7%). This study therefore confirms that applying this diagnostic strategy is effective and safe.

PART II: MANAGEMENT AND PROGNOSIS OF SYMPTOMATIC PULMONARY EMBOLISM

The widespread use of multi-detector CTPA, which allows better visualization of segmental and subsegmental pulmonary arteries, has led to an increased detection of small peripheral emboli confined to subsegmental branches of the pulmonary artery tree. It has been doubted whether isolated subsegmental PE (SSPE) is of clinical relevance and requires anticoagulant treatment. Therefore, in **chapter 5**, we compared the risk profile and clinical outcome of patients with SSPE compared to patients with more proximal PE and a reference group of patients in whom PE was suspected but ruled out. No differences were seen in the prevalence of VTE risk factors, the 3-month risk of recurrent VTE (3.6% vs 2.5%; P=0.42), and mortality (10.7% vs 6.5%; P= 0.17) between patients with SSPE and those with more proximal PE. When SSPE patients were compared to patients in whom clinically suspected PE was ruled out, age >60 years, recent surgery, estrogen use, and male gender were found to be independent predictors of SSPE, and patients with SSPE were at an increased risk of VTE during follow-up (hazard ratio: 3.8; 95% CI: 1.3-11.1). This study indicates that patients with SSPE mimic those with more proximally located PE and differ from patients without PE, with regard to their risk profile and clinical outcome.

In recent years, the possibility of treating patients with acute PE at home has emerged. Because the initial prognosis of acute PE can be complicated by serious, potentially life-threatening events, it is of vital importance that careful risk stratification takes place when considering outpatient treatment. For this purpose, several methods for risk stratification are available. In **chapter 6**, the Hestia criteria were compared to the simplified PE severity index (sPESI) for prediction of 30-day mortality. Results showed that both methods had an equally good performance in selecting patients with a low-risk of 30-day mortality. The negative predictive value was 99% for the Hestia rule versus 100% for the sPESI score. However, this study indicated that the Hestia criteria are able to identify a significant proportion of patients who were classified as high-risk with use of the sPESI, who could still be safely treated at home.

To assess whether NT-proBNP, a marker of myocardial stress, would provide additional safety to the Hestia criteria in selecting outpatient treatment candidates, we performed a multicentre randomized trial of which the results are reported in **chapter 7**. A total of 530 patients with acute PE who met the Hestia criteria were either assigned to NT-proBNP testing or to direct discharge. Patients assigned to NT-proBNP testing were initially admitted if NT-proBNP levels were > 500ng/L. The risk of adverse outcome was similar in patients assigned to the NT-proBNP group (0%; 95% CI: 0-1.3%) versus patients assigned to the direct discharge group (1.1%; 95% CI: 0.2-3.2%). None of the patients who experienced an adverse outcome had elevated NT-proBNP levels at baseline. We therefore concluded that selecting PE patients for outpatient treatment with use of the clinical Hestia criteria alone, appears to be as safe as performing additional prognostic assessment with NT-proBNP testing.

In **chapter 8**, we assessed the rate of thromboembolic resolution in patients diagnosed with and treated for acute PE. In this multicenter prospective study of 157 PE patients, we found that complete PE resolution occurred in 84.1% of the patients (95% CI: 77.4–89.4%) after six months of treatment. The presence of residual thromboembolic obstruction was not associated with recurrent VTE (adjusted hazard ratio: 0.92; 95% CI: 0.2–4.1). This study indicates that the incidence of residual thrombotic obstruction following treatment for PE is considerably lower than currently anticipated. Therefore, routine use of follow-up CT-imaging in patients treated for acute PE does not seem warranted.

PART III: DIAGNOSIS AND PROGNOSIS OF INCIDENTAL PULMONARY EMBOLISM

Since computed tomography (CT) imaging techniques have evolved significantly over the past few decades, PE is increasingly detected incidentally in patients in whom PE was not clinically suspected at the time of the CT examination. This is true for cancer patients in particular, who display an increased risk of PE and who frequently undergo CT-scanning for reasons such as tumor staging and treatment evaluation. To determine the clinical relevance of these incidental findings, data on the prognosis of cancer patients with incidental PE is of great importance. **Chapter 9** provides an overview of the scope of this problem and summarizes recent studies addressing the clinical course and outcome of cancer patients with incidental PE. In **chapter 10**, we aimed to assess the accuracy of diagnosing incidental PE. The CT-scans of 62 cancer patients with incidental PE and 19 cancer patients without PE, were reassessed in a blinded fashion by two thoracic radiologists. The level of agreement between the two expert readers was high: they disagreed on the presence of PE in only two patients (3.2%), resulting in a Kappa

statistic of 0.93. Therefore, this study indicates that an incidental PE diagnosis is reliable and highly reproducible.

In **chapter 11**, we aimed to evaluate the current management of incidental PE by distributing a questionnaire to a large number of physicians worldwide. All of the 183 physicians that responded reported that they would treat a patient with central incidental PE with anticoagulants. In case of segmental PE, 98% would initiate treatment, regardless of the presence or absence of malignancy. When a patient with subsegmental PE (SSPE) was presented, 11% (95%CI: 6-15%) and 28% (95%CI: 21-35%) opted not to treat in the presence and the absence of malignancy respectively. This study reveals that most physicians would treat a patient with incidental PE. However, uncertainty exists about the need for anticoagulants in patients with incidental SSPE.

To assess the clinical implications of incidental PE in cancer patients, we compared 51 cancer patients with incidental PE and 144 with symptomatic PE in **chapter 12.** All patients included in this study received anticoagulant therapy. We did not find a difference in the one year cumulative risk of symptomatic recurrent VTE in the incidental PE group compared to the symptomatic PE patients (13.3% and 16.9% respectively, P = 0.77). In addition, we observed similar one-year mortality rates in incidental PE patients (52.9%) compared to symptomatic PE patients (53.3%; P = 0.7). These findings suggest that incidental PE mimics symptomatic PE with regard to the long-term clinical outcome, thereby justifying a similar management approach.

FUTURE PERSPECTIVES

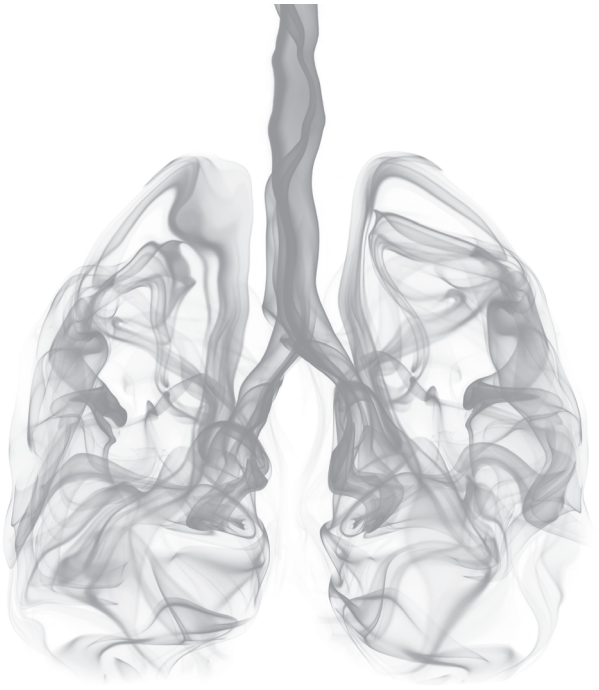
Current diagnostic algorithms, combining clinical probability estimation with D-dimer testing and imaging tests, are very safe for excluding PE but require high numbers of CT-examinations. In view of cost- and time-saving as well as safety issues, future studies should attempt to reduce the number of required imaging tests without affecting the sensitivity of current diagnostic algorithms. At present, the YEARS study is being undertaken to investigate a simplified diagnostic algorithm, with a higher D-dimer cut-off for patients with a low pre-test probability. If this algorithm is found to be safe and is implemented in clinical practice, the need for CTPA will likely be reduced.

As for the management of acute PE, the most important development in recent years is the introduction of a new class of anticoagulant agents: the non-vitamin K-dependent oral anticoagulants (NOACs). These agents overcome several of the disadvantages of vitamin K antagonists (VKAs), including its slow onset and offset of action, many interactions with food and drugs, and the need for close monitoring and frequent dose adjustments. The efficacy and safety of NOACs have been evaluated in large, well-designed randomized clinical trials, which demonstrated that these agents are at least non-inferior

compared to VKAs. However, experience with these drugs in large patient populations is lacking, and real-world patient outcomes will need to be carefully monitored. Furthermore, prospective management studies are required to assess the potential of NOACs for outpatient treatment of low-risk PE. As NOACs do not require laboratory monitoring and continuous dose-adjustment, these agents may further facilitate the management of acute PE on an outpatient basis.

CHAPTER 14

Nederlandse samenvatting



Dit proefschrift heeft als doel de diagnostiek van patiënten met een klinische verdenking op een acute longembolie te evalueren en te verbeteren. Daarnaast worden in dit proefschrift de uitkomsten van patiënten met longembolie bestudeerd en de mogelijkheid tot thuisbehandeling van laag-risico patiënten geëvalueerd. Tot slot worden de klinische consequenties van per toeval gediagnosticeerde longembolieën beschreven. **Hoofdstuk 1** geeft een algemeen overzicht van de diagnostiek en behandelingsstrategieën van de acute longembolie en adresseert de gebieden waarin nog verder onderzoek noodzakelijk is.

DEEL I: DIAGNOSTIEK NAAR SYMPTOMATISCHE LONGEMBOLIEËN

Hoofdstuk 2 beschrijft de recente ontwikkelingen en identificeert valkuilen bij de diagnostiek van patiënten met een klinische verdenking op een acute longembolie. Een verdenking op een acute longembolie komt in de dagelijkse praktijk veel voor. Het tijdig stellen van de diagnose wordt bemoeilijkt door de weinig specifieke klachten en symptomen. Om het diagnostisch proces te vereenvoudigen en standaardiseren zijn er verschillende klinische beslisregels ontwikkeld. De Wells-regel is de best gevalideerde en wereldwijd meest toegepaste klinische beslisregel. Gecombineerd met een normale D-dimeertest uitslag, is een lage klinische voorafkans zoals berekend met de Wells-regel in staat de diagnose longembolie veilig uit te sluiten. Voor patiënten met een hoge klinische voorafkans of een verhoogde D-dimeer waarde, is een CT-scan noodzakelijk om de diagnose longembolie te bevestigen dan wel uit te sluiten. In de literatuur wordt gesuggereerd dat de D-dimeertest vaker een vals-negatieve uitslag geeft bij patiënten die zich presenteren met reeds langer bestaande klachten. In **hoofdstuk 3** trachten wij de consequenties van een vertraagde klinische presentatie op de veiligheid van de diagnostische strategie, bestaande uit de Wells-regel en D-dimeertest, te onderzoeken. Daarnaast evalueert deze studie de impact van een vertraagd gestelde diagnose longembolie op de klinische uitkomsten van patiënten met longembolie. Wij bestudeerden hiervoor een groot cohort van 4044 met een klinische verdenking op een longembolie. In 19% van de patiënten bestonden de klachten al tenminste 7 dagen, hetgeen wij definieerden als een vertraagde klinische presentatie. Zowel voor patiënten met als zonder vertraging in klinische presentatie bedroeg de vals-negatief ratio 0.5%. Wij concludeerden hieruit dat de combinatie van een lage voorafkans en normale D-dimeertest uitslag bij patiënten met een vertraagde klinische presentatie nog steeds een veilige methode is om de diagnose longembolie te verwerpen. Een vertraagde klinische presentatie was echter wel geassocieerd met een meer centrale locatie van de longembolieën, hoewel dit de klinische uitkomsten gedurende drie maanden follow-up niet leek te beïnvloeden.

De belangrijkste tekortkoming van de D-dimeertest is de lage specificiteit. Bij de gebruikelijke afkapwaarde van 500 µg/l, bedraagt de specificiteit circa 35-40% voor de hedendaags gebruikte hoog sensitieve assays. Omdat D-dimeer waarden in het bloed toenemen met de leeftijd, ongeacht de aanwezigheid van longembolieën, is de klinische bruikbaarheid van de D-dimeertest met name beperkt bij oudere patiënten. Dit heeft als consequentie dat bij oudere patiënten met een verdenking longembolie vaker CT-scans geïndiceerd zijn om longembolieën uit te sluiten. In **hoofdstuk 4** beoogden wij de effectiviteit en veiligheid van een recent voorgestelde leeftijdsafhankelijke D-dimeer afkapwaarde, te weten de leeftijd van de patiënt vermenigvuldigd met 10 voor patiënten ouder dan 50 jaar, te valideren. Hiervoor hebben wij een grote prospectieve studie uitgevoerd in verschillende ziekenhuizen gesitueerd in Nederland, België, Zwitserland en Frankrijk. In totaal werden 3346 patiënten met een klinische verdenking longembolie ingesloten. Onder de 2898 patiënten met een lage klinische voorafkans waren er 337 patiënten (11.6%) met een D-dimeer waarde tussen de 500 µg/L en hun leeftijdsafhankelijke afkapwaarde (95% betrouwbaarheidsinterval (BI): 10.5-12.9%). Gedurende 3 maanden follow-up was de incidentie veneuze trombo-embolie laag: 0.3% (95% BI: 0.1%-1.7%). Hiermee bevestigt deze studie dat deze diagnostische strategie veilig is en leidt tot een aanzienlijke reductie in het aantal benodigde CT-scans.

DEEL II: BEHANDELING EN PROGNOSE VAN SYMPTOMATISCHE LONGEMBOLIEËN

Het wijdverspreide gebruik van multidetector CT-scanners, welke beter in staat zijn de perifere pulmonale arteriën af te beelden, heeft geleid tot een toename in de detectie van kleine longembolieën geïsoleerd tot de subsegmentale vertakkingen van de pulmonaal arteriën. Aangezien deze kleine longembolieën vroeger veelal niet werden gediagnosticeerd en daarom niet werden behandeld, bestaat er onder artsen onzekerheid over de klinische betekenis van deze bevindingen. Om te onderzoeken of een subsegmentale longembolie kan worden beschouwd als een mildere vorm van trombo-embolische ziekte, of zelfs als een klinisch irrelevante bevinding, vergeleken wij in **hoofdstuk 5** patiënten met subsegmentale longembolie met patiënten met meer proximale longembolieën en met patiënten zonder longembolie. Hierbij werd gekeken naar het trombo-embolische risicoprofiel, de symptomen en prognose. Er werden geen verschillen gezien in de prevalentie van risicofactoren voor veneuze trombose en klinische uitkomsten tijdens 3 maanden follow-up in termen van recidief veneuze trombo-embolie (3,6% versus 2,5%; p=0,42) en mortaliteit (10,7% versus 6,5%) tussen patiënten met een subsegmentale longembolie en die met een meer proximaal gelokaliseerde longembolie. In vergelijking met patiënten zonder longembolie werden leeftijd >60

jaar, recente operatie, oestrogeengebruik en mannelijk geslacht geïdentificeerd als onafhankelijke risicofactoren voor subsegmentale longembolie; daarnaast hadden zij een verhoogd risico op veneuze trombo-embolie tijdens follow-up (hazardratio 3,8; 95%-BI 1,3-11,1). Deze studie suggereert dat zowel het risicoprofiel als de klinische uitkomsten van patiënten met subsegmentale longembolie sterk overeenkomen met patiënten met een meer proximale longembolie.

Van oudsher begint de behandeling van patiënten met een bewezen longembolie in het ziekenhuis. Recente studies hebben echter gesuggereerd dat patiënten met acute longembolie in sommige gevallen veilig thuis kunnen worden behandeld. Wanneer thuisbehandeling bij deze patiënten wordt overwogen, is het van vitaal belang dat die patiënten worden geïdentificeerd bij wie het risico op complicaties op korte termijn laag is. Voor dit doeleinde zijn verschillende manieren van risicostratificatie onderzocht. In **hoofdstuk 6** vergeleken wij de eerder door ons voorgestelde Hestia criteria met de gesimplificeerde "Pulmonary Embolism Severity Index" (sPESI) voor de predictie van mortaliteit binnen 30 dagen. Wij toonden aan dat beide methoden even goed presteerden in het selecteren van patiënten met een laag risico op 30-dagen mortaliteit. De negatief voorspellende waarde was 99% voor de Hestia criteria en 100% voor de sPESI. Deze studie suggereert echter dat de Hestia criteria in staat zijn een groter gedeelte van de longembolie patiënten als laag-risico te classificeren, bij wie thuisbehandeling nog steeds veilig is.

Om te onderzoeken of het bepalen van NT-proBNP waarden in het bloed, hetgeen een biomarker vormt voor myocardiale stress, van meerwaarde is in de risicostratificatie toegevoegd aan de klinische Hestia criteria, voerden wij een gerandomiseerde studie uit. De resultaten van deze studie zijn beschreven in **hoofdstuk 7**. In totaal werden 530 patiënten met acute longembolie die voldeden aan de Hestia criteria gerandomiseerd tussen het verrichten van een NT-proBNP bepaling of direct ontslag. Patiënten die werden toegewezen aan het ondergaan van een NT-proBNP bepaling werden in het ziekenhuis opgenomen wanneer de NT-proBNP waarde meer dan 500 ng/L bedroeg. Het risico op "adverse outcome" na één maand, hieronder rekenden wij Intensive Care opnames en longembolie- en bloeding gerelateerde mortaliteit, was vergelijkbaar in beide groepen (0%; 95% BI: 0-1.3%). Geen van de patiënten met adverse outcome had verhoogde NT-proBNP waarden bij aanvang van de studie. Ook bestond er geen significant verschil in het risico op majeure bloedingen, recidief veneuze trombo-embolie of mortaliteit na 3 maanden tussen beide groepen. Wij concluderen daarom dat risicostratificatie voor thuisbehandeling van longembolie patiënten op basis van de Hestia criteria alleen, even veilig is als op basis van de Hestia criteria met hieraan toegevoegd een NT-proBNP bepaling.

In **hoofdstuk 8** onderzochten we de mate waarin trombo-embolische resolutie op treed bij patiënten die behandeld zijn voor een acute longembolie. In deze prospectieve multi-center studie namen 157 longembolie patiënten deel. Na zes maanden behandeling trad bij 84% van de patiënten (95% BI: 77.4–89.4%) complete trombo-embolische resolutie op. De aanwezigheid van residuale trombo-embolische obstructie was niet geassocieerd met het optreden van recidief VTE (gecorrigeerde hazard ratio: 0.92; 95% CI: 0.2–4.1). Deze studie impliceert dat de mate van residuale trombo-embolische obstructie aanzienlijk lager is dan tot nu toe werd aangenomen. Het routinematig uitvoeren van follow-up CT-scans bij patiënten die behandeld zijn voor een acute longembolie lijkt dan ook niet geïndiceerd.

DEEL III: DIAGNOSE EN PROGNOSE VAN INCIDENTELE LONGEMBOLIE

Doordat CT beeldvormingstechnieken zich de afgelopen decennia sterk hebben ontwikkeld, worden longembolieën steeds vaker als toevalsbevinding vastgesteld, zonder dat hier ten tijde van de CT-scan een klinische verdenking op bestaat. In dit geval spreekt men in de literatuur over 'incidentele longembolieën'. Dit komt met name relatief frequent voor bij kankerpatiënten, die enerzijds een verhoogde kans hebben op het ontwikkelen van VTE en anderzijds frequent CT-onderzoek ondergaan ter stadieren van de tumor en ter evaluatie van de behandeling. Om de klinische relevantie van deze toevalsbevindingen te bepalen, zijn gegevens over de prognose van kankerpatiënten met incidentele longembolieën van belang. **Hoofdstuk 9** geeft een overzicht over de omvang van dit probleem en geeft een samenvatting van recente studies die de klinische uitkomst van kankerpatiënten met incidentele longembolieën beschrijven. In **hoofdstuk 10** hebben we getracht de nauwkeurigheid van het stellen van de diagnose incidentele longembolie vast te stellen. Hiervoor werden de CT beelden van 62 kankerpatiënten bij wie per toeval een diagnose longembolie was gesteld en 19 kankerpatiënten zonder longembolie geblindeerd geëvalueerd door twee radiologen met veel ervaring op het gebied van longembolie diagnostiek. De mate van overeenkomst tussen beide radiologen was hoog: slechts bij 1 patiënt was er geen overeenstemming over de aanwezigheid van longembolie (3.2%), wat resulteerde in een Kappa van 0.93. Deze studie laat daarom zien dat het stellen van de diagnose incidentele longembolie betrouwbaar en goed reproduceerbaar is.

Door wereldwijd onder artsen een vragenlijst te verspreiden hebben we getracht de huidige behandelstrategie van incidentele longembolieën te evalueren. De resultaten van deze enquête zijn beschreven in **hoofdstuk 11**. Alle 183 respondenten gaven aan dat zij antistollingstherapie zouden starten wanneer het een incidentele longembolie in de centrale pulmonale arteriën betrof. In het geval van een segmentale longembolie

zou 98% van de ondervraagden behandeling starten, ongeacht de aanwezigheid van een maligniteit. Wanneer het ging om een incidentele longembolie op subsegmentaal niveau, zou 11% van de artsen geen behandeling starten indien het patiënt met maligniteit betrof, en 28% wanneer het ging om een patiënt zonder maligniteit. Deze studie laat dus zien dat artsen in het algemeen besluiten tot antistollingsbehandeling wanneer zij geconfronteerd worden met een patiënt met incidentele longembolie. Er bestaat echter enige onzekerheid over de noodzaak tot antistollingstherapie bij patiënten met per toeval gevonden subsegmentale longembolieën.

Om de klinische implicaties van incidentele longembolieën bij kankerpatiënten te bepalen, hebben wij 51 kankerpatiënten met incidentele longembolie vergeleken met 144 kankerpatiënten met symptomatische longembolie. De resultaten van deze studie zijn beschreven in **hoofdstuk 12**. Alle patiënten geïncludeerd in deze studie werden na vaststellen van de diagnose longembolie behandeld met antistollingstherapie. Er werd geen verschil gevonden in het risico op recidief VTE gedurende één jaar follow-up: respectievelijk 13.3% voor patiënten met incidentele longembolie versus 16.9% voor patiënten met symptomatische longembolie (P =0.77). Tevens werd er geen verschil gezien in overleving tussen beide groepen, na één jaar bedroeg de mortaliteitskans respectievelijk 52.9% en 53.3% (P=0.70). Hiermee suggereert deze studie dat de prognose van kankerpatiënten met incidentele longembolie sterk gelijkt op die van kankerpatiënten met symptomatische longembolie. Een gelijke behandelstrategie voor beide patiënten groepen valt dan ook te verdedigen.

TOEKOMSTPERSPECTIEF

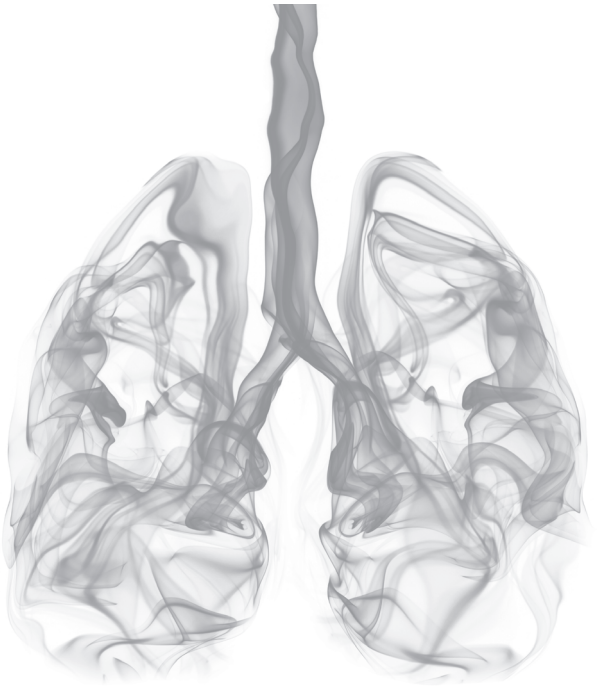
De huidige diagnostische algoritmes, waarin een klinische beslisregel wordt gecombineerd met een D-dimeertest, zijn zeer veilig om de diagnose longembolie uit te sluiten. Echter dient hierbij frequent gebruik te worden gemaakt van beeldvorming, tegenwoordig veelal in de vorm CT-scans. Met het oog op kosten- en tijdsbesparing, dienen toekomstige onderzoeken te evalueren of het mogelijk is de noodzaak tot beeldvorming te reduceren, zonder dat hiermee de sensitiviteit van de diagnostische algoritmes verminderd. In de Years studie, een grote Nederlandse registratie studie, wordt onderzocht of het veilig is een hogere D-dimeer afkapwaarde te hanteren bij patiënten met een lage klinische voorafkans, waarbij gebruik wordt gemaakt van een vereenvoudigd diagnostisch algoritme. Indien veilig bevonden, kan dit leiden tot een reductie van het aantal benodigde CT-scan onderzoeken.

Voor wat betreft de behandeling van de acute longembolie, is de belangrijkste ontwikkeling die zich de afgelopen jaren heeft voorgedaan de introductie van een nieuwe klasse orale antistollingsmiddelen: de niet-vitamine K afhankelijke orale anticoagulantia

(NOACs). Deze nieuwe middelen komen tegemoet aan enkele van de nadelen van de vitamine K-antagonisten, te weten hun trage werkingsmechanisme, vele interacties met voedingsmiddelen en andere medicamenten en de noodzaak tot nauwlettend monitoren en frequente dosis aanpassingen. Daarnaast vormen NOACs een aantrekkelijk optie om thuisbehandeling van longembolie patiënten verder te vereenvoudigen. De effectiviteit en veiligheid van de NOACs is geëvalueerd in een aantal grote, adequaat opgezette gerandomiseerde studies, waaruit is gebleken dat NOACs tenminste non-inferieur zijn aan vitamine K-antagonisten. Grootschalige ervaring met deze nieuwe geneesmiddelen ontbreekt echter nog, derhalve dienen gegevens uit de routinematige klinische praktijk zorgvuldig te worden geregistreerd en geëvalueerd.

APPENDICES

List of publications
Dankwoord
Curriculum vitae



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CURRICULUM VITAE

Paul Louis den Exter werd geboren op 7 augustus 1985 te Rotterdam. In 2003 behaalde hij zijn Atheneum diploma aan scholengemeenschap Spieringshoek te Schiedam. In datzelfde jaar startte hij met de studie Geneeskunde aan de Universiteit Leiden. In 2008 vingen zijn coschappen aan. Zijn semi-artsstage liep hij op de afdeling Algemene Interne Geneeskunde van het Leids Universitair Medisch Centrum. Aansluitend verrichte hij, tijdens zijn wetenschapsstage op dezelfde afdeling, onderzoek naar de behandeling van veneuze tromboembolie bij patiënten met maligniteit. Dit heeft geresulteerd in een scriptie getiteld: "Clinical course of incidentally diagnosed pulmonary embolism in patients with malignancy". Na het behalen van zijn artsexamen in oktober 2010, zette hij zijn onderzoek voort als arts-onderzoeker op de afdeling Trombose en Hemostase van het Leids Universitair Medisch Centrum onder begeleiding van Prof.dr. M.V. Huisman. De resultaten van deze werkzaamheden zijn beschreven in dit proefschrift. In september 2014 is hij begonnen met de opleiding tot internist in het Bronovo Ziekenhuis te 's-Gravenhage (opleiders: Dr. Y.W.J. Sijpkens, Prof.dr. J.W. de Fijter).