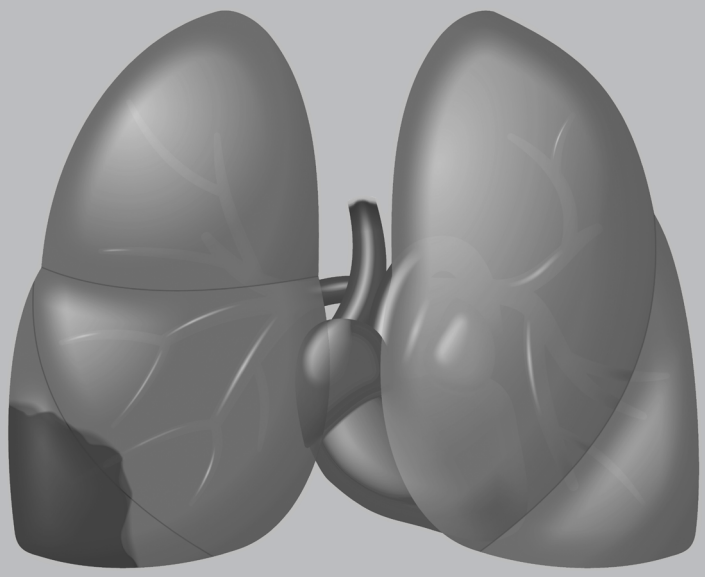
A MORE GRANULAR VIEW ON PULMONARY EMBOLISM

Inge C.M. Mos



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A More Granular View on Pulmonary Embolism

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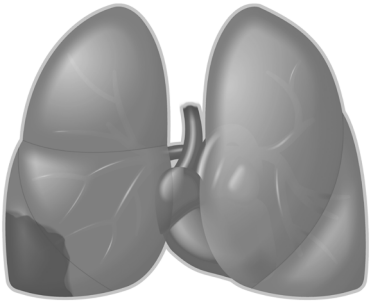
CHAPTER 1

General introduction



INTRODUCTION

Pulmonary embolism (PE) is characterized by an obstruction of the pulmonary arteries with a thrombotic embolus. These pulmonary emboli commonly originate from thrombi of the deep venous system of the lower extremities. The phenomenon venous thrombo-embolism (VTE) consisting of both deep vein thrombosis (DVT) and PE, was first described by Laennec, whereas Virchow was the first to coin the term pulmonary embolus in 1846.[1] PE is a potentially fatal condition which requires a rapid and correct diagnosis and treatment with anticoagulants that could prevent morbidity and mortality. It is important to treat patients with PE, but also to withheld treatment with concomitant bleeding risks to patients without PE. However, with varying and non-specific symptoms, clinical recognition is challenging, making objective testing a necessity in patients with clinical suspicion of PE. The diagnosis of PE can only be confirmed in 20 to 30% of the patients with a clinical suspicion of PE, and has an incidence of 0.6-1.2 per 1000 inhabitants per year.[2]

Clinical suspicion of PE arises in the majority of patients with presentation of sudden onset of dyspnea without an apparent cause (approximately 80%), acute (pleuritic) chest pain which worsens with breathing (52%), or less commonly occurring symptoms such as syncope, cough or hemoptysis.[3] Common indicators are tachypnea, tachycardia or the presence of a swollen, red leg.

Diagnostics in patients with suspected PE has been a subject of research for many years and the first objective diagnostic method became available in the 60s with the introduction of pulmonary angiography[4,5], followed by the ventilation-perfusion scintigraphy (1968) and helical computed tomography (CT).[6,7] CT-scanning is applicable since 1992, and widely applied for diagnosis nowadays. The diagnosis derived from CT imaging is often more conclusive since it also has the possibility to reveal an alternative diagnosis than PE. This is in contrast to ventilation perfusion scintigraphy, which has a high percentage of non-conclusive results. However, CT-scanning has drawbacks, including exposure to radiation, the possibility of allergic reactions to venous contrast as well as nephrotoxicity.

The development of clinical decision rules (CDRs) and D-dimer tests has made it possible to limit the use of CT-scanning. A CDR stratifies patients with suspected PE to a low or a high pretest probability of having PE according to a predefined algorithm using information from clinical history and physical examination. The first and one of the best validated and widely integrated CDRs is the Wells rule.[8] In addition to CDRs, a D-dimer blood test can be used. D-dimer is a degradation product of fibrin and indirectly indicates activation of blood coagulation. An elevated D-dimer concentration is an indication of the presence of thrombosis. However, this test is nonspecific; elevation

can also be found in patients with other conditions like malignancy, pregnancy or an infection. A low clinical probability according to a CDR combined with a normal D-dimer test result safely excludes PE without the need for further imaging. In case of high clinical probability according to the CDR or abnormal D-dimer test, further imaging is necessary to confirm or rule out the diagnosis of PE. Several algorithms integrating CDRs, D-dimer testing and imaging modalities have been developed and focus on excluding PE in a safe and efficient way. The Christopher study for instance revealed that CT-scanning can be avoided in approximately one third of the patients by combining an unlikely clinical probability and a normal D-dimer test.[9]

According to current guidelines, patients with proven PE should be admitted to the hospital and start treatment with anticoagulants. Standard treatment consists of at least five days of weight based therapeutic dose low molecular weight heparin along with vitamin K antagonists. After approximately one week, the low molecular weight heparin is discontinued while the vitamin K antagonist is continued for a period of three to six months with a target international normalized ratio (INR) in the therapeutic range (2.0-3.0).[10] For hemodynamically instable patients more aggressive treatment could be necessary, like thrombolytic treatment or thrombectomy. Risk-stratification could help to identify patients who could benefit from more intensive treatment, and on the other hand, some patients might be treated less aggressively at home.

OUTLINE OF THIS THESIS

The first part of this thesis focuses on the diagnosis of PE. An overview of the current diagnostic tools available in patients with clinically suspected acute PE to exclude or confirm the diagnosis is presented in **chapter 2**. **Chapter 3** of this thesis describes the simplification of a recently developed CDR, the revised Geneva score, and its validation for safety and clinical utility for the exclusion of PE. Simplification by awarding one point for all variables was performed because the individual weights of the CDR variables from the revised Geneva score are difficult to memorize and could lead to miscalculations in an acute setting. Four recently introduced and widely used CDRs are prospectively compared for the exclusion of PE in combination with D-dimer testing in **chapter 4**. The use of CDRs decreases the need for imaging techniques involving intravenous contrast and radiation. Several CDRs are available of which the Wells rule and revised Geneva score are well established. Both scores have been simplified, facilitating an easy computation of the CDR score. The four scores have never been directly compared for safety and clinical utility of excluding PE in combination with a D-dimer test. Therefore, we performed a prospective multi-center study in patients suspected of PE to directly compare the performance of

the four CDRs in excluding PE in combination with D-dimer testing. Currently, CT pulmonary angiography (CTPA) is the radiological imaging test of choice for suspected PE. It has an excellent sensitivity and specificity for diagnosing acute PE. However, concern for false negative results have raised, especially in patients with a high clinical pretest probability for PE[3]. Therefore, we have studied the safety of withholding anticoagulant treatment in patients with suspected acute PE and a strict indication for CTPA, i.e. likely or high clinical probability or an elevated D-dimer concentration, in whom CTPA revealed no PE. In addition, we have evaluated the additional value of performing compression ultrasonography of the legs, subsequent to normal CTPA to exclude DVT before deciding to withhold treatment. The results of this study are described in **chapter 5**.

Part two of this thesis focuses on recurrent acute PE. Patients being treated for PE are at increased risk for developing a recurrent PE. Although studies have reported on the cumulative incidence of recurrent VTE, no study has assessed the incidence of recurrent VTE in a well defined population. The epidemiology in this group of patients is of particular interest because of implications for prevention of morbidity and mortality, and consequences of management with the indication for prolonged anticoagulant treatment with associated bleeding risks and costs. The aim of **chapter 6** was to determine the incidence of acute recurrent VTE in a defined general population and to assess this incidence according to age and gender. Diagnostic strategies in patients with clinically suspected acute PE are well defined. However, the value in patients presenting with recurrent symptoms has not been established. In **chapter 7** the safety of withholding anticoagulant treatment in patients, in whom recurrent acute PE was excluded on the basis of a of a simple diagnostic algorithm using the Wells CDR, quantitative D-dimer test and CTPA, was evaluated.

In **chapter 8**, we investigate the predictive value for adverse clinical events of the biomarker (N-terminal-pro-) brain-type natriuretic peptide, which is a marker of ventricular overload, in patients with acute PE. Obstruction of the pulmonary arteries causes an increase in right ventricular afterload and might induce right ventricle enlargement and dysfunction, depending on the extent of the embolus load and comorbid conditions.

Finally, according to current guidelines, patients with proven PE will be admitted to the hospital and start with anticoagulant treatment. It may be possible to identify patients with a low risk for complications who may be treated safely at home, like the current standard for patients with DVT of the lower extremities. We conducted a cohort study in patients with objectively proven acute PE. Patients who met predefined criteria were considered as low risk patients and were treated at home. These results are presented in **chapter 9**. The findings of this thesis including the limitations and implications are discussed in **chapter 10**. This final chapter also offers a perspective for future research.

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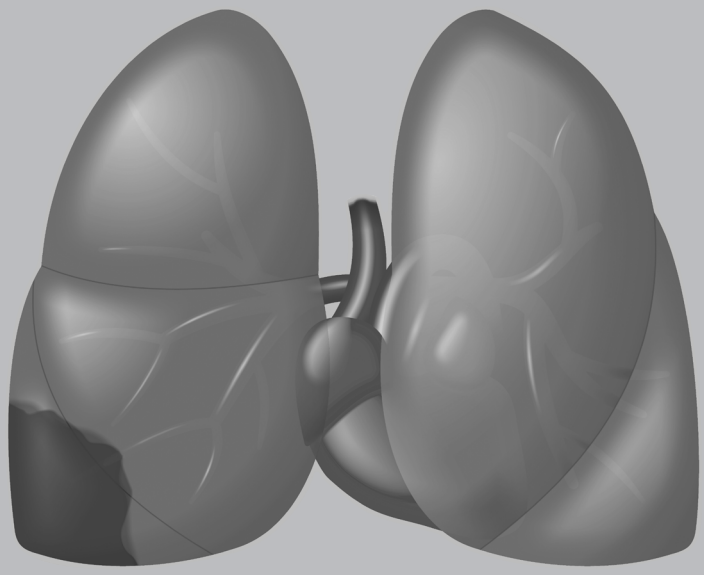
PART I

Diagnostic Management of Acute Pulmonary Embolism

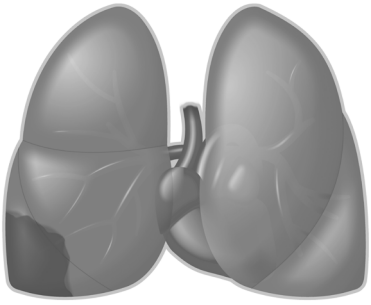


CHAPTER 2

Update on diagnostic techniques for the diagnosis of pulmonary embolism

I.C.M. Mos, F.A. Klok, L.J.M. Kroft and M.V. Huisman

Expert Opinion On Medical Diagnostics, 2011;5:49-61



ABSTRACT

Importance of the field

The clinical suspicion of acute pulmonary embolism (PE) is frequently raised. However, the diagnosis PE is confirmed in only 20-30% of these patients. The high incidence in addition to the potential harm from false positive or negative diagnostic decisions, underlines the importance of a standardized diagnostic algorithm with high sensitivity as well as specificity.

Areas covered in this review

This article reviews the diagnostic tests for the diagnosis of PE.

What the reader will gain

This review provides an overview of the different clinical decision rules (CDRs), D-dimer tests and imaging techniques in patients suspected of PE. Furthermore, the diagnostic process in patients with clinically suspected recurrent PE, suspicion during pregnancy and new research areas will be discussed.

Take home message

Various diagnostic tests are available to detect or exclude PE with good accuracy. CDRs and D-dimer tests play an important role in the exclusion of PE. Neither is sufficient as single test, but the combination of an "unlikely" clinical prediction and a normal D-dimer test result safely excludes PE. In case of a high CDR score and/or an elevated D-dimer concentration, additional imaging is necessary with multi-slice computed tomography as first choice modality.

INTRODUCTION

Venous thromboembolism (VTE), including both pulmonary embolism (PE) and deep venous thrombosis (DVT), is the third most common cardiovascular disorder in industrialized countries and in addition, a potentially fatal one.[1] The incidence of PE is 0.6-1.2 per 1000 inhabitants per year.[2] The diagnosis of PE can only be confirmed in 20-30% of the patients with a clinical suspicion of PE.[3,4] The signs and symptoms of PE are diverse and non-specific. Clinical suspicion of PE arises in approximately 80% of patients with eventually proven PE with presentation of sudden onset of dyspea without an apparent cause. Other symptoms are acute (pleuritic) chest pain worsening with breathing (present in 52%), or less frequent syncope, cough or hemoptysis.[5] Common signs are tachypnea, tachycardia or the presence of a swollen and red leg. Objective diagnostics are very important, because of the increased risk on morbidity and mortality when the diagnosis is missed, and because of the risk of bleeding in case of anticoagulant use. Mortality due to PE if left untreated is not precisely known. One small study in 1960 reported an outcome of 26% fatal PE in these patients.[6] The 3-month mortality ranges from 6-11% in patients with hemodynamically stable PE on anticoagulant treatment, to approximately 30% in hemodynamically unstable patients receiving treatment for PE.[7]

Various diagnostic tests are available to confirm or exclude PE. Nowadays, diverse tests have been integrated in diagnostic algorithms. The combination of a clinical decision rule (CDR), which provides a standardized determination of the clinical probability of the disease based on medical history and physical examination, and a D-dimer test comprise the initial diagnostic steps in patients with suspected PE. Depending on the results of these tests, additional imaging testing should be performed, including conventional angiography, computed tomography pulmonary angiography (CTPA), ventilation perfusion (V/Q) scintigraphy or magnetic resonance angiography (MRA).

In this review, the role of the CDR, D-dimer test and different imaging modalities in the diagnostic management of patients with suspected PE is discussed. Finally, new areas of research are explored.

CLINICAL DECISION RULES

The diagnostic management of acute PE represents a challenge, since the signs and symptoms of PE are various and largely nonspecific (e.g. dyspnea, pleuritic chest pain and palpitations). Clinical probability by implicit evaluation of an experienced clinician has a reasonably good accuracy but decreases with less experienced physicians and is subject of interobserver variability.[8-10] To simplify and standardize the diagnostic process, several CDRs have been developed to evaluate the pretest probability of patients

suspected of having PE. The best validated and widely integrated decision rules are the original Wells rule, the Geneva score and the revised Geneva score.[11-13] The original Wells rule is composed of seven items, obtained from medical history and physical examination and one subjective variable, by which the physician must consider the possibility of an alternative diagnosis for the patient's complaints (Table 1).[11] This latter variable carries a major weight in the score and is often debated because of its subjective nature.[14] On the other hand, it permits the clinician to use other test results and symptoms that are not considered in the score.[9] The Geneva score consist of 13 objective items. The major

Table 1. Clinical decision rules.

The Geneva score [12]		**Revised Geneva score[13]**			**Wells rule[11]**		
Items	**Score**	**Items**	**Original score**	**Simplified score**	**Items**	**Original score**	**Simplified score**
Previous PE or DVT	2	Previous DVT or PE	3	1	Previous PE or DVT	1.5	1
Heart rate > 100/min	1	Heart rate - 75 – 94/min - ≥95/min	 3 5	 1 2	Heart rate >100/ min	1.5	1
Recent surgery	3	Surgery or fracture within 1 month	2	1	Surgery or immobilization < 4 weeks	1.5	1
Atelectasis	1	Hemoptysis	2	1	Hemoptysis	1	1
Elevated hemidiaphragm	1	Active malignancy	2	1	Active malignancy	1	1
PaCO2* - < 4.8 kPa - 4.8-5.19 kPa	 2 1	Unilateral lower limb pain	3	1	Clinical signs of DVT	3	1
PaO2* - < 6.5 kPa - 6.5-7.99 kPa - 8-9.49 kPa - 9.5-10.99 kPa	 4 3 2 1	Pain on lower limb deep vein palpation and unilateral edema	4	1	Alternative diagnosis less likely than PE	3	1
Age - 60-79 years - ≥ 80 years	 1 2	Age > 65 years	1	1			
Clinical probability		**Clinical probability**			**Clinical probability**		
Low	0-4	Low	0-3		Low	< 2	
Intermediate	5-8	Intermediate	4-10		Intermediate	2-6	
High	≥ 9	High	≥ 11		High	> 6	
		Dichotomized			**Dichotomized**		
		PE unlikely		≤ 2	PE unlikely	≤ 4	≤ 1
		PE likely		> 2	PE likely	> 4	> 1

PE: pulmonary embolism; DVT: deep vein thrombosis; *breathing room air.

limitation of this score is the need of a blood gas analysis while breathing room air.[12] The revised Geneva rule contains only objective variables but does not require blood gas analysis (Table 1).[13]

The clinical probability can be categorized in low, intermediate or high clinical probability, corresponding to a prevalence of PE of 4-10% in the low, 21-38% in the intermediate, and 67-81% in the high clinical probability cohort for the three rules mentioned above.[11-13]

To facilitate more practical clinical use, the Wells rule and the revised Geneva score have been dichotomized (unlikely or likely clinical probability). The Wells rule has a higher interobserver agreement using the dichotomized rule than using a three level scheme.[15] Since these CDRs have never been directly compared in a prospective outcome study, there is no evidence to prefer one above another and a recent meta-analysis showed similar accuracy for the available CDRs.[16] The revised Geneva score and Wells rules have also been simplified recently, to facilitate computation and memorization, by assigning one point to all items, with the exception of the heart rate in the simplified revised Geneva score (Table 1). The prevalence of PE was 12% for both rules in the "unlikely" cohort and 47% and 42% in the "likely" cohort for the Wells rule and revised Geneva score respectively.[17,18] However, at present, these simplified rules have only been studied retrospectively.

Of note, the CDRs mentioned above have been validated for outpatients and only the combination of the Wells rule and D-dimer testing has been studied in (a small number of) inpatients which appeared to be safe.[19]

Importantly, a CDR alone is not reliable enough to exclude or confirm the diagnosis of PE, and additional testing is always necessary. For instance, the negative predictive value (NPV) of a Wells rule indicating low probability is only 90-94%. Also, the positive predictive value of high Wells rule is in the order of 70-85%. In conclusion, several CDRs exist to aid the physician in estimating the probability of the presence of acute PE, however, treatment decisions cannot be taken on the basis of a CDR alone.

D-DIMER TESTS

The formation of a thrombus is associated with elevated fibrinolytic activity leading to the production of fibrin degradation products including D-dimers.[20] Therefore, the presence of an elevated D-dimer concentration is an indication for the presence of thrombosis. D-dimer concentration also increases in several other conditions, including malignancy, inflammation, postoperative state, pregnancy, reduced creatinine clearance and increasing age which leads to a low specificity.[21] Hence, the diagnostic strength of D-dimer tests in patients with suspected acute PE lies therefore in ruling out this disease.

Nowadays, several techniques exist to measure the D-dimer concentration. Most commonly used are the enzyme-linked immunosorbent assays (ELISA), with high sensitivity of 95% (95% CI 84-99) and a moderate specificity of 50% (95% CI 29-71).[22] Quantitative latex agglutination assays are frequently used, with a sensitivity and specificity of 95% (95%CI 88-98) and 50% (95%CI 36-64) respectively. Finally, the whole-blood erythrocyte agglutination tests have a sensitivity of 87% (95%CI 64-96) and a specificity of 69% (95%CI 48-84) to detect PE.[22] The basic principle of all tests is the use of D-dimer specific antibodies, but the tests differ on several aspects. First, in general, a test has a moderate sensitivity and specificity or a high sensitivity at the cost of a lower specificity. In daily practice, especially the high-sensitive D-dimer tests are recommended because of the associated high NPV of a normal test result. Of note, the sensitivity of the D-dimer test is dependent of the location of the thrombus. While in segmental, lobar and central pulmonary emboli the sensitivity is 93%, sensitivity decreases to 50% in case of sub-segmental emboli.[23] Second, quantitative as well as qualitative tests are available. A major disadvantage of the qualitative D-dimer tests is the moderate inter-observer variability (kappa=0.65), especially in case of an intermediate test result (kappa=0.04).[24] For this reason, the use of these tests is discouraged. Third, the time to get a test result differs; varying from 35 minutes (ELISA) to less than 5 minutes (full-blood agglutination tests).

Beside the regular D-dimer assays, so-called point-of-care D-dimer tests have been evaluated. Despite the advantage of an immediate test result, most of these tests are qualitative. The SimpliRed point-of-care D-dimer test, a type of whole-blood agglutination assay, has a sensitivity of 82-86% and a specificity of 70-72%.[22] A second quantitative point–of-care D-dimer test, the CARDIAC D-dimer test, had a promising sensitivity of 96.6% with a specificity of 60.8% in a study evaluating patients with suspected DVT.[25] The potential role of point-of-care D-dimer tests in the diagnostic management of suspected PE should be further evaluated in future prospective management studies.

Although the diagnostic strength of the D-dimer tests is not sufficient to confirm or exclude the presence of PE in every patient, it can be used to safely rule out PE in certain patient categories with non-high pretest probability, assessed by a formal CDR. A recent meta-analysis demonstrated an incidence of VTE of 0.3% (95%CI 0.04-1.0%), resulting in a NPV of 99.7% (95%CI 99.0-100%) during 3-month follow-up in patients with clinically suspected PE and an "unlikely" CDR and a normal D-dimer concentration.[26]

IMAGING TECHNIQUES

Conventional pulmonary angiography

Catheter pulmonary angiography is traditionally regarded as the reference imaging test in patients suspected of having PE.[27] However, the 3-month incidence of recurrent

VTE after a normal pulmonary angiography has been reported to be 1.7% (95%CI 1.0%-2.7%).[28] An important disadvantage is the invasive character of this investigation, with right heart catheterization and injection of contrast material. With the availability of the V/Q-scan and CTPA, the role for invasive pulmonary angiography nowadays is negligible.

Ventilation-perfusion scintigraphy

Before the introduction of CTPA, V/Q scintigraphy has replaced invasive pulmonary angiography for several years. This non-invasive technique entails scintigraphic imaging of pulmonary perfusion by intravenous albumin aggregates labeled with technetium 99 m and a ventilation scan imaging (Figure 1). The scintigrams can be classified in three categories: normal, high probability and non-high probability. A normal perfusion scan excludes the diagnosis of PE (3-month VTE failure rate of 0.9%; upper 95%CI 2.3%).[29] A high probability lung scan (i.e. at least one segmental defect on the perfusion scan, combined with a normal ventilation scan) has a positive predictive value of 85-90% and a specificity of 97% (95% CI: 96-98) for PE.[8,30] The major problem of the V/Q imaging technique is that the scintigram is non-diagnostic (non-high probability) in up to 30%-70% of the patients requiring further investigation.[8,31] The non-diagnostic number may decrease if the V/Q technique is used in patients with a normal chest X-ray result. Furthermore, the nucleated gas needed to perform a ventilation scan may not always available. Several studies explored the replacement of the ventilation scan by chest X-ray.[32-34] Perfusion scintigraphy combined with chest radiography had a sensitivity of 84.9% and a specificity of 92.7% which was similar to the diagnostic accuracy to V/Q scintigraphy in the PIOPED II study and 20.6% of the patients had a non-diagnostic result.[33] This strategy

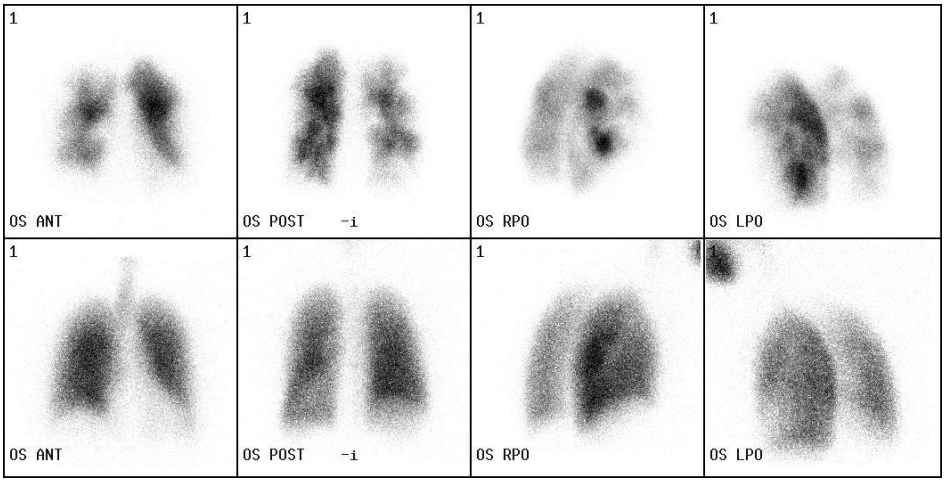


Figure 1. Ventilation perfusion scintigraphy showing multiple perfusion defects (upper panels) and homogenous ventilation (lower panels) diagnostic for pulmonary embolism.

has the advantage of lower costs and radiation dose. Using the PISAPED criteria for interpretation of the lung scan, the number of non-diagnostic results decreased compared to V/Q scanning.[33,34]

Young women might benefit from a strategy including chest X-ray and perfusion scintigraphy as alternative for CTPA because of the concern of radiation exposure to the breasts in this particular patient cohort.[35,36] The positive predictive value of a strategy including clinical probability, D-dimer, chest X-ray and perfusion-scintigraphy in woman younger than 50 years, has been shown 82% and 100% in two retrospective cohorts.[37] Patients with an intermediate probability result still require CTPA. However, the proportion of intermediate results in this particular group of patients is expected to be lower due to less co-morbidity in comparison with the average population suspected of PE.[32] Nevertheless, this strategy needs a prospective validation before it can be generally applied.

Computed tomography

Currently, multi-slice CTPA is the first-line imaging test for acute suspected PE. CTPA is very accurate in excluding or demonstrating pulmonary emboli (Figure 2,3). With the current scanners, CTPA can be performed within 4-6 seconds during breath-holding, acquiring thin 0.5-1 mm slices that can be reconstructed to 2-4 mm slices for evaluation on the post-processing workstation. Single or two-row detector contrast CTPA has a sensitivity of 86% (95%CI 80-92) with a specificity of 94% (95%CI 91-96).[38] The sensitivity of CTPA is depending on the location of the embolus; 89% for main, lobar or segmental PE and only 21% for distal subsegmental PE.[39] The PIOPED II study, using multi-slice CTPA showed a sensitivity of 83% with a specificity of 96%.[40] Other studies showed higher sensitivity using multi-detector row CTPA varying from 96 to 100%.[41,42] Since the introduction of multi-slice CTPA, the sensitivity has increased and according to expert panels, the multi-detector row CTPA technique fulfilled the conditions to replace pulmonary angiography as the reference test for acute PE.[43] CTPA, compared to V/Q scintigraphy, showed a similar prevalence of PE (19 vs 14%) and a similar incidence of recurrent VTE during a 3-month follow-up (0.6 vs. 1.0%).[31] Important advantages of CTPA over V/Q scintigraphy are the low number of inconclusive investigations (0.9-3.0% vs. 30-70% for V/Q scintigraphy)[3,31] and the possibility of finding an alternative diagnosis such as aortic dissection, pneumonia or pneumothorax.[39,43] With the evolvement of this technique, new challenges arise like the increased accuracy for smaller, subsegmental emboli with uncertain clinical relevance.[44] Multi-slice CTPA seem to increase the proportion of patients diagnosed with subsegmental PE without lowering the 3-month risk of thromboembolism in patients without PE, suggesting that treatment of subsegmental PE might be redundant.[45] Disadvantages of this technique include the relatively contra-indication in patients with renal insufficiency or allergy to iodinated contrast material, allergic contrast reactions occur in about 0.7% of patients.[46] Two studies have reported

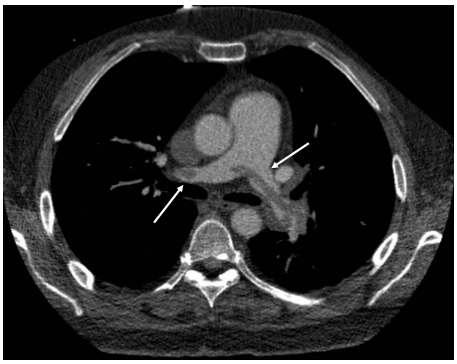


Figure 2. Computed tomography pulmonary angiography (CTPA) of patient with saddle embolus. Large central pulmonary emboli are well recognizable by CTPA.

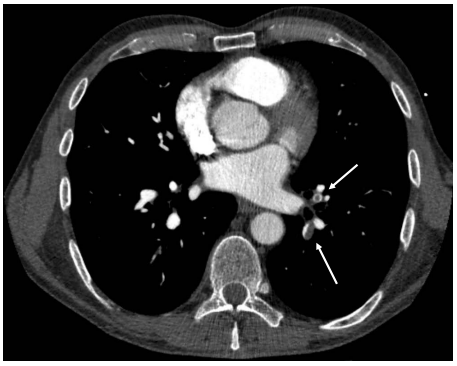


Figure 3. Computed tomography pulmonary angiography of patient with segmental pulmonary emboli in the left pulmonary artery.

the incidence of contrast induced nephropathy after CTPA in patients with suspected acute PE to be between 8.9% and 12%.[47,48] Finally, there is rising concern for long term radiation complications. The radiation dose of a single CTPA is in the range of 3-5 mSv and the cancer risk has been estimated at approximately 150 excess cancer deaths per million when exposed to a single CT examination for PE.[43]

Overuse of CTPA as first imaging test in patients suspected of PE may lead to a very high rate (>90%) of negative CT results,[49-51] which underlines the need of assessing pretest probability before performing CTPA.

Magnetic resonance angiography

Magnetic resonance angiography has potential to be an alternative to CTPA. The less nephrotoxic gadolinium contrast-enhanced acquisitions can be used for thrombus imaging with the advantage of avoiding ionizing radiation and iodinated contrast material. Some early studies using MRA reported a sensitivity of 75-100% and a specificity of

95-100% for detecting PE.[52,53] However, in the recently published PIOPED III study that included 371 patients, a 25% rate of technically inadequate images was observed. Diagnostic MRA images had a sensitivity of only 78% with a specificity of 99%. Sensitivity was 79% for detecting PE in a main or lobar pulmonary artery and decreased to 50% in segmental and even 0% in subsegmental arteries.[54] Hence, MRA is not an optimal alternative for CTPA.

Compression ultrasonography

A proximal DVT can be found in 18% of patients with suspected PE and 36-45% in patients with proven PE.[55] DVT can be found around four times more often in patients with clinical signs and symptoms of DVT compared to patients without DVT complaints.[4] Because patients with DVT receive the same treatment as patients with proven PE, further imaging tests to detect PE can be avoided.[56] Compression ultrasonography could also be interesting as an alternative in patients with contra-indications to CTPA (e.g. renal failure or allergy to iodine contrast agents). Nevertheless, the sensitivity of compression ultrasonography for patients suspected of PE is limited to 23-29% and false positive compression ultrasonography will result in anticoagulation treatment in 2-3% of patients.[57,58] Furthermore, it is not cost effective to apply compression ultrasonography as first imaging test in all patients.[4] Therefore, compression ultrasonography should be reserved for patients suspected of PE who display clinical signs of DVT and for patients with contra-indications for CTPA.

Combination of clinical decision rules, D-dimer testing and imaging

Diagnostic management of suspected acute PE that does not adhere to guidelines is common and unsafe. In one study, 7.7% of patients who received inappropriate management experienced a VTE during follow-up in contrast to 1.2% patients after appropriate management.[59]

The use of standardized diagnostic algorithms combining different diagnostic test has reduced the number of radiological imaging tests without losing safety. PE could be ruled out safely without the need for imaging testing in patients with a low, low or intermediate or unlikely clinical probability with a normal D-dimer test result.[60,61] Notably, the combination of some CDRs with non-highly sensitive D-dimer tests could not rule out PE with enough safety.[16] Currently, in patients with suspected PE, a diagnostic strategy is used in which a highly sensitive quantitative D-dimer test is combined with a CDR, followed by a CTPA (Figure 4). This diagnostic strategy has been evaluated in outpatients as well as inpatients.[3] In case of a CDR result indicating PE unlikely in combination with a normal D-dimer test result, further imaging can safely be withheld. The 3-month failure rate in patients who were not treated with anticoagulants after applying such a strategy was found to be only 0.3% (95%CI 0.04-1.0%), resulting in a NPV of 99.7% (95%CI: 99.0-

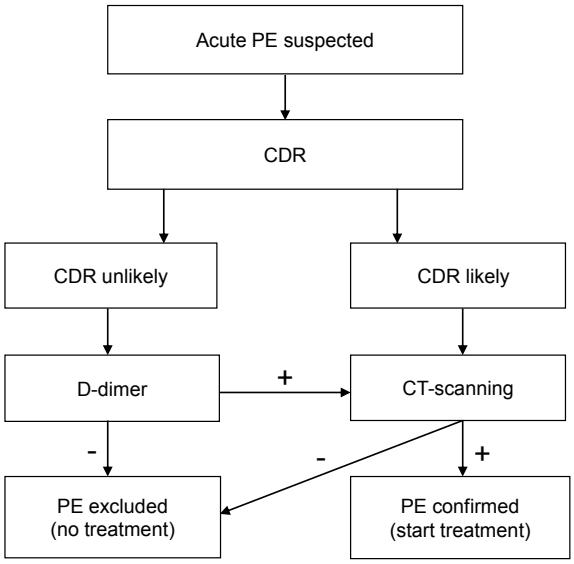


Figure 4. Flow chart diagnostics in patients suspected of having pulmonary embolism. PE: pulmonary embolism; CDR: clinical decision rule; D-dimer (+): elevated D-dimer concentration; D-dimer (-): normal D-dimer concentration.

100%).[26] In a large prospective multicenter study, this percentage was 0.5% (95% CI 0.2-1.1). In this particular study, PE was excluded safely in 32% without using additional imaging tests and the algorithm allowed a management decision in 98% of patients.[3] Only 1.3% (95% CI 0.7-2.0%) of patients with CTPA indicated because of either a high CDR or an abnormal D-dimer test, and with PE excluded by CTPA, were eventually diagnosed with VTE during follow-up. The strategy using a negative CTPA to exclude PE was demonstrated to be as safe as a negative CTPA followed by a compression ultrasonography negative for DVT, both with a 3-month VTE recurrence of 0.3%.[62,63] Consequently, additional compression ultrasonography (CUS) to rule out VTE is unnecessary.

V/Q scintigraphy can be used as an alternative initial imaging technique to CTPA in patients suspected of PE, but is more complicated. The results of the V/Q scintigraphy should be interpreted in combination with the pretest probability.[64] If the CDR indicates low probability or unlikely and the V/Q scintigraphy is normal, anticoagulant treatment can be safely withheld.[29] The diagnosis is confirmed by a clinical decision rule indicating "likely" in combination with high probability for PE. However, in case of a high probability V/Q scintigraphy with an unlikely pretest probability, further imaging (CTPA or compression ultrasonography) should be considered.[65] With a non-diagnostic V/Q scintigraphy (neither normal nor high probability V/Q scintigraphy), compression ultrasonography is recommended.[8,66] With a normal compression ultrasonography in combination with an unlikely clinical pretest probability, PE can be excluded. Combined with a likely pretest

probability, a D-dimer test should be performed. With a normal D-dimer test, PE could be excluded and in case of an elevated D-dimer concentration, a repeated compression ultrasonography should be performed before PE could be excluded safely and treatment can be withheld. In the meantime, until the repeated compression ultrasonography, treatment can be withheld (Figure 5).[64]

In conclusion, in patients with clinically suspected PE, the first diagnostic step is to determine the clinical probability by performing a CDR. In case of a non high clinical probability (PE 'unlikely'), a normal D-dimer test result can safely exclude PE. When the CDR indicates a high clinical probability or if the D-dimer test reveals a concentration above the predefined cut-off level, additional imaging is necessary and CTPA is the first choice imaging modality. If PE is proven by CTPA, the patient must be treated with anti-coagulants. If CTPA excludes PE, an alternative diagnosis should be considered (Figure 4).

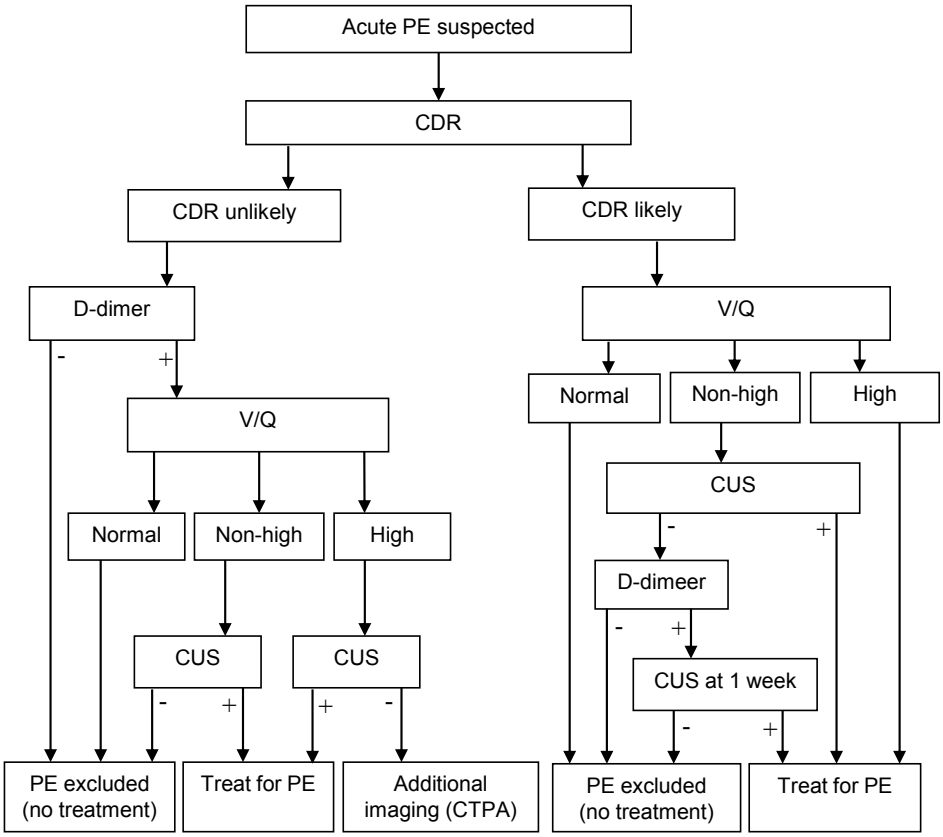


Figure 5. Flowchart in patients suspected of having pulmonary embolism (PE) using ventilation perfusion (V/Q) scintigraphy; CDR: clinical decision rule; D-dimer ventilation perfusion (+): elevated D-dimer concentration; D-dimer (-): normal D-dimer concentration; non high: non high probability (nondiagnostic); high: high probability; CUS: compression ultrasonography; CUS (-): CUS negative for deep venous thrombosis; CUS (+): CUS positive for deep vein thrombosis.

Suspected recurrent pulmonary embolism

The management of patients with suspected recurrent PE is challenging as it is unclear whether the above-mentioned diagnostic strategies are valid in patients with a prior history of proven PE. Nevertheless, the diagnosis of recurrent PE is associated with major therapeutic consequences since lifelong treatment with anticoagulants is usually required.

A diagnostic strategy consisting of a D-dimer test and a CDR could be useful in patients suspected of recurrent PE without anticoagulant treatment.[67] In a post-hoc analysis of the Christopher study, none of the 124 patients with suspected recurrent PE who were not treated based on a low clinical probability according to the Wells rule and a normal D-dimer test result, developed a VTE during a 3-month follow-up period (0%; 95%- CI 0-6.9).[67] Further research is warranted to provide definitive evidence regarding the use of CDRs and the diagnostic value of the D-dimer test in patients suspected of recurrent PE. Of note, it has been suggested that (especially initiation of) anticoagulant treatment is associated with a decrease in D-dimer concentration and therefore with decreased sensitivity[68-70] and CDRs are not validated in patients using anticoagulants. Hence, direct imaging tests are recommended in patients on anticoagulant treatment.

In patients with a history of PE, it may be difficult to differentiate between a residual thrombus or new thrombus on CTPA. It has been estimated that up to 50% of patients have residual thrombus, 6 months after diagnosis of PE.[71] In patients with high risk of recurrence, studies are required to determine whether repeating CTPA six months after anticoagulant treatment may be valuable, as to provide a baseline-imaging test in case patients return with new complaints suspected for recurrent PE. A strategy of CRD and D-dimer testing can be used in patients suspected of recurrent PE without receiving anticoagulant treatment and direct imaging tests are needed in patients on treatment In these latter patients, CTPA is the first choice imaging test.

Diagnostic management during pregnancy

During pregnancy and puerperium the risk of thrombosis is increased due to immobilization, venous stasis, hormonal changes or after caesarian section. During pregnancy, the inappropriateness in diagnostic management increases.[59] Dyspnea and swelling of legs frequently occurs during normal pregnancy, but may also be an indicator of PE. Because pregnancy has been a strict exclusion criterion in most diagnostic studies, the possible diagnostic value of a CDR is not known in this specific population.

The value of the D-dimer test during pregnancy and post partum is also limited. During pregnancy, a physiological elevation of the D-dimer concentration occurs decreasing the specificity of the test: from 35 weeks pregnancy through the post partum period, the values are almost always elevated above the commonly used threshold of 500 ng/ml.[72] In conclusion, further studies in pregnant patients are needed and the use of a CDR

and D-dimer test is discouraged during pregnancy and puerperium and imaging tests are always required.

Prospective studies about the safety of ruling out PE by V/Q scintigraphy or CTPA are lacking. Most experience in patients suspected of PE during pregnancy is with V/Q scintigraphy and this technique is considered as first line imaging test in pregnant women.[73,74] The percentage of patients with a high probability V/Q scan is very low (1.8% versus ~10% without pregnancy), the percentage of normal perfusion scans is high (73.5% versus 33% without pregnancy) whereas 25% of the V/Q scans are inconclusive.[75] Additional imaging is needed in these latter patients, potentially exposing them to further radiation.

Although pregnant patients have been excluded from participation in most clinical outcome studies using CTPA, the calculated radiation dose received by the fetus as a result of CTPA has always been lower compared to V/Q scintigraphy.[76-78] Furthermore, CTPA shows fewer non diagnostic tests compared to V/Q scintigraphy and has the ability to show alternative diagnosis. Disadvantage of CTPA compared to V/Q scintigraphy is the 150 times higher amount of radiation exposure to the breasts.[79] It is also possible to start with compression ultrasonography of the lower extremities. If a DVT is identified, treatment with anticoagulants is indicated and CTPA or V/Q scintigraphy can be avoided.

CONCLUSIONS

Various diagnostic tests are available to accurately confirm or exclude PE. The CDR and D-dimer test play an important role in the diagnostic algorithm. The CDR as well as the D-dimer test can not be used as single tests, but the combination of a low clinical probability and a normal D-dimer test result can exclude PE safely without the need of additional testing. In case of a likely clinical probability and/or an elevated D-dimer value, additional testing is required. Multi-slice CTPA is the first choice imaging test and can safely exclude PE. V/Q scintigraphy may be used if CTPA is contra-indicated.

EXPERT OPINION

Our recommended diagnostic strategy in patients with suspected PE starts with a standardized CDR to assess the pretest probability. If this rule indicates PE "unlikely", a quantitative, highly sensitive D-dimer test should be performed. A normal D-dimer test result excludes PE safely. With a CDR indicating "likely" pretest probability or an elevated D-dimer test result, additional diagnostic testing is needed, with multi-slice CTPA as imaging test of first choice. When the CTPA is negative, the diagnosis PE is ex-

cluded without the need for additional testing (e.g. compression ultrasonography). All patients with a CTPA demonstrating PE should be treated with anticoagulants. In case of inconclusive CTPA, we recommend repeating CTPA within 24 hours and patients with high clinical probability should be treated by anticoagulants while awaiting diagnostic confirmation.[80] V/Q scintigraphy may be used as an alternative to CTPA in case of contraindications, MRA may be used as an alternative when CTPA is contra-indicated, but accuracy is currently insufficient for implementation in routine clinical care.

The main goal in diagnostic management of PE is to achieve a standardized, accurate and relative simple diagnostic strategy that can be easily applied to the majority of patients suspected of acute PE. This should be a strategy with a minimum of false positive or false negative test results, and with acceptable use of radiation and contrast material. We recommend the use of the Wells rule for inpatients. Because there is no evidence to prefer one CDR above another for outpatients, the preference may depend on the familiarity with a score or the type of D-dimer assay. The type of D-dimer assay has consequences on the proportion of the population on which D-dimer testing can be applied; highly sensitive D-dimer assays can be used in patients with low and intermediate probabilities in a three level scheme and patients categorized as 'unlikely' to rule out PE. In case of a less sensitive D-dimer, PE could be ruled out in patients with a normal D-dimer test and a low clinical probability of a trichotomized score.[16]

One topic of interest is the prospective validation and implementation of the simplified CDRs (mentioned before) in clinical practice. The potential role of quantitative point-of-care D-dimer tests should be further evaluated in prospective management studies.

On the other hand, risk estimation of specific subgroups become of more interest. Using specific diagnostic strategies and cut-off points may help in predicting the individual chance for having PE. Implementation in daily clinical practice seems more difficult, but using electronic assistance may help in improved individual based risk estimation and diagnostic decision-making.[81]

Concerning subgroup analysis, standard strategies may not be applicable to all patients. For example, in the elderly patients, with increasing age, D-dimer testing becomes less accurate. Also, in patients with impaired renal function, avoiding or limiting the use of iodinated contrast material is desirable. In patients suspected of having a recurrent PE, it is difficult to differ between old and new emboli on CTPA. In young women, radiation dose, especially to the breasts, is of concern. Finally, data for woman with a suspicion of PE during pregnancy are limited at the moment and it is a challenge to avoid radiation to the fetus. Diagnostic management strategies in pregnant women have to be validated in future research. Studies concerning CDR and D-dimer testing already exists in pregnant patients suspected of DVT and seems promising with a high NPV (100%; 95%CI 95-100) of the D-dimer test and also the use of the "LEFt" prediction rule excludes DVT during pregnancy but prospective validation is still needed.[82,83]

In the future, development of existing imaging modalities will also be subject of research. With the development of faster CT scanners with high spatial resolution, more (subsegmental) emboli can be detected. However, the clinical relevance of isolated subsegmental emboli is not exactly known and must be subject of research. Using ECG-gated CTPA, it is possible to obtain information about pulmonary arteries, thoracic aorta, heart and even the coronary arteries within a single examination. This is of interest because the clinical differentiation between cardiac events and PE is not always clear and this information can be helpful to predict clinical outcome in patients diagnosed with PE. However, ECG-gated protocols may result in a higher radiation dose and more contrast is needed compared to non-gated CTPA.[84] Therefore, these protocols are not recommended for routine use; only patients suspected of either PE, aorta dissection or cardiac events may benefit from these techniques.[85]

The development of single photon emission computed tomography (SPECT), acquiring 3D images, may be of growing interest and may further improve V/Q imaging, which may be used as an alternative when CTPA is contraindicated.[86,87] New experimental MRA-techniques show potential for improved PE imaging. MR-direct thrombus imaging by methemoglobin, a transformation product of hemoglobin in a thrombus, may be used as endogenous contrast to depict subacute thrombosis.[88] Further, new MRI contrast agents such as fibrin or alpha(2)-antiplasmin (activated factor XIII covalently cross-links alpha(2)-antiplasmin to fibrin) will be evaluated to visualize PE. Labeling using bimodal contrast agents consisting of gadolinium and a peptide that binds to alpha(2)-antiplasmin or to fibrin in the thrombus seems to be a promising technique. These latter methods are under investigation in experimental in-vivo models for arterial thrombosis and should be evaluated further.[89,90]

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CHAPTER 3

Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism

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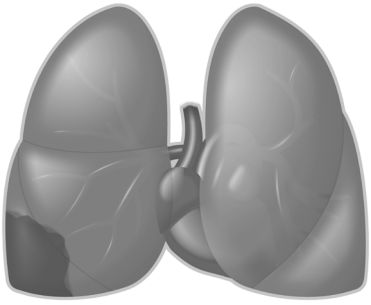

ABSTRACT

Introduction

The simplified revised Geneva score is a fully standardized clinical decision rule (CDR) in the diagnostic work-up of patients with suspected pulmonary embolism (PE). The individual weights of the CDR variables are difficult to memorize and could lead to miscalculations in an acute setting. We have validated a simplified version of the revised Geneva score.

Methods

Patients from 2 large prospective diagnostic trials were analyzed. The simplified CDR was constructed by awarding one point for all items of the original CDR. Diagnostic accuracy of the simplified CDR was compared to the original CDR by comparing the AUC of ROC analysis. Further, clinical utility of the simplified CDR was studied by assessing the safety of ruling out PE on the basis of either a low-, intermediate- (in case of trichotomized outcome), or an unlikely (in case of dichotomized outcome) clinical probability in combination with a normal highly sensitive D-dimer test.

Results

The diagnostic accuracy between the two CDR's did not differ (AUC 0.75 {95%CI 0.71-0.78} vs 0.74 {0.70-0.77}). After 3 months of follow-up, no patients with a combination of either a low- (0%; 95%CI 0.0-1.6), intermediate- (0%; 0.0-2.6), or an unlikely (0%; 0.0-1.1) clinical probability using the simplified score and a normal D-dimer test was diagnosed with VTE.

Conclusions

This study shows that simplification of the revised Geneva score does not lead to a decrease in diagnostic accuracy and clinical utility. Prospective outcome studies are needed to confirm these findings.

INTRODUCTION

A clinical decision rule (CDR) can be defined as a clinical tool containing variables obtained from history, physical examination and simple diagnostic tests quantifying likelihood for diagnosis, prognosis or likely response to treatment in an individual patient.[1] Pulmonary embolism (PE) is clinically suspected in many patients with respiratory or chest complaints because of the non-specific nature of the presenting signs and symptoms. Nevertheless, the prevalence of PE in this population is relatively low. Several CDR's to assist the clinician diagnostic decision making have been developed.[2] Correct implementation of CDR's in diagnostic strategies have been proved to decrease the need for expensive, time consuming and invasive diagnostic imaging procedures, whereas the venous thromboembolism failure rate in patients in whom anticoagulant treatment is withheld, is acceptably low.[3-5]

Although two CDR's for the pretest probability of PE have been extensively validated, i.e. the Wells rule and the Geneva score,[6,7] both have practical limitations.[7-10] A fully standardized rule, the revised Geneva score, has been developed and validated recently.[9,10] The revised Geneva score is independent from physicians' implicit judgment, which makes this CDR objective and easily reproducible.[10] The score consists of 9 different variables with diverse individual weights (Table 1). It could be reasoned that these diverse individual weights of the variables in the CDR's are difficult to memorize and this could lead to miscalculations in acute patient care. Therefore, we hypothesized that we could simplify the revised Geneva score by awarding one point for all variables (Table 1) in two large patients cohorts in which the revised Geneva score was assessed.[3,4] Subsequently, we compared diagnostic accuracy and clinical utility of the simplified revised Geneva score and the original revised Geneva score.

Table 1. Simplification of the revised Geneva score.

Variable	Original	Simplified
Age >65 years	1	1
Previous DVT or PE	3	1
Surgery or fracture within 1 month	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Hemoptysis	2	1
Heart rate 74-94 beats/min	3	1
Heart rate ≥95 beats/min*	5	1
Pain on lower limb deep vein palpation and unilateral edema	4	1

*By the original score, patients are awarded 0 points (heart beat <74 beats/min), 3 points (heart rate 74-94 beats/min) or 5 points (heart rate ≥95 beats/min); by the simplified score, patients are awarded 1 point if the heart rate exceeds 73 beats/min and one additional point (2 points in total) if the heart rate exceeds 94 beats/min. DVT: deep vein thrombosis, PE: pulmonary embolism.

MATERIAL AND METHODS

Patients

Data of two large prospective diagnostic trials were used and combined for the validation of the simplified revised Geneva score.[3,4] In the first trial consecutive patients with suspected PE, presented to the emergency department of 3 teaching hospitals (Geneva University Hospital; Angers University Hospital; and Hôpital Européen Georges-Pompidou, Paris, France) between September 2002 and October 2003, were eligible for inclusion.[3] Further we will refer to this as study A. In all patients, the Geneva score[7] was assessed. In patients with either a low or intermediate probability, plasma D-dimer levels (VIDAS, Biomerieux) were measured. Pulmonary embolism was ruled out in patients with a level below the cutoff value of 500 ng/l. Patients with a D-dimer level >500 ng/l with high clinical probability underwent proximal venous-compression ultrasonography of the lower limbs and multidetector-row computed tomography (CT). Patients with a CT that was positive for pulmonary embolism or ultrasonography that showed a deep venous thrombosis received anticoagulant treatment, where such therapy was withheld in patients in whom both tests were negative.

In the second study, the clinical effectiveness of a simplified algorithm using the dichotomized Wells rule, D-dimer testing, and CT in patients with suspected pulmonary embolism was evaluated.[4] A random set of patients referred to the Leiden Medical University Hospital (Netherlands) were taken for the present study. We will refer to this as study B. If the diagnosis of PE was unlikely (Wells score ≤ 4) in combination with a normal quantitative (VIDAS) D-dimer test result, PE was considered to be excluded. When the Wells score was 4 or less in combination with increased D-dimer (> 500 ng/l) or when the diagnosis of PE was likely (Wells score > 4), then the diagnosis of PE was confirmed with multi-detector spiral CT-scanning.

Patients of both studies were followed up for 3 months. Both studies were approved by the ethics committees of all participating hospitals and all patients provided written informed consent before they were enrolled.

In study A, D-dimer testing was part of the diagnostic work-up of all patients with either a low or intermediate probability with the Geneva Score.[7] In study B, D-dimer tests were only performed in patients with a Wells rule of 4 points or less. This resulted in missing D-dimer data for 69 patients in the low- and intermediate probability and for 29 patients in the unlikely clinical probability group as assessed by the simplified revised Geneva score.

Assessment of the revised Geneva score

In study A[3], the data collection form was identical to that used in the derivation study of the revised Geneva score, allowing retrospective calculation of the simplified revised Geneva score for each patient. In study B,[4] the Wells rule was used for assessing clinical

probability. The revised Geneva score comprises four variables not included in the Wells rule: age over 65 years, unilateral lower-limb pain, heart rate 75-94 beats per minute or more than 94 beats per minute, and pain on lower-limb deep venous palpation and unilateral edema. These items were abstracted from the patient charts after masking the final diagnosis. Values for each item were scored on the day of inclusion.[10]

In the simplified revised Geneva score, all variables were given one point if present (Table 1). In addition, contrary to the original score, where scores of either 0, 3 or 5 points for heart rate were given, in the simplified score 0 points was awarded to a heart rate under 75 beats per minute, one point was awarded to patients with a heart rate with 75 beats or more and one additional point was awarded to all patients with a heart rate of more than 94 beats per minute.

Data analysis

Patient characteristics and study outcomes of both studies were combined in one database. Optimal cut-off points (both dichotomized and trichotomized) of the simplified revised Geneva score scores were calculated by comparing the area under curve (AUC) in ROC analyses. Accuracy of the simplified revised Geneva score and the revised Geneva score was compared by comparison of the AUC in ROC analyses. We studied the clinical course of patients with a normal D-dimer result in different clinical probability categories using the simplified revised Geneva score. Statistical analysis was performed by using SPSS software (SPSS for windows 14.0.2, Inc. 1989-2005). P-values of <0.05 were considered statistically significant.

RESULTS

Study A comprised of 756 patients. They had a mean (±SD) age of 60±19 years, 60 percent were female. All patients were outpatients. The overall prevalence of pulmonary embolism in this cohort was 26%. However, due to missing values mainly for heart rate, the revised Geneva score could not be computed in seven patients, leaving 749 for the present analysis. Three hundred patients of study B with suspected PE were included in the present study. These patients were 47±16 years old at time of diagnosis, 60% were female and 96% were outpatients. The overall prevalence of PE was 16%. Taken as a whole, the complete validation population of the simplified revised Geneva score consisted of 1049 patients.

The optimal margin of low-, intermediate and high probability groups was set at 0-1, 2-4 and 5-9 points (Table 2, Figure 1). Using these cut-off points, 378 patients were assigned to the low clinical probability (0-1 points, 36% of total population, 7.7% PE {95% confidence interval 5.2-11%}), 629 patients to the intermediate clinical probability (2-4 points, 60% of total population, 29% PE {95% CI 26-33%}) and 42 patients to the

Table 2. Score application in the study population, percentage with PE, and proportions of the population in the 3-level and 2-level clinical probability categories.

	Three-level scheme			Two-level scheme	
	Low	Intermediate	High	PE unlikely	PE likely
Number	378	629	42	681	368
% population	36	60	4.0	65	35
% PE	7.7	29	64	13	42

PE: pulmonary embolism.

high clinical probability category (5-9 points, 4% of total population, 64% PE {95% CI 48-78%}). The optimal margin for dichotomization of the rule was set at 0-2 and 3-9 points (Table 2); 681 patients were designated PE unlikely (0-2 points, 65% of total population, 13% PE {95% CI 11-16}) and 368 patients were designated PE likely (3-9 points, 35% of total population, 42% PE {95% CI 36-47}). Flowcharts of both dichotomized and the trichotomized study outcome are shown in Figure 2 and 3.

We compared the AUC in the ROC curve for the revised Geneva score and simplified revised Geneva score (Figure 1a and b). The AUC of the continuous prediction rules was 0.75 (95%CI 0.71-0.78) for the revised Geneva score and 0.74 (95%CI 0.70-0.77) for the simplified revised Geneva score. The AUC of the categorized rules was 0.70 (95%CI 0.66-0.74) for the revised Geneva score and 0.68 (95%CI 0.64-0.72) for the simplified revised Geneva score.

Finally, we studied the clinical utility of the simplified revised Geneva score. After 3-month follow up in the combined patient population, no patient with a low (0%; 95%CI 0.0-1.6) or intermediate (0%; 95%CI 0.0-2.6) clinical probability score by the simplified revised Geneva score and a normal D-dimer result at inclusion was subsequently diagnosed with venous thromboembolism (Figure 2). Even so, in case of dichotomous outcome, no patient with an unlikely clinical probability (0%; 95%CI 0.0-1.1) was subsequently diagnosed with venous thromboembolism after the 3-month follow-up period (Figure 3).

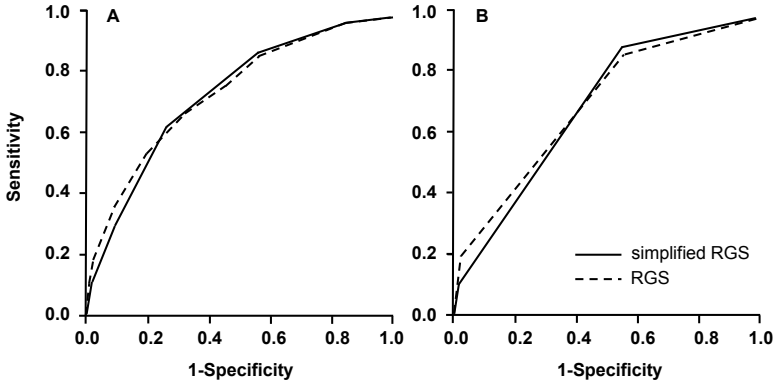

Figure 1A and 1B. Receiver operating characteristic curves of the continuous revised Geneva score (RGS) and simplified RGS (A) and 3-level categorized RGS and simplified RGS (B).

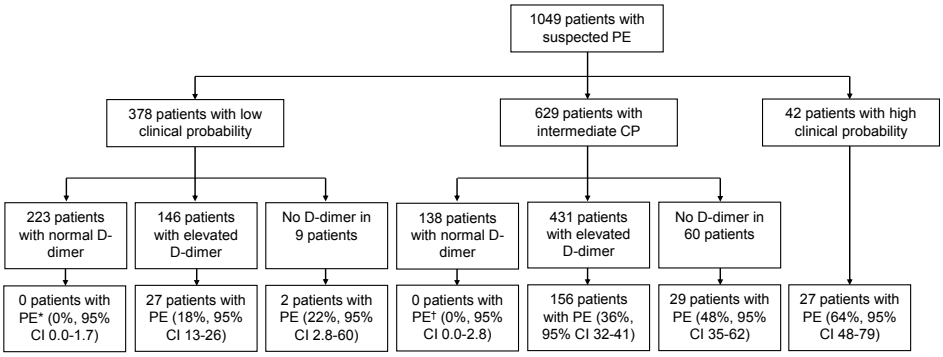

Figure 2. Flowchart of patients showing outcomes by 3-level simplified revised Geneva score. †One patient was lost to follow-up and 3 patients were treated with anticoagulant therapy for other reasons than pulmonary embolism (PE). §One patient was lost to follow-up and 7 patients were treated with anticoagulant therapy for other reasons than PE. CI: confidence interval; CP: clinical probability.

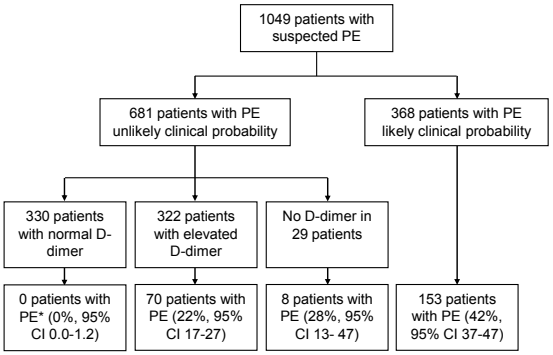

Figure 3. Flowchart of patients showing outcomes with dichotomous use of simplified revised Geneva score. †Two patients were lost to follow-up and 10 patients were treated with anticoagulant therapy for other reasons than pulmonary embolism (PE). CI: confidence interval.

DISCUSSION

This study shows that a simplification of the revised Geneva score doesn't decrease the diagnostic accuracy of the rule The distribution of the patient proportions by the simplified revised Geneva score in both trichotomized and dichotomized categories and the prevalence of PE in these categories were well comparable to those of the original revised Geneva score[9] as well as to two other validated and widely used CDR's, the Wells rule[4,6] and the Geneva score.[7] The simplified revised Geneva score remained to have great clinical utility because a combination of a low, intermediate or unlikely clinical probability with a normal D-dimer test result had low venous thromboembolism failure rates. Moreover, this simplified score has two potential advantages over the original revised Geneva score, i.e. clinicians will have less trouble memorizing and remembering the score and the final sum of the score is easier to calculate.

Several studies have shown D-dimer assays to have a high negative predictive value and to be a sensitive but nonspecific marker of PE.[14] However, different sensitivity for several D-dimer assays has been described in the literature.[2,14-16] In case of decreased sensitivity, the negative predictive value will be reduced. Also, the negative predictive value of a combined low clinical probability and a normal D-dimer test diminishes as disease prevalence rises.[14] Consequently, the sub-population of patients with suspected PE in which D-dimer testing is safe to exclude PE, is dependent on prevalence of disease and sensitivity of the D-dimer assay. In the present study, a highly sensitive quantitative D-dimer assay with a reported sensitivity of 95-98% was used.[2] For this reason, the dichotomized outcome of this CDR could be used safely. When a physician using the simplified revised Geneva score to assess pretest probability in patients with suspected PE has only availability over a D-dimer assay with a lower sensibility, he could decide to use the trichotomized outcome and perform D-dimer tests only in case of low clinical pretest probability to exclude PE.

Simplification of the score did not decrease the AUC of the ROC. One rationale for this could be differences in tested patient populations.[12] This phenomenon could also have been caused by statistical instability and overfitting of the multivariate Model.[12,13] Instability of multivariate models is caused by dependency of the variables selected as predictors in a clinical model on what other variables are used.[12] Overfitting is a concept related to regression to the mean.[13]

This study requires several comments. First, we performed a retrospective analysis. Nonetheless, consecutive patients were included and they were followed prospectively. In addition, both study A and B report a minimal loss to follow-up, being respectively 0.5 and 0.1%. In all study patients, the simplified revised Geneva score was easily calculated and our study organization could not have lead to selective inclusion of patients. Second, data of patients of two large trials were combined for this analysis. There were some differences in general characteristics between both study populations, i.e. mean age and prevalence of PE. However, the prevalence of PE according to the number of points in the simplified revised Geneva score was similar in the two groups (data not shown). For this reason, we don't believe that the differences in patient characteristics have influenced our conclusions. Finally, by study design, D-dimer results were not available for all patients. Data were missing in 9 (2.4%) patients with low, in 60 (9.5%) patients with intermediate and in 29 (4.3%) patients with unlikely clinical probability.

In summary, we have shown that simplification of the revised Geneva score doesn't decrease the score's diagnostic accuracy and clinical utility. Prospective outcome studies are however needed to confirm our findings.

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CHAPTER 4

Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study.

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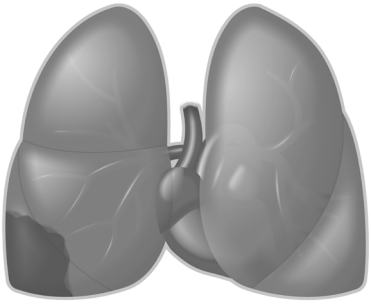

ABSTRACT

Background

Several clinical decision rules (CDRs) are available to exclude acute pulmonary embolism (PE), but they have not been directly compared.

Objectives

To directly compare the performance of 4 CDRs (Wells rule, revised Geneva score, simplified Wells rule, and simplified revised Geneva score) in combination with D-dimer testing to exclude PE.

Design

Prospective cohort study.

Setting

Seven hospitals in the Netherlands.

Patients

807 consecutive patients with suspected acute PE.

Interventions

The clinical probability of PE was assessed by using a computer program that calculated all CDRs and indicated the next diagnostic step. Results of the CDRs and D-dimer tests guided clinical care.

Measurements

Results of the CDRs were compared with the prevalence of PE identified by computed tomography or venous thromboembolism at 3-month follow-up.

Results

Prevalence of PE was 23%. The proportion of patients categorized as PE-unlikely ranged from 62% (simplified Wells rule) to 72% (Wells rule). Combined with a normal D-dimer result, the CDRs excluded PE in 22% to 24% of patients. The total failure rates of the CDR and D-dimer combinations were similar (1 failure, 0.5% to 0.6% [upper-limit 95% CI, 2.9% to 3.1%]). Even though 30% of patients had discordant CDR outcomes, PE was not detected in any patient with discordant CDRs and a normal D-dimer result.

Limitation

Management was based on a combination of decision rules and d-dimer testing rather than only 1 CDR combined with D-dimer testing.

Primary Funding Source

This study was supported by unrestricted grants from the participating hospitals.

Conclusions

All 4 CDRs show similar performance for exclusion of acute PE in combination with a normal D-dimer result. This prospective validation indicates that the simplified scores may be used in clinical practice.

INTRODUCTION

The introduction of standardized clinical decision rules (CDRs) to determine the clinical probability of pulmonary embolism (PE) has improved the diagnostic workup of patients with suspected PE. A CDR indicated PE "unlikely" in combination with a normal D-dimer test result can exclude the diagnosis of PE in a large proportion of the patients who present for evaluation (20-40%), without the need for additional imaging with computed tomographic pulmonary angiography (CT) or ventilation-perfusion scintigraphy, which both involve radiation and intravenous contrast or radioisotopes. In these patients anticoagulants can be safely withheld.[1-4]

Several clinical decision rules, which incorporate information from medical history and physical examination, have been developed and validated. Next to six objective variables, the Wells rule contains one subjective variable: the physician should consider the possibility of an alternative diagnosis than PE for the patient's complaints (Table 1).[5] In contrast, the more recently introduced revised Geneva score is composed of eight objective clinical variables.[6] Both scores assign different weights to the variables, meaning that depending on the variable either 1, 1.5, 2, 3, 4, or 5 points need to be assigned (Table 1). Because miscalculations can occur, the scores have recently been simplified (Table 1).[7,8]

Until now, the simplified Wells rule and the simplified revised Geneva score have not been validated prospectively. Also, while some of the scores have retrospectively or prospectively been compared with each other,[9-12] the four scores have never been directly compared for the performance of excluding PE in combination with a normal D-dimer test result. Therefore, we performed a prospective multi-center clinical accuracy study to assess and directly compare the performance of these four different CDRs (Wells rule, revised Geneva score, simplified Wells rule and simplified revised Geneva score) in

excluding PE in combination with D-dimer testing, using a computer-based program to calculate the CDR scores.

METHODS

The study was a prospective multi-center cohort study on clinical accuracy study of 4 CDRs in consecutive patients with a suspected first episode of acute PE. The study population consisted of consecutive outpatients and inpatients in whom a first acute PE was clinically suspected. Clinically suspected acute PE was defined as sudden onset of dyspnea, deterioration of existing dyspnea and/or sudden onset of pleuritic chest pain. Patients were included in seven participating academic or non-academic hospitals in the Netherlands.

Exclusion criteria were age below 18 years of age, life expectancy of less than 3 months, treatment with therapeutic-dose low molecular weight heparin or unfractionated heparin that was initiated 24 hours or more prior to eligibility assessment, treatment with vitamin K antagonists, previous PE, contraindication to helical CT scan because of allergy to intravenous iodinated contrast or renal insufficiency (creatinine clearance < 30 ml/min using the Cockroft-Gault formula), pregnancy and inability to return for follow-up. Institutional review boards of all participating hospitals approved the study protocol and written informed consent was obtained from all included patients.

Study flow

Patients included in the study underwent a sequential work-up of clinical probability assessment, D-dimer testing and CT scanning. In all patients, the items of four clinical decision rules were assessed by the treating physicians (Table 1). In addition, a high-sensitivity quantitative D-dimer test was performed (VIDAS D-dimer assay, Biomerieux, Marcy L'Etoile, France; Tinaquant assay, Roche Diagnostica, Mannheim, Germany; STA-Liatest D-Di, Diagnostica Stago, Asnieres, France; or Innovance D-dimer, Siemens, Marburg, Germany), in all included patients, irrespective of CDR results. The type of D-dimer assay that was used depended on local practice. Pulmonary embolism was considered "unlikely" in case of a Wells rule of 4 points or less, a simplified Wells rule of 1 point or less,[7,10] and a simplified revised Geneva score with a score of 2 points or less (Table 1).[8] The revised Geneva score, until now only available in a three-category scheme, was transformed to a two-category scheme similar to the other scores. This was done by a beforehand calculation of the optimal cut-off, using an existing cohort of patients with suspected PE[8] for whom the revised Geneva score variables were available for calculation of the score. The optimal cut-off point was determined by calculation of the area under the Receiver Operating Characteristic (ROC) curve, and the proportions of patients in

Table 1. Clinical decision rules.

Wells rule			**Revised Geneva score**		
Items	**Original**	**Simplified**	**Items**	**Original**	**Simplified**
Previous PE or DVT	1.5	1	Previous DVT or PE	3	1
Heart rate >100/min	1.5	1	Heart rate 75 – 94/min Heart rate ≥ 95/min	3 5	1 2
Surgery or immobilization within 4 weeks	1.5	1	Surgery or fracture within 1 month	2	1
Hemoptysis	1	1	Hemoptysis	2	1
Active malignancy	1	1	Active malignancy	2	1
Clinical signs of DVT	3	1	Unilateral lower limb pain	3	1
Alternative diagnosis less likely than PE	3	1	Pain on lower limb deep vein palpation and unilateral edema	4	1
			Age > 65 years	1	1
Clinical probability			**Clinical probability**		
PE unlikely	≤ 4	≤ 1	PE unlikely	≤ 5	≤ 2
PE likely	> 4	> 1	PE likely	> 5	> 2

PE: pulmonary embolism; DVT: deep vein thrombosis.

the "likely" and "unlikely" categories were calculated. Based on these calculations, PE was considered "unlikely" with a score of 5 points or less (Table 1). For any of the CDRs, a score above the respective cut-off indicated PE "likely".

Clinical care was guided by the results of the CDRs and D-dimer results (Figure 1). When PE was considered "unlikely" according to all four CDRs in combination with a normal D-dimer test result (cut-off < 500 µg/L), PE was excluded. In all remaining patients (i.e. a "likely" result according to at least one of the CDRs or an abnormal D-dimer test result), CT scanning was indicated to confirm or exclude the diagnosis. Patients with CT indicating PE were treated with anticoagulants and treatment was withheld from all patients in whom the diagnosis was excluded. These latter patients were followed for a 3-month period. The study flow is illustrated in Figure 1.

Standard contrast enhanced MDCT was performed using a 4-slice, 16-slice, or 64-slice MDCT scanner with acquisition of 0.5 or 1 mm sections (depending on the weight of the subject) of the entire chest for diagnosing or excluding PE. The rotation time is 0.4 s and the pitch factor 1.4; the tube current is 250-300 mA and the tube voltage 100 kV. Acquisitions are performed during a single breath-hold, lasting 10-12 seconds or less, depending on the type of scanner. 80-100 ml of contrast agent is injected in the antecubital vein with an injection rate of 4.0 ml/sec. The acquisition of the static pulmonary angiography scan is started after automated threshold enhancement detection in the pulmonary trunk. A threshold difference of 100 Hounsfield units is selected for starting the acquisition. CT images were read by skilled radiologists to determine if PE was present or could be excluded. The radiologists were aware of an indication for CT-

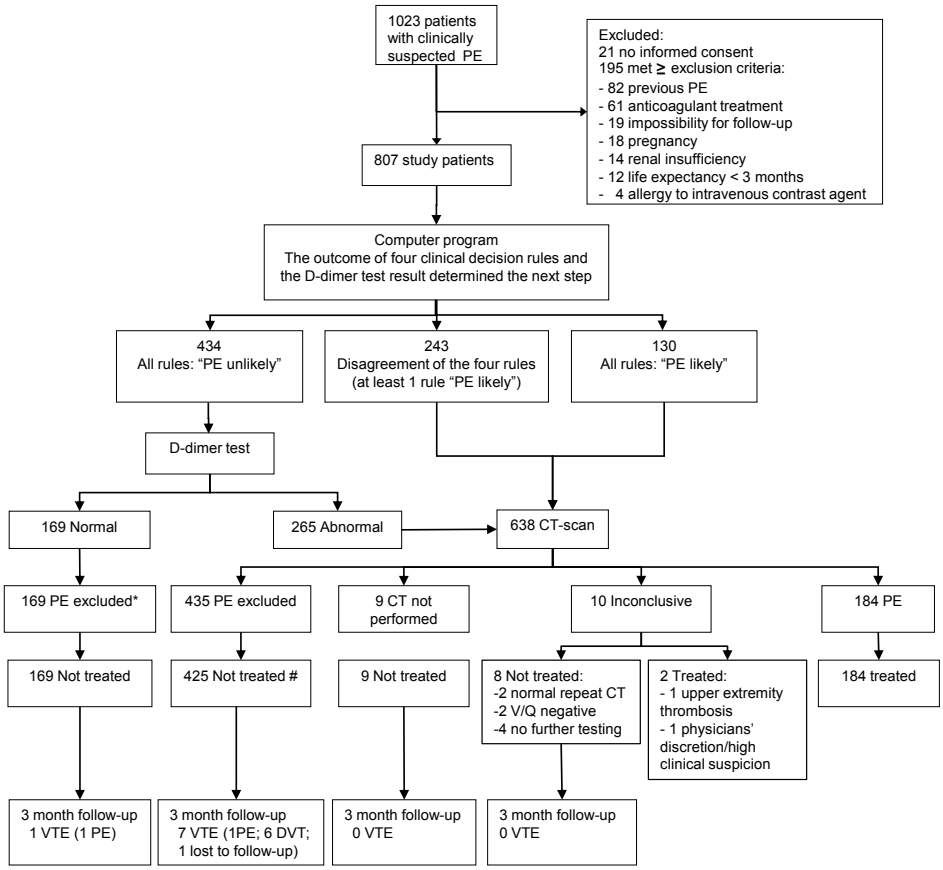

Figure 1. Flow-chart with results of the diagnostic strategy. PE: pulmonary embolism; DVT: deep vein thrombosis; VTE: venous thromboembolism; CT: computed tomography; V/Q: ventilation perfusion scintigraphy; *in seven patients a CT-scan was performed while not indicated and confirmed the diagnosis in one patient; "Treated or not treated" concerns treatment with anticoagulants; #ten patients in whom PE was excluded by CT-scan received anticoagulant treatment for reasons other than VTE.

scanning but not if this was based on a high CDR and/or an elevated D-dimer test result. The diagnosis of PE was confirmed by the presence of at least one filling defect in the pulmonary artery tree. Management of patients with an inconclusive CT result was left to the attending physician and could include repeat CT scanning, ventilation-perfusion scintigraphy or conventional pulmonary angiography.

Computerized program

Clinical evaluations and the collection of data were performed by the treating physicians at baseline. In each participating center, a study coordinator was available for advice regarding the study. This coordinator also checked the completeness and correctness of the data. Demographic data and additional relevant information

(e.g. recent trauma or surgery, cancer, use of anticoagulants, duration of time since symptom onset and D-dimer test result) were collected on a Case Report Form (CRF), available in paper and digital format. The computerized design forced the physician to start the diagnostic process with clinical evaluation of the patient and to enter all variables necessary to calculate the four CDRs and the D-dimer test result into the computer. The computer program calculated the four individual CDR scores and, after combining these scores with the D-dimer result indicated to the physician the next recommended step in the diagnostic process according to the predefined study flow: either exclusion of PE based on the CDR and D-dimer level or performing a CT scan (Figure 1).

Follow-up

Patients in whom PE was excluded, either based on the CDR/D-dimer combination (for all four CDRs) or based on a normal CT, were followed up for 3 months. All patients were instructed to return to the hospital should complaints of venous thromboembolism (PE or DVT) or bleeding occur. Objective diagnostic tests were performed if a suspicion of VTE was raised e.g. CT-scanning, V/Q-scanning and/or compression ultrasonography. Patients were interviewed by telephone by one of the study coordinators at the end of a 3-month follow-up period and were questioned on health-related events during the past three months, especially for symptoms suggestive of PE or DVT, interval initiation of anticoagulants and possible haemorrhagic complications. If relevant, the patient's general practitioner was contacted for additional information. If a patient had died, the case of death was obtained from hospital records, autopsy reports or from information of the general practitioner. Deaths were classified as due to pulmonary embolism in case of confirmation by autopsy, an objective diagnostic test positive for PE prior to death, or if the cause of death could not completely be explained by reasons other than VTE. All outcomes were adjudicated by a panel of three experts.

Statistical analysis

We calculated that, based on a β of 10% (power 90%) and an alpha of 0.05, 128 positive CT-scans would be needed to detect a difference of more than 5% (55% vs. 50%) in sensitivity among the two primary CDRs (i.e. Wells and revised Geneva score). Based on a prevalence of PE of 20%,[2] a sample size of 753 participants with suspected pulmonary embolism was required. All additional sample size calculations on other outcomes needed a smaller sample size. Because of possible dropout, we aimed for a total sample size of 800 patients.

In this study, the four CDRs were directly compared for their performance in identifying patients as having PE or not. This included four primary analyses: 1) the ability of each CDR to correctly categorize patients with suspected PE as "unlikely" or "likely";

2) the proportion of patients in whom the diagnosis was excluded based on an "unlikely" CDR combined with a normal D-dimer test at the time of the acute evaluation; 3) the safety of clinical management based upon each CDR-D-dimer combination to exclude the diagnosis, i.e. the true negative results (proportion of patients safely managed without CT scan) and false negative results. The latter was defined as the VTE rate during the 3-month follow-up in patients in whom PE was considered ruled out by the initial diagnostic work-up and who did not receive anticoagulants during follow-up; 4) The distribution of patients in the probability categories according to the four CDRs was studied using sensitivity, specificity and receiving operating characteristic (ROC) analysis. Also, the discordant cases (patients classified as "unlikely" by one CDR but "likely" by another) were described. The reference standard in patients, in whom CT scanning was not indicated, was the recurrent VTE rate during 3-month follow-up. For patients who had to undergo CT scanning, the reference standard was CT scanning and 3-month follow-up.

Performance of the four CDRs and the combination of the CDRs and D-dimer testing were examined using sensitivity, specificity, ROC analysis, event rates and predictive values. To assess differences between the four CDRs in sensitivity, specificity, predictive values and to compare the categorization of patients into the probability groups (paired data), multiple testing was performed using McNemar's test. Each CDR was compared with the other CDRs individually. Furthermore, stratification by type of hospital (academic and non-academic hospitals) was performed to give insight into possible type of hospital-associated differences using stratified Mantel-Haenszel test (CDR "likely"/"unlikely" versus outcome of PE stratified for academic versus non-academic hospitals). Exact 95% confidence intervals (CI) were calculated around the observed incidences using Confidence Interval Analysis.[13] Descriptive parameters were calculated using SPSS software, version 16.0 (SPSS Inc, Chicago, Ill). Mean values and frequencies such as the clinical characteristics of subgroups were compared using Students t-test and χ^2-test respectively. Statistical significance was set at $p<0.05$.

RESULTS

Study patients

Between July 2008 and November 2009, a total of 1023 consecutive patients with clinically suspected pulmonary embolism were screened, of whom 195 (19%) were excluded because of one or more of the predefined exclusion criteria (Figure 1). In addition, 21 patients refused to give informed consent. The final study population of 807 participants included 644 (80%) outpatients and 163 (20%) inpatients. The baseline demographic and clinical characteristics of the 807 study participants are shown in Table 2.

Table 2. Clinical characteristics of the 807 patients with suspected pulmonary embolism.

Characteristic	Value
Age, mean (SD), y	53 (17.7)
Female, n (%)	487 (60.3)
Outpatient, n (%)	644 (79.8)
Duration of complaints, median (IQR), d	2 (1-7)
Body mass index, mean (SD), kg/m2	26.3 (5.5)
Risk factors	
Immobilization or recent surgery, n (%)	176 (21.8)
Previous VTE, n (%)	39 (4.8)
COPD with treatment, n (%)	75 (9.3)
Heart failure with treatment, n (%)	47 (5.8)
Active malignancy, n (%)	114 (14.1)
Estrogen use, women, n (%)	97 (19.9)
Body mass index ≥ 30 kg/m2, n (%)	152 (4.6)
Symptoms and clinical presentation	
Clinical symptoms of deep vein thrombosis, n (%)	47 (5.8)
Heart rate, mean (SD), bpm	88 (18.8)
Hemoptysis, n (%)	40 (5.0)

Bpm: beats per minute; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; SD: standard deviation; VTE: venous thromboembolism.

Result of Diagnostic Algorithm

Patients were managed according to the results of CDRs combined with the D-dimer test result as illustrated in Figure 1. Discordant CDR results were observed in 243 patients (29%), while in 564 patients the CDR results were concordant. In total, PE was ruled out by a combination of an "unlikely" CDR result according to all four CDRs and a normal D-dimer test result in 169 patients (21%). In 638 patients (79%) CT was indicated; either due to an abnormal D-dimer test result (265 patients) or due to having at least one of CDRs indicating "PE likely" in 373 patients.

D-dimer testing was not performed in 19 patients (protocol violations). This happened in one patient with "PE unlikely" according to all four CDRs; this patient was regarded as having a positive D-dimer test and a CTPA was performed (this patient is one of the 265 patients with an 'abnormal' D-dimer). In 18 other patients, the CDR results were discordant. The missing D-dimer result had no impact on the next step in the strategy, for a CTPA was to be performed based on the discordant CDRs.

Protocol violations regarding CTPA occurred in 16 patients: in nine of them CT scanning was indicated but not performed, these patients were all followed for three months; in seven patients, CT scanning was performed while it was not indicated, and showed PE in one of these patients.

In total, CT confirmed the diagnosis of PE in 185 patients, 184 with at least one "likely PE" CDR and a positive D-dimer result and 1 for whom the CT scan was not indicated based on the study criteria, but was done based on clinical judgment (Table 3, patient

Table 3. Characteristics of patients in whom venous thromboembolism was found during the 3-month follow-up, despite initial exclusion of the diagnosis.

Patient			Outcome of diagnostic tests at inclusion						Follow-up		
Pt.	**Sex**	**Age**	**Wells**	**SW**	**RGS**	**sRGS**	**DD**	**CT at presentation**	**VTE**	**Day (d)**	**Brief description**
1	Male	65	↓	↓	↓	↓	482	Indicating PE	PE	0	CT was performed although not indicated (all CDR unlikely and a normal D-dimer), and positive for PE: multiple subsegmental emboli were found, as well as signs suggesting pulmonary infarction
2	Female	63	↑	↑	↑	↑	1535	Normal	DVT	19	Also suspected for DVT at presentation, CUS was negative for DVT at presentation
3	Male	63	↓	↑	↑	↑	1100	Normal	PE	22	PE found by coincidence on CT-scan made for other reasons
4	Female	39	↓	↓	↓	↓	1100	Normal	DVT	27	DVT was found on CUS at day 27 (during hospitalisation). Despite this finding, anticoagulant treatment was delayed till day 51 after another CUS positive for DVT
5	Female	58	↓	↓	↓	↓	2600	Normal	DVT	62	DVT of jugular and subclavian vein, patient had Takayasu arteritis
6	Female	43	↓	↑	↓	↓	2100	Normal	DVT	21	DVT of jugular vein found by coincidence on staging CT-scan after chemo-radiotherapy
7	Male	87	↓	↓	↑	↑	3420	Normal	DVT	0	DVT found on CUS made directly after CT negative for PE, patient also had complaints of the leg
8	Female	62	↑	↑	↓	↓	-*	Normal	DVT	7	DVT after surgery and immobilisation

Wells: original Wells rule; SW: simplified Wells rule; RGS: revised Geneva score; sRGS: simplified revised Geneva score; DD: D-dimer test; CT: computed tomography; VTE: venous thromboembolism; ↑: clinical decision rule indicating "likely"; ↓: clinical decision rule indicating "unlikely"; PE: pulmonary embolism; DVT: deep vein thrombosis; CDR: clinical decision rule; CUS: compression ultrasonography

*D-dimer was not performed.

number 1; Figure 1). The diagnosis was excluded in 435 patients; in 164 of them an alternative diagnosis for the complaints was found. CT was inconclusive in 10 patients: repeat CT scanning excluded the diagnosis in two of these patients, and ventilation/perfusion scintigraphy excluded the diagnosis in two other patients. In one patient, anticoagulant treatment was started based on an inconclusive CT scan combined with high clinical suspicion of PE and in another, thrombosis of the subclavian vein was found with the same scan; these patients were treated accordingly. In the remaining 4 patients with inconclusive CT scans, the diagnosis was considered to be excluded without further testing and as a result these patients were not treated with anticoagulation medication. A final diagnosis could be established within an hour in the majority of the patients or at maximum within 24 hours after presentation. The overall prevalence of PE in this total study population was therefore 185/807 (23%, 95% CI: 20% to 26%).

Follow Up

In seven patients of the 169 patients in the all-unlikely group who had a normal D-dimer, the protocol was violated and a CT scan was performed while not indicated; in one of these patients, PE was diagnosed as already mentioned above. This was regarded as a diagnostic failure in the CDR-D-dimer strategy (1/169; 0.6%, 95% CI: 0.02% to 3.3%) (Figure 2; patient number 1 in Table 3). None of the remaining 168 patients in this group were treated with anticoagulants during follow-up and all of these patients had an uneventful follow-up. The nine patients, in whom a CT scan was indicated but not performed, were also left untreated and had an uneventful follow-up. Of the 435 patients in whom PE was excluded with CT scanning and the eight untreated patients with inconclusive results, 10 patients (2.3%) were treated with anticoagulants during follow-up for reasons other than VTE. Seven of the 433 patients with a normal or inconclusive CT scan result without anticoagulant treatment for other reasons returned with symptomatic and objectively confirmed VTE events during the 3-month follow up (Figure 1; patient numbers 2 to 8 in Table 3). Eighteen patients died during follow-up. In one of these patients, a DVT had already been diagnosed during follow-up; in another patient PE was excluded by autopsy as cause of death; while in the remaining 16 patients, the cause of death was adjudicated to be unrelated to a possible VTE. Therefore, the failure rate of a normal or inconclusive CT in this study was 7 in 433 (1.6%, 95% CI: 0.7% to 3.3%). One patient (1/807, 0.1%) was lost to follow-up. In a "worst case" scenario, in which this patient would have developed VTE, the failure rate after CT-scanning that excluded PE would have been 8 in 433 (1.9%, 95% CI: 0.8% to 3.6%). Allergy to intravenous iodinated contrast or contrast induced nephropathy was not recognized in the included patients during the study period.

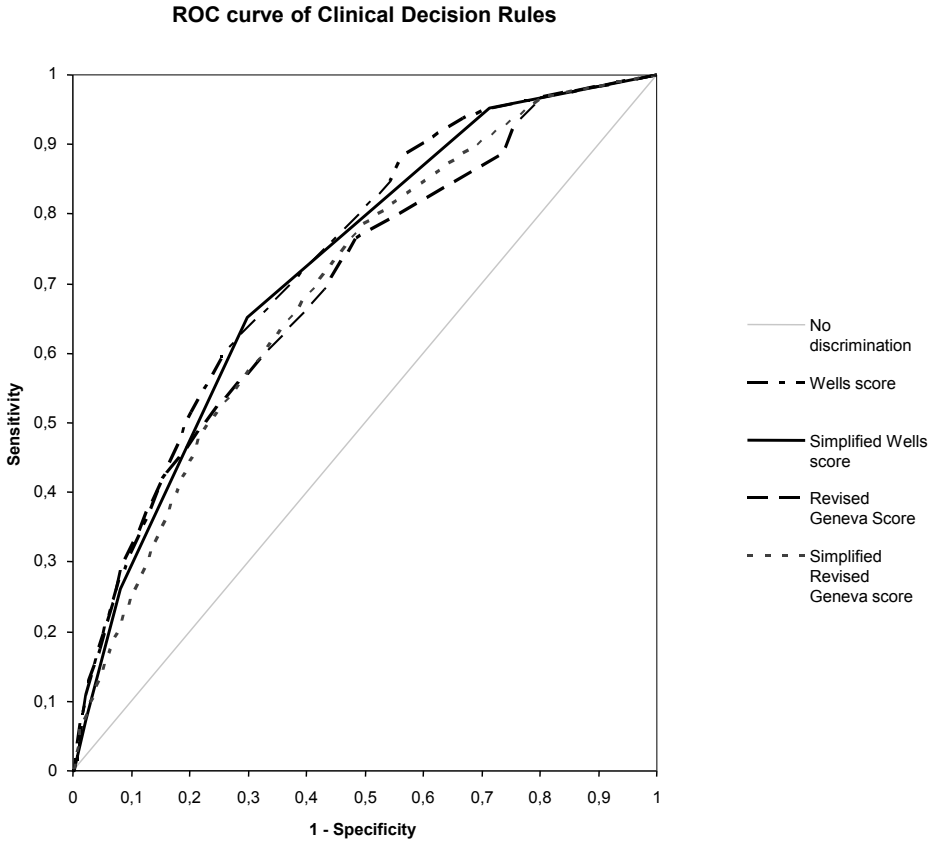

Figure 2. Receiver operating characteristics curves of the four clinical decision rules. Continuous clinical Decision Rules. Area under the curves: 0.73 (95% CI 0.69-0.77) for the Wells rule, 0.72 (95% CI 0.68-0.76) for the simplified Wells rule, 0.70 (95% CI 0.65-0.74) for the revised Geneva score and 0.69 (95% CI 0.65-0.74) for the simplified revised Geneva score, respectively.

Categorization of patients in probability groups with the four CDRs

Table 4 describes how the patients were categorized by the two probability categories of the four CDRs without taking the D-dimer test results into account. The proportion of patients classified as "unlikely PE" was similar for the four CDRs. Also, the prevalence of PE in the "unlikely" categories was comparable. Overall, the proportion of patients classified as "likely" was largest using the simplified Wells rule: 38% versus 28% to 32% with the other three CDRs (Table 4). The sensitivity and specificity of each CDR alone (without D-dimer results) ranged from 49% to 65% (sensitivity) and from 70% to 80% (specificity), respectively (Table 5a).

The Receiver Operator Characteristics-curves for the four CDRs were comparable and showed areas under the curve ranging from 0.69 to 0.73 (Figure 2).

Table 4. Distribution of patients in unlikely and likely clinical probability based on four clinical decision rules and the combination of the CDR and D-dimer test (n=807).

	Original Wells rule	Simplified Wells rule	Original Revised Geneva rule	Simplified revised Geneva rule
CDR unlikely, n (%, 95% CI)	584 (72, 69-76)	499 (62, 59-65)	553 (69, 65-72)	576 (71, 68-75)
Prevalence of PE in patients with CDR 'unlikely', n (%, 95% CI)	90/584 (15, 13-18)	65/499 (13, 10-16)	88/553 (16, 13-19)	95/576 (17, 14-20)
CDR likely, n (%, 95% CI)	223 (28, 25-31)	308 (38, 35-41)	254 (32, 28-35)	231 (29, 26-32)
Prevalence of PE in patients with CDR likely, n (%, 95% CI)	95/223 (43, 36-49)	120/308 (39, 34-44)	97/254 (38, 32-44)	90/231 (39, 32-45)
CDR unlikely and D-dimer normal, n (%, 95% CI)	184 (23, 20-26)	178 (22, 19-25)	185 (23, 20-26)	190 (24, 21-27)
VTE incidence in patients with CDR unlikely and a normal D-dimer, n (%, 95%CI)	1/184 (0.5, 0.0-3.0)	1/178 (0.6, 0.0-3.1)	1/185 (0.5, 0.0-3.0)	1/190 (0.5, 0.0-2.9)

CDR: Clinical decision rule; PE: pulmonary embolism; VTE: venous thromboembolism.

Performance of the four CDRs together with D-dimer

Combined with a normal D-dimer, the four CDRs excluded PE in similar proportions of patients, ranging from 22% to 24% (Table 4). There was no difference between the 3-month VTE failure rates of the different CDR-D-dimer combinations. This failure rate ranged from 0.5% to 0.6% (Table 4). The 95% CI is 0 to 3% for all CDRs (Table 4). When combined with the D-dimer test result, the sensitivities of the various CDRs did not differ, while there were small differences in specificity (Table 5b).

Discordance between the CDRs

Of the 434 patients with all 4 CDRs indicating PE unlikely, 52 (12%) were diagnosed with PE; all patients except one had an abnormal D-dimer test result, the latter which indicated the need for CT-scanning.

In 243 of 807 patients (29%) discordance between CDRs was observed (Figure 1); the D-dimer test result was normal in 29 abnormal in 196, and incorrectly not performed in 18. In the latter 18 patients, CT-scanning was performed which confirmed the diagnosis of PE in one patient.

The number of discordant cases between two scores ranged from 25/807 (3.1%) between the revised Geneva score and the simplified revised Geneva score, to 199/807 (25%) between the Wells rule and the revised Geneva score (Table 6a). The agreement was greatest between the original scores (Wells, revised Geneva score) and their simplified versions (simplified Wells and simplified Geneva score; discordance 11% and 3.1% of the total cohort, respectively, while discordance was above 20% between all other scores.

Table 5a. Accuracy indices the clinical decision rules alone in 807 patients with a suspected event.

	Wells rule	Simplified Wells rule	RGS	Simplified RGS
Sensitivity, n, % (95% CI)	99/192, 52 (45-59)	125/192, 65 (58-72)	101/192, 53 (46-60)	94/192, 49 (42-56)
Specificity, n, % (95% CI)	491/615, 80 (77-83)	432/615, 70 (67-74)	462/615, 75 (72-79)	478/615, 78 (74-81)
NPV, n, % (95% CI)	491/584, 84 (81-87)	432/499, 87 (84-90)	462/553, 84 (81-87)	478/576, 83 (80-86)

RGS: revised Geneva score; CI: confidence interval; NPV: negative predictive value; PE: pulmonary embolism.
Sensitivity: the number of patients correctly identified as having PE by the CDR alone (independent of D-dimer results), divided by the total number of patients with proven PE identified by CT scan at the time of initial evaluation or VTE during 3-month follow-up.
Specificity: the number of patients correctly identified as not having PE by the CDR alone (independent of D-dimer results), divided by the total number of patients in whom PE was excluded by CT scan at the time of initial evaluation or VTE during 3-month follow-up.
NPV: the number of patients correctly identified as not having PE based on the CDR alone (independent of D-dimer results); divided by the total number of patients with CDR unlikely.
VTE: venous thromboembolism (i.e. PE and deep vein thrombosis).

Sensitivity was significantly different between the Wells rule and the simplified Wells rule ($p<0.001$); the simplified Wells rule and the RGS ($p=0.001$); the simplified Wells rule and the simplified RGS ($p<0.001$); and the RGS and simplified RGS ($p=0.039$). Other differences in sensitivity were not statistically significant.
Specificity was significantly different between the Wells rule and the simplified Wells rule ($p<0.001$); the Wells rule and the RGS ($p=0.020$); the simplified Wells rule and the RGS ($p=0.011$); the simplified Wells rule and the simplified RGS ($p<0.001$); and the RGS and the simplified RGS ($p<0.001$). Other differences in specificity were not statistically significant.

Despite the discordant scores, PE was not missed in any of the patients from the discordant group who had a normal D-dimer (Table 6b). Therefore, the scores performed equally well in excluding PE when combined with a D-dimer.

Inpatients

Both inpatients and outpatients were included in the study. The proportions of inpatients who were categorized as "unlikely" were as follows: 37% using the simplified Wells rule, 48% using the revised Geneva rule, 50% using the simplified revised Geneva rule and 57% using the Wells rule. These proportions were smaller compared to the proportions of outpatients categorized as "unlikely": 68%, 74%, 77% and 76% for the four CDRs, respectively (multiple tests, all with $p< 0.01$).

The failure rate of excluding PE based on an "unlikely" CDR and normal D-dimer test was similar for both inpatients and outpatients with all four CDRs. However, the proportion of inpatients in which PE could be excluded non-invasively was very low: only three inpatients using the simplified Wells rule (3/163; 1.8%); four patients using the Wells rule (2.5%); and 5 patients using the revised Geneva score and the simplified revised Geneva

Table 4/5b. Accuracy indices of the clinical decision rules in combination with a normal D-dimer test in patients with a suspected event.

	Original Wells rule N=796*	Simplified Wells rule N=803*	RGS N=796*	Simplified RGS N=795*
Sensitivity, n, % (95% CI)	190/191 99.5 (97-100)	191/192, 99.5 (97-100)	188/189, 99.5 (97-100)	187/188, 99.5 (97-100)
Specificity, n, % (95% CI)	183/605, 30 (27-34)	177/611, 29 (25-33)	184/607, 30 (27-34)	189/607, 31 (28-34)
NPV, n, % (95% CI)	183/184, 99.5 (97-100)	177/178, 99.4 (97-100)	184/185, 99.5 (97-100)	189/190, 99.5 (97-100)

RGS: revised Geneva rule; CI: confidence interval; NPV: negative predictive value; PE: pulmonary embolism.
*Patients with a CDR indicating "PE unlikely" but in whom the D-dimer result was missing (protocol violation) were not included in this analysis, this number differed between the four CDRs.
Sensitivity: the number of patients correctly identified as having PE by the combination of CDR and D-dimer testing, divided by the total number of patients with proven PE identified by CT scan at the time of initial evaluation or VTE during 3-month follow-up.
Specificity: the number of patients correctly identified as not having PE by the combination of CDR and D-dimer testing, divided by the total number of patients in whom PE was excluded by CT scan at the time of initial evaluation or VTE during 3-month follow-up.
NPV: the number of patients correctly identified as not having PE by the combination of CDR and D-dimer testing, divided by the total number of patients with CDR/D-dimer combination indicating PE excluded.
VTE: venous thromboembolism (i.e. PE and deep vein thrombosis).

Sensitivities did not differ between the four CDRs in combination with D-dimer test. Specificity was significantly different between the Wells rule and the simplified Wells rule (p=0.031) and the simplified Wells rule and simplified RGS (p=0.017). Other differences in specificity were not statistically significant.

score (3.1%). No failures occurred in the inpatients in whom PE was excluded without the need for CTPA.

Stratification by academic versus non-academic hospitals

In total, 5 academic hospitals included 598 (74%) patients, while the 2 non-academic hospitals included 209 patients (26%). The demographic characteristics as described in Table 2 did not differ for patients from academic versus non-academic hospitals, except for malignancy (16% vs. 8.1%, p<0.001) and recent surgery or immobilization (26% vs. 11%, p<0.001). Adjusting the results for academic and non-academic hospitals, a correct categorization of probability (categorization as "unlikely" or "likely" with respect to the outcome of PE) was found more often at non-academic sites. A correct categorization of 66% up to 71% was found at academic hospitals versus 75% up to 79% at non-academic hospitals; p<0.001 for all four CDRs.

Table 6a. Discordances between the categorization in "unlikely" and "likely" clinical probability groups according to four clinical decision rules in 807 patients with suspected pulmonary embolism. In total, 243 patients had discordant results.

	Wells "likely" (n=223)		**SW "likely"** (n=308)		**RGS "likely"** (n=254)		**SRGS "likely"** (n=231)	
	n	n with PE	n	n with PE	n	n with PE	n	n with PE
Wells "unlikely" (n=584)	X		85	25	115	26	100	23
SW "unlikely" (n=499)	0	0	X		65	14	51	11
RGS "unlikely" (n=553)	84	24	119	37	X		1	1
SRGS "unlikely" (n=576)	92	28	128	41	24	8	X	

Wells: Original Wells rule; SW: simplified Wells Rule; RGS: Revised Geneva score; SRGS: simplified revised Geneva score; PE: pulmonary embolism.
The number of patients with discordant CDR results when two CDRs are compared can be calculated by adding the number of patients with an "unlikely" score according to one CDR, but a "likely" score according to the other CDR, to the number of patients with a "likely" score according to the first CDR but an "unlikely" score according to the second CDR. For instance: to find the number of patients with discordant results comparing the RGS with the simplified RGS: There are 24 patients with a "likely" RGS result who have an "unlikely" simplified RGS result. Also, there is one patient with an "unlikely" RGS results but with a "likely" simplified RGS result. This means there is a total 24 + 1 = 25 patients with discordances when the RGS and simplified RGS are compared, out of a total of 807 patients (3.1%).

Table 6b. Discordances between the categorization in "unlikely" and "likely" clinical probability groups according to four clinical decision rules in 205 patients with suspected pulmonary embolism and a normal D-dimer test result. In total, 29 patients had discordant clinical decision rule results.

	Wells "likely" (n=21)		**SW "likely"** (n=27)		**RGS "likely"** (n=20)		**SRGS "likely"** (n=15)	
	n	n with PE	n	n with PE	n	n with PE	n	n with PE
Wells "unlikely" (n=184)	X		6	0	12	0	8	0
SW "unlikely" (n=178)	0	0	X		9	0	5	0
RGS "unlikely" (n=185)	13	0	16	0	X		0	0
SRGS "unlikely" (n=190)	14	0	17	0	5	0	X	

Wells: Original Wells rule; SW: simplified Wells Rule; RGS: Revised Geneva score; SRGS: simplified revised Geneva score; PE: pulmonary embolism.

DISCUSSION

This accuracy study directly compared four CDRs for the probability assessment of PE and showed that the CDRs are similar in 1) their ability to categorize patients in an "unlikely" and "likely" clinical probability group; 2) the proportion of patients in whom CTPA was not indicated on the basis of an "unlikely" CDR result and a normal D-dimer test and 3) the 3-month failure rate for VTE in the patients in whom PE was excluded by CDR and D-dimer testing. Importantly, although discordances in the categorization of patients in an "unlikely" or "likely" group by the scores were present in 30% of the

patients, this did not result in a difference in failure rates when the CDR was combined with the D-dimer.

Our results are important and relevant for clinical practice. Despite the debate on the subjective variable in the Wells rule, in this direct comparison, the Wells rule and simplified Wells rule showed to be equivalent in performance compared to the fully objective revised Geneva score. Additional to the comparison of these two rules, we were able to validate the performance of the recently introduced simplifications of the Wells rule and revised Geneva score. Both simplified scores had similar diagnostic performance to their original and extensively validated versions. Despite discordances between the CDR outcomes in 30% of patients, there was no difference in safety using a management strategy based on any of the CDRs combined with D-dimer testing. This equal performance could be explained by the use of a highly sensitive D-dimer test in patients with a CDR indication of "PE unlikely".

The importance of clinical probability estimation has been emphasized on many occasions.[14-18] Although the D-dimer is a sensitive assay in the diagnosis of PE, false negative results are more likely to occur when the pre-test clinical probability is high.[18] This prospective validation of the simplified CDRs has relevant practical implications, for they enable easier computation of the clinical probability score, which in turn could lead to better implementation of CDR use in daily clinical care. Our findings are in line with previous studies using these CDRs in a two-category scheme.[14] With the Wells rule, 51-84% of patients were categorized as "unlikely" in previous reports, with prevalence of PE ranging from 3.4-12%, compared to 72% categorized as "unlikely" in this study with a prevalence of PE of 15%. Using the simplified Wells rule, the proportion of "PE unlikely" patients was slightly lower in our cohort (62%) compared to a previous validation study (78%), but prevalence of PE in this "unlikely" group was comparable (13% in both studies).[10] Similarly, in an earlier retrospective study, the simplified revised Geneva score classified 65% of the patients as "unlikely" compared to 62% in the current analysis, with PE prevalence of 13% in the previous study and 16% in our study.[8] As this is the first study to report a two-category scheme for the revised Geneva score, we cannot compare our data of the two-category revised Geneva score with previous findings. However, the 69% patients with an "unlikely" CDR result according to the revised Geneva score as well as the 16% prevalence of PE in this group overlap well with the results from the other three decision rules.

Four highly sensitive but different D-dimer assays were used. Because the CDRs were determined in all patients, the types of D-dimers assays were equally represented in the different CDR groups, which enable comparison of the CDRs, irrespective of the D-dimer assay. Type of assay was not based on randomization, but was dependent on the prefer-

ence of the study center. Unfortunately, therefore, comparisons between the various D-dimer assays are limited by the sample sizes.

After several retrospective or small prospective comparisons, this is the first large study to directly compare the most widely used CDRs (original Wells rule and original Revised Geneva score) in the diagnostic management of PE. Furthermore, this study prospectively validated the performance of the recently introduced simplified Wells rule and simplified revised Geneva score. Calculation of the scores in all patients allowed a direct comparison of the CDRs in a single patient population. Also, due to the computer-aided design of the study, calculation errors were minimized. Likewise, this use of a computer program to guide the physician on the next step in the diagnostic algorithm excluded the possibility of allowing the physician's preference for a certain CDR to influence the management of a patient. There are several arguments for the results of our study to be applicable in a wide range of clinical settings. First, the clinical characteristics of the patients in the study are comparable with those in other population-based studies,[2,4] and the 23% prevalence of PE in this cohort is comparable to other reports.[2,4,6] Second, consecutive patients were included from both academic and non-academic medical centers.

Several potential limitations of our study require comment. First, a randomized controlled trial between the four CDRs is an alternative study design, but in view of the reasonably high concordance rates would likely have been very inefficient. In addition, by study design, CT scans were performed in all patients with discordant CDRs and ensured that an imaging diagnosis was available in all those patients. The diagnostic protocol was violated in four patients, in whom CT was not performed despite discordance of the CDRs. Three-month follow-up, however, was uneventful in these patients. Second, we did not manage on one of the separate CDRs in combination with D-dimer testing but the combination of the four CDRs and D-dimer testing. According to the protocol, all patients with discordant CDR results underwent CT scanning. The majority of these patients had elevated D-dimer levels and would have an indication for CT-scanning, even if just one of the CDRs was used for decision making. Only patients with discordant results and a normal D-dimer level (29; 3.6% of the included patients), did not have an indication for a CT scan using one of the separate rules combined with D-dimer testing; they underwent CT scanning because at least one of the other rules indicated PE "likely". Third, use of a computerized decision-support system improves the diagnosis of pulmonary embolism.[19] However, in daily clinical practice, these systems may not be widely available and our results may therefore differ from a setting in which more miscalculations are possible.

Finally, although both inpatients and outpatients were included in this study and no failures occurred in the patients in whom the diagnosis could be excluded, we are

unable to validate that any of the CDRs/D-dimer combinations can safely exclude the diagnosis in inpatients.

Further research may include an outcome study using one of the simplified CDRs in combination with D-dimer testing. Since patients with suspected recurrent PE were not included, the performance of the CDRs in this group will need additional research.

In conclusion, the Wells rule, the revised Geneva score, the simplified Wells rule as well as the simplified revised Geneva score, in combination with a D-dimer test, all performed similarly in the exclusion of acute PE. This prospective validation indicates that the simplified, more straightforward CDRs may be used in clinical practice. Which rule a physician will use should depend on local preference and acquaintance, in order to accomplish correct use of the CDR and prevent miscalculations.

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CHAPTER 5

Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: systematic review and meta-analysis.

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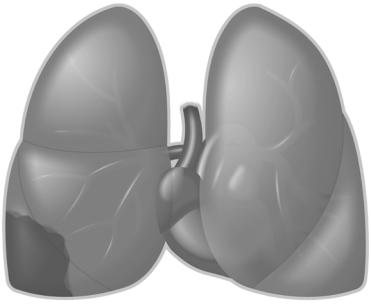

ABSTRACT

Introduction

Several outcome studies have ruled out acute pulmonary embolism (PE) by normal computed tomography pulmonary angiography (CTPA). We performed a meta-analysis in order to determine the safety of this strategy in a specific group of patients with a strict indication for CTPA, i.e. 'likely' or 'high' clinical probability for PE, an elevated D-dimer concentration, or both.

Methods

Studies that ruled out PE by normal CTPA, with or without subsequent normal bilateral compression ultrasonography (CUS), in patients with a strict indication for CTPA, were searched for in Medline, EMBASE, Web of Science and the Cochrane dataset. Primary endpoint was the occurrence of (fatal) thromboembolic events (VTE) in a 3-month follow-up period.

Results

Three studies were identified that excluded PE by CTPA alone (2020 patients) and three studies that performed additional CUS of the legs after normal CTPA (1069 patients). The pooled incidence of VTE at three months was 1.2% (95%CI 0.8-1.8%) based on a normal CTPA as a sole test and 1.1% (95%CI 0.6-2.0%) based on normal CTPA and negative CUS, resulting in a NPV of 98.8% (95%CI 98.2-99.2%) and 98.9% (95%CI 98.0-99.4%) respectively. This compares favorably with the VTE failure rate after normal pulmonary angiography (1.7%, 95%CI 1.0-2.7). Risk of fatal PE did not differ between both diagnostic strategies (0.6% vs. 0.5%).

Conclusion

A normal CTPA alone can safely exclude PE in all patients in whom CTPA is required to rule out this disease. There is no need for additional ultrasonography to rule out VTE in these patients.

INTRODUCTION

Computed tomography pulmonary angiography (CTPA) is currently the preferred thoracic imaging test for patients suspected of having pulmonary embolism (PE).[1] This is the result of the high negative predictive value (NPV) of CTPA that was shown to range from 98.7 to 99.9%.[2,3] In addition, it has been demonstrated that there is no necessity of performing additional imaging, e.g. compression ultrasonography after a normal multidetector- row CTPA before excluding venous thromboembolic disease and withholding anticoagulant therapy.[2,3] However, in these reports, patients with low, intermediate as well as patients with high clinical pretest probability for having PE were selected for CTPA. In several recent studies, it has been shown that acute PE can be ruled out without the need for radiological imaging tests in a specific patient population with 'low' or 'unlikely' clinical probability for PE in combination with a normal high-sensitive D-dimer test result.[4-6] Since the NPV of a test is dependent on the prevalence of the disease in the tested population, the NPV of CTPA in patients in whom PE can not be ruled out by a clinical decision rule and a D-dimer test, i.e. with 'likely' or 'high' pretest probability for PE or an abnormal D-dimer test result (prevalence of PE 37-47%[7]), is likely to be less favorable than the NPV of CTPA in the overall population suspected of having PE (prevalence of PE 20-26%[7]). Furthermore, several studies have shown that despite of a negative CTPA, deep vein thrombosis (DVT) can be identified by compression ultrasonography (CUS) in patients with suspected PE.[4,8,9]

Our objective was to perform a systematic review and meta-analysis to determine the safety of excluding acute PE on the basis of a normal CTPA alone for all patients with clinically suspected acute PE and a strict indication for CTPA to rule out PE, i.e. with a 'likely' or 'high' clinical probability or an elevated D-dimer concentration. In addition, we studied the additional value of CUS after a normal CTPA in this specific patient cohort.

METHODS

Data sources

A literature search was performed to identify all published prospective outcome studies that excluded PE on the basis of a normal CTPA result. MEDLINE, EMBASE, Web of Science and the Cochrane dataset were searched using pre-defined search terms. Search criteria included "pulmonary embolism" or "venous thromboembolism" or "venous thrombosis" and "computed tomography" or "spiral CT", a complete overview of the search criteria is attached (appendix 1). Articles published from January 1990 till September 2008 were eligible for this analysis. Papers were not limited to the English language. All references of the included studies were reviewed for potential relevant articles.

Study outcome

Outcome of this meta-analysis was the NPV of CTPA and the safety of withholding anticoagulant therapy based on a normal CTPA result in patients with a strict indication for CTPA, i.e. a clinical decision rule indicating 'likely' or 'high' probability, an elevated D-dimer concentration or both. Endpoints were objectively confirmed adverse thrombotic events subsequent to a normal CTPA, including all occurrences of venous thromboembolism (VTE), i.e. both deep vein thrombosis (DVT) and PE, and mortality attributable to PE.

Study selection and inclusion criteria

Mandatory for inclusion was a diagnostic strategy based on a clinical decision rule and a D-dimer test without additional imaging tests prior to CT scanning. In addition to studies that used CTPA as only imaging test, we also included studies that had used CUS of the legs following a normal CTPA to study the additional value of CUS for ruling out VTE. Further criteria for selection were: a prospective design, consecutive selection, predefined endpoints, clear description of inclusion and exclusion criteria and a clinical follow-up of more than one month. Two reviewers (I.M. and F.K.) independently reviewed all identified studies. In case of disagreement, a third reviewer (M.H.) was consulted.

Data abstraction

Data regarding study design, patient characteristics, diagnostic algorithm (clinical decision rule, D-dimer assay and CT modality), follow-up period, completeness of follow-up and endpoints were abstracted by two independent researchers. Guidelines proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group were followed to extract and present the data.[10] Individual study quality was assessed by the following items: patient enrollment, outcome assessment, duration of follow-up, loss-to-follow-up and funding source.

Statistical analysis

We identified the reported number of objectively confirmed VTE's and in addition all deaths attributed to PE for each study. Patients who received anticoagulants for reasons other than VTE and patients who were lost to follow-up were excluded from the analysis. A meta-analysis was performed by pooling the proportions in a fixed effect as well as in a random effects model. Because the criteria for the performance of CTPA in the included studies were comparable, the disease prevalence was expected to be similar between the studies. For this reason pooling of the NPV was reasonable. The proportions were weighted according to the inverse of the squared standard error. Shown proportions and confidence intervals in the text represent a fixed effects model calculated proportion. Studies with CTPA alone and with additional CUS following a normal CTPA were pooled separately. For assessment of heterogeneity, I^2 was calculated for all comparisons.[11] We defined the upper

limit of the 95% confidence interval of the fatal and non-fatal 3-month thromboembolic rate after a normal invasive pulmonary angiography as the cut-off point for the safe exclusion of PE by CTPA, thereby comparing CTPA with the reference standard. For assessment of the effect of the additive use of CUS following a normal CTPA on mortality, the weighted relative risk of fatal PE was calculated. And finally the sensitivity for both diagnostic strategies was calculated. For statistical analysis SPSS version 16.0 and Comprehensive Meta-Analysis (version 2.0, Biostat, Englewood, New Jersey, USA) were used.

RESULTS

Study selection

The literature search revealed 1075 studies; 1052 studies were excluded after review of title and abstract and 23 studies were identified for more detailed evaluation. After full review, an additional 18 studies were excluded due to a diagnostic algorithm that did not meet are predefined criteria, i.e. no clinical decision rule, D-dimer or CTPA performed, or performance of supplementary imaging before the CTPA. Three studies using CTPA without further imaging[5,12,13] and three studies that incorporated CUS after to the CTPA[4,8,9] were left for inclusion in this meta-analysis (Figure 1). No new articles were identified by reviewing the references of these included studies.

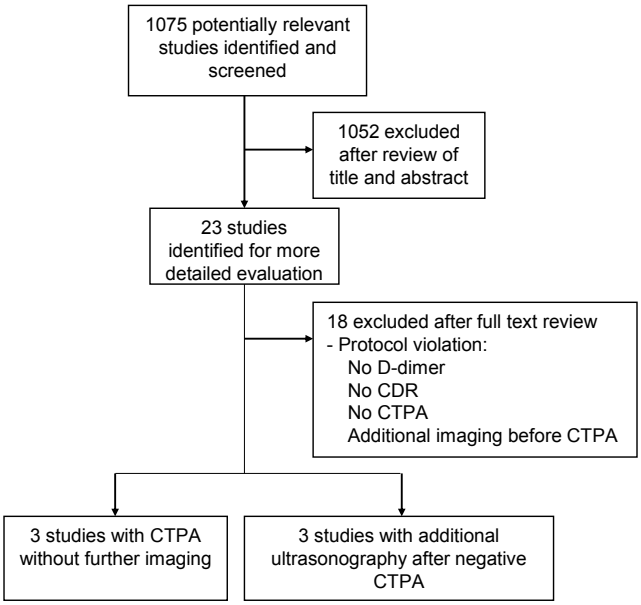

Figure 1. Flow diagram of study selection. CDR: clinical decision rule; CTPA: computed tomography pulmonary angiography.

Quality and characteristics of included studies

All six included studies were of prospective design with consecutive patient enrolment. The duration of follow-up was three months in all studies and loss to follow-up varied between 0.0 and 1.3% (Table 1). The demographic characteristics of patients in the studies were comparable (Table 2). Mean age varied from 50.2 to 60 years, the proportion of male gender ranged between 35 and 46% and the majority of patients were outpatients (Table 2). Different clinical decision rules were used, i.e. the Geneva score[14], the revised Geneva score[15,16], the Wells rule[17] or the Hyers criteria[18], in a two or three level scheme (Table 2). Also, different quantitative D-dimer tests were used: VIDAS D-dimer assay (BioMérieux, Marcy- l'Etoile, France), STA Liatest (Diagnostica Stago, Asnières, France, SimpliRED (Agen Biomedical Limited, Acaccia Ridge, Australia), Tinaquant assay (Roche Diagnostica, Mannheim, Germany) and an immunoturbimetric latex agglutination assay (IL-Test, Instrumentation Laboratory, Lexington, MA). Furthermore, the use of single- or multi detector row CT modalities varied between the studies (Table 2). In two studies, patients were randomized between two diagnostic strategies, i.e. CTPA or ventilation

Table 1. Study quality assessment.

Study	Study design	Patient enrollment	Outcome assessment	Duration of follow-up (months)	Lost to follow-up (n, %)	Funding source
van Belle[5]	Multicenter	Prospective, consecutive	Radiologist and adjudication committee; blinded	3	4 (0.1)	Unrestricted grants from the participating hospitals
Righini[12]	Multicenter, RCT	Prospective, consecutive	Independent and adjudication committee; blinded	3	1 (0.1)	Grant from the Swiss National Research Foundation, from the Projects Hospitaliers de Recherche Clinique and from Pneumonlogie Développement
Ghanima[13]	Single center	Prospective, consecutive	Independent adjudication committee	3	0 (0)	Grant from the Eastern Norway Regional Health Authory
Anderson 2005[9]	Multicenter	Prospective, consecutive	Laboratory, radiologist and adjudication committee; blinded	3	11 (1.3)	Grant from Heart and stroke foundation of Nova Scotia
Anderson 2007[4]	Multicenter, RCT	Prospective, consecutive	Radiologists and adjudication committee; blinded	3	7 (1.0)	Grant from the Canadian Institutes of Health Research
Perrier[8]	Multicenter	Prospective, consecutive	Independent adjudication committee	3	4 (1.2)	Grant from the Hirsch Fund of the University of Geneva

RCT: randomized controlled trial.

Table 2. Patient characteristics of included studies.

Study	Number	Mean age (year ±SD)	Male (n, %)	History of VT (n, %)	Cancer (n, %)	Surgery, immobilization or trauma (n, %)	Outpatient (n, %)	CDR (2- or 3-level scheme)[¶]	Single/ multi slice CT	D-Dimer assay
van Belle[5]	3306	53 ±18	1409 (43)	480 (15)	476 (14)	610 (19)	2701 (82)	Wells (2)	Single / MSCT	VIDAS / Tinaquant
Righini[12]	901*	60 ±19	410 (46)	121 (14)	72 (8.0)	59 (6.5)[#]	901 (100)	RGS (3)	MSCT	VIDAS
Ghanima[13]	432	58	201 (47)	43 (10)	31 (7.2)	38 (8.8)	432 (100)	Hyers criteria (3)	MSCT	STA-Lia
Anderson 2005[9]	858	50 ±18	300 (35)	77 (9.0)	58 (6.8)	160 (19)	858 (100)	Wells (3)	Single	SimpliRED/IL test[+]
Anderson 2007[4]	694*	53 ±19	259 (37)	64 (9.2)	67 (9.7)	161 (23)[#]	619 (90)	Wells (2)	Single / MSCT	Local practice
Perrier[8]	756	60 ±19	302 (40)	142 (19)	75 (9.9)	146 (19)	756 (100)	GS (3)	MSCT	VIDAS

*Only patients included in the CT-group after randomization; [#]number of patients with recent immobilization not mentioned; [¶]two level scheme: likely/less likely; three level scheme: low, intermediate and high clinical probability; [+]immunoturbimetric latex agglutination assay. CDR: clinical decision rule; RGS: revised Geneva score; GS: Geneva score; MSCT: multi-detector-row computed tomography; n: number; SD: standard deviation.

perfusion scintigraphy and CTPA or CUS preceding CTPA.[4,12] Only the patients randomized to CTPA were included in this analysis. Overall, the fraction of patients who had an indication for CTPA was 70% (range 35-93%). The overall proportion of inconclusive CT scan results was reported to be 1.8% (range 0.9-4.6%). The overall prevalence of PE by positive CTPA in these cohorts was 28% (range 18-36%).

Meta-analysis

Three studies were identified that excluded PE in symptomatic patients with an indication for CT-scanning based on a normal CTPA without additional imaging tests. Of all 2020 patients with an initial normal CTPA result, 25 (1.2%, 95%CI 0.80-1.8) were diagnosed with VTE in a 3-month follow-up period (Tables 3 and 4, Figure 2). Of these, 12 (12/2020; 0.60%, 95%CI 0.40-1.1) were classified as fatal PE. Markedly, only in two of these 12 patients, an autopsy was performed and PE was objectively identified as cause of death. The NPV for symptomatic VTE in three months following a negative CTPA in patients with an indication for CTPA was 98.8% (95% CI 98.2-99.2).

Table 3. Outcome of negative CT scans of the included studies.

Study	Patients (n)	CTPA performed (n, %)	Inconclusive CTPA result (n, %)	CTPA positive for PE (n, %)	CTPA negative for PE (n, %)	Resulting study population† (n)	VTE in follow-up (by immediate CUS according to protocol/ symptomatic)	Fatal PE (certain/ possible) (n/n)
CTPA alone								
van Belle[5]	3306	2249 (68)	20 (0.9)	647 (30)	1505 (67)	1435	-/18	2/5
Righini[12]	838#	558 (67)	15 (2.7)	179 (32)	364 (65)	364*	-/5	0/3
Ghanima[13]	432#	329 (76)	15 (4.6)	93 (28)	221 (67)	221	-/2	0/2
CTPA followed by CUS								
Anderson 2005[9]	858	300 (35)+	8¥ (1.7)	59 (20)	241 (80)	241‡	11/0	0/0
Anderson 2007[4]	694	646 (93)	10 (1.5)	115 (18)	531 (82)	531	7/4	0/2
Perrier[8]	756#	524 (69)	13 (2.5)	187 (36)	324 (62)	297	3/5	0/2

*In the follow-up of the complete study population without PE, one patient was lost to follow-up and 30 patients used anticoagulant therapy for other reasons than PE (the fraction of the latter patients in the normal CTPA cohort was not reported); #this number does not include study patients in case of protocol violation, lost to follow-up or use of oral anticoagulants for other reasons than VTE; +only CT scans performed in case of either 'high' clinical probability or elevated D-dimer test in combination with 'low' or 'intermediate' clinical probability; ¥number of inconclusive CTPA results for all performed CT scans in this study (n=467); †total number of patients with normal CTPA, complete follow-up and without anticoagulant therapy; ‡of the total study population, PE was ruled out by other means than by CTPA in 26 patients (CT indicated but not performed or inconclusive CTPA result followed by additional imaging; the fraction of the latter patients in the normal CTPA cohort was not reported). PE: pulmonary embolism; VTE: venous thromboembolism; CUS: compression ultrasonography.

Table 4. Random and fixed model proportions of study endpoints.

Model	VTE in FU after normal CTPA without CUS	Fatal PE in FU after normal CTPA without CUS	Positive echo directly subsequent to normal CTPA followed by CUS	VTE in FU after normal CTPA and negative CUS	Fatal PE in FU after normal CTPA and negative CUS
Fixed	1.2	0.6	2.4	1.1	0.5
95% CI	0.8-1.8	0.4-1.1	1.6-3.7	0.6-2.0	0.2-1.1
Random	1.2	0.6	2.0	1.0	0.5
95% CI	0.8-1.8	0.4-1.1	0.7-5.2	0.4-2.3	0.2-1.1
I^2	0.000	0.000	78.98	29.35	0.000

PE: pulmonary embolism; VTE:venous thromboembolism; FU: follow-up; CI: confidence interval; CTPA: computed tomography pulmonary angiography; CUS: compression ultrasonography.

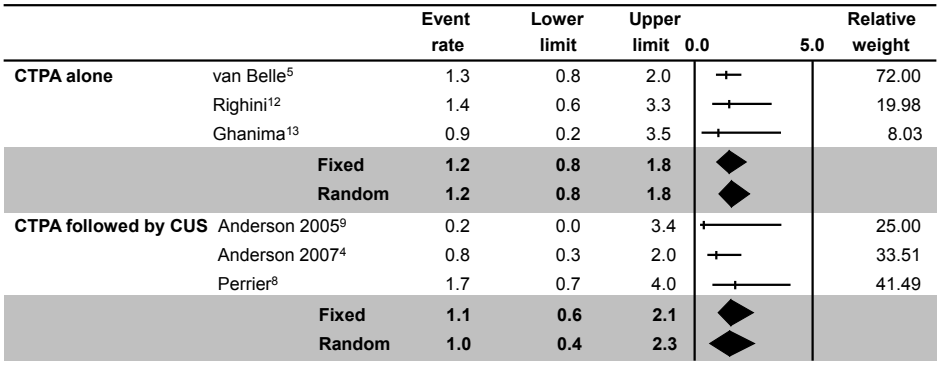

Figure 2. Pooled proportions (fixed as well as random effects model) of confirmed venous thromboembolism event rate after a normal computed tomography pulmonary embolism (CTPA) and after a normal CTPA followed by a negative compression ultrasonography (CUS) of the legs.

In the three studies that included CUS of the legs subsequent to a normal CTPA, 1069 symptomatic patients with an indication for CTPA and eventually a normal CTPA were identified. Twenty-one cases of DVT (21/1069; 2.4%, 95%CI 1.6-3.7) were identified by compression ultrasonography performed shortly after the CTPA (Tables 3 and 4). During 3-month follow-up, nine additional patients (9/1048; 1.1%, 95% CI 0.60-2.0) with initially normal CTPA and a normal CUS were diagnosed with symptomatic VTE. Four of these 1048 patients in whom VTE was excluded and who were not treated with anticoagulants, died (4/1048; 0.50%, 95%CI 0.20-1.1) possibly as a consequence of PE. The NPV for symptomatic VTE in three months after a normal CTPA followed by CUS was 98.9% (95% CI 98.0-99.4). Therefore, the NPV of CTPA alone was equal to the NPV of CTPA followed by CUS (98.8% vs. 98.9%).

The pooled proportions of fatal PE in follow-up were comparable (0.6% and 0.5%, Table 4), indicating a relative risk of 1.2. The use of a random effects model did not materially influences the study results (Table 4). The pooled sensitivity for detecting PE by CTPA alone was 97.3% (95%CI 96.1-98.2), the sensitivity for detecting PE of CTPA combined with additional CUS was 97.4% (95%CI 95.1-98.6).

DISCUSSION

The main finding of this study is that the NVP of CTPA to rule out PE in a patient population with an indication for CT scanning to exclude acute PE is 98.8% (95% CI 98.2-99.2). Furthermore, the 3-month mortality risk of PE after a normal CTPA in this particular patient population is very small (0.60%, 95%CI 0.40-1.1). An invasive pulmonary angiography is the reference standard for the diagnosis of PE.[1] The upper limit of the 95% confidence interval of the 3-month VTE rate after normal pulmonary angiography is 2.7%.[19] Using this fraction as the upper posttest probability limit above which it is no longer safe to rule out PE by a diagnostic test, our data show that a normal CTPA alone is a valid criterion for the safe exclusion of acute PE, even in this specific population. Furthermore, the 3-month PE associated mortality rate after a normal invasive pulmonary angiography is 0.3% (95%CI 0.02-0.7%) which is comparable with the pooled mortality rate observed in our study (0.60%, 95%CI 0.40-1.1).[19]

Our analysis of the three studies that included CUS after a normal CTPA allowed us to test the additional value of CUS for ruling out VTE. In these three studies, the proportion of patients with CUS proved DVT in spite of a normal CTPA result was low (2.4%). Furthermore, the NPV for symptomatic VTE in 3 months of follow-up of CTPA alone was comparable to the NPV of CTPA followed by CUS (98.8 and 98.9%). In accordance with this finding, the VTE-related mortality risk was not different between both diagnostic strategies.

Some additional observations require comment. We intended to study the performance of CTPA in all patients in whom this imaging modality is required to rule out PE. For this reason, our study patients had an overall moderate probability for having PE (28%). It could be reasoned that the NPV of the CTPA is lower in more selected patients with a high clinical probability than in the population that we studied in this report. Of note, in the recent guidelines of the European Society of Cardiology on the diagnosis of acute PE, the safe exclusion of PE in a high clinical probability population by a normal CTPA result alone is being debated because of the possible false negative CTPA result.[1] Nonetheless, no current evidence exists that additional imaging, e.g. CUS or ventilation perfusion scintigraphy, would prevent VTE in a 3-month follow-up period in this small selected group of patients. In our analysis it was not possible to study this issue in more detail, since none of the included studies had reported the incidence of symptomatic VTE after normal CTPA result alone in a selection of high probability patients only. In addition, the distinction of patients with a high clinical probability for PE is clinically unpractical since this would imply a different diagnostic strategy for the same (normal) CTPA result, as it would be unpractical and unnecessary to distinguish patients with a 'low' from patients with a 'less likely' clinical probability for the interpretation of a normal D-dimer test result. Furthermore, the best threshold, i.e. clinical decision rule cut-off or

D-dimer concentration cut-off, for defining a high risk population in whom negative CTPA does not safely rule out PE is unknown.

We consider our results to be representative because our findings are based on a pooled analysis of a large cohort of over 3000 patients. Second, the analyzed studies were of high quality with a prospective design, including consecutive patients and using standardized diagnostic tests. Third, follow-up time was consistent in all studies (three months) and all endpoints were well-defined and confirmed by objective tests by pre-defined criteria. Finally, demographic characteristics of the patients were comparable between all included studies.

This meta-analysis has some limitations. Inherent to the design of a meta-analysis, pooling observational or non-randomized data could lead to biases. Specifically for our analysis, different clinical decision rules, D-dimer assays and CT-scanners were used between the included studies. The distinct use of the clinical decision rules, with either 2- (PE 'likely' or 'unlikely') or 3-level schemes ('low', 'intermediate' or 'high' probability of PE), resulted in differences in the fraction of patients who were eligible for CTPA without the need for D-dimer testing. Nevertheless, quantitative, highly sensitive D-dimer tests were used in all 6 included studies and all patients with an abnormal D-dimer test result underwent CTPA. Thus, the different use of clinical decision rules did not affect the overall proportion of patients that was finally selected for CTPA. Also, we could not correct for differences between the performances of single- and multi-detector-row CT scanners. In addition, all included studies reported a low number of inconclusive CTPA results (1.8%). We excluded these cases from our analysis. Finally, by study design, we could not objectively assess whether the reported VTE-related mortality was actually caused by an acute PE. Definite cause of death was only determined by autopsy in 11% of the fatal cases. As a consequence, our mortality rates are likely to be overestimated.

In summary, the NPV and safety of excluding acute PE in patients with an indication for CTPA, i.e. 'likely' or 'high' clinical probability, an elevated D-dimer concentration or both, by a normal CTPA without further imaging tests is comparable to the NPV and safety of a normal invasive pulmonary angiography. Furthermore, a strategy including CUS of the legs following a normal CTPA did not improve diagnostic performance. The clinical implication of our findings is that anticoagulant therapy can safely be withheld in all patients with suspected PE after using CDR and D-dimer testing, and a normal CTPA. In our view, there is no need for additional compression ultrasonography of the legs to rule out VTE in these patients.

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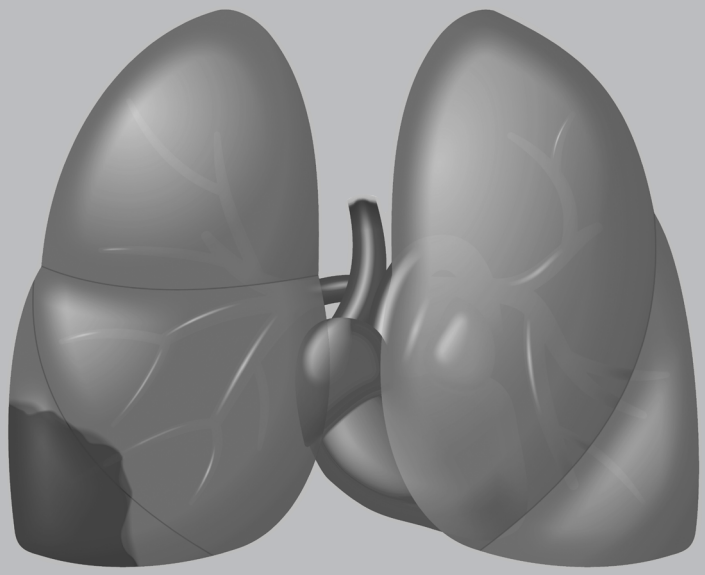
PART II

Recurrent Acute Pulmonary Embolism



CHAPTER 6

The incidence of recurrent venous thromboembolism in a defined population

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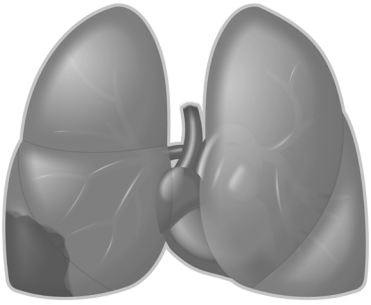
*Equally contributed

Submitted



ABSTRACT

Background

Recurrent venous thromboembolism (VTE) is a common disorder, but the incidence of recurrent VTE within a defined population has never been formally assessed. The aim of this study was to determine the incidence of acute recurrent VTE in a defined population.

Methods

All patients with an objectively confirmed acute recurrent VTE in the selected period, January 2003 until December 2007 who were registered at the Thrombosis Service in the region of Leiden were identified. Medical records of included patients were reviewed for demographic characteristics and risk factors and questionnaires were sent to all potential study patients who were alive. The incidence was stratified by age and sex.

Results

A total of 516 patients were identified with recurrent VTE within the 5 year study period in a defined population of 513.143 inhabitants. The overall incidence of recurrent VTE was found to be 0.22 per 1000 inhabitants per year. The incidence of recurrent deep venous thrombosis, pulmonary embolism and arm vein thrombosis were respectively 0.13, 0.08 and 0.008 per 1000 per year. The incidence was different between men and women; 0.24 per 1000 male inhabitants per year and 0.20 per 1000 female inhabitants per year respectively. The most frequent risk factor associated with recurrent VTE was malignancy (16%).

Conclusions

The incidence of recurrent VTE in a defined urban population is 0.22 per 1000 inhabitants per year.

INTRODUCTION

Venous thromboembolism (VTE) consisting of deep venous thrombosis (DVT) and pulmonary embolism (PE) is a common disorder with an incidence of 1.2-1.8 per 1000 inhabitants per year.[1,2] The reported incidence of DVT varies between 0.48 and 1.6 per 1000 per year[2-4] and 0.2-0.69 per 1000 per year for PE.[2,5] The two-year cumulative incidence of recurrent VTE has been reported to be 17.5% after a first DVT and 17.3% after a first PE.[6,7] Patients with symptomatic VTE have a high risk for recurrent VTE that persist for many years, with a risk of recurrence after 5 years of 20-25%.[8] The risk profile differs between first and recurrent events. Risk factors associated with a higher risk of a recurrent VTE are e.g. male sex and cancer.[9,10] Patients with VTE provoked by surgery, trauma, immobilization, pregnancy or female hormone intake or patients with arm vein thrombosis are at low risk of a recurrent event.[9,10] However, whether patients with a pulmonary embolism have a higher risk of recurrence than patients with DVT is uncertain.[11]

Although studies have reported on the cumulative incidence of recurrent VTE after a first event, no study has specifically assessed the incidence of recurrent VTE in a well defined urban population. The epidemiology in this group of patients is of particular interest because of implications for prevention of morbidity and mortality, and management with consequences of the indication for prolonged anticoagulant therapy. The aim of this study is to determine the incidence of recurrent VTE in a well defined general population (the region of Leiden, The Netherlands) and to assess this incidence according to age and gender.

METHODS

Data sources

For the determination of the incidence of recurrent VTE, all consecutive patients with a confirmed recurrent VTE who received anticoagulation treatment for this recurrent episode in the period January 1st 2003 until December 31st 2007 in the region of Leiden were identified.

In The Netherlands, all patients who have a (recurrent) VTE event are referred to local Thrombosis Services. All potential patients with recurrent VTE were identified from the database of the Thrombosis Services Leiden by the following methods: 1) patients who were registered as 'recurrent VTE' by the treating physician during the study period; 2) patients who were already registered prior to the study period for a VTE event and were registered for a new VTE event (i.e. the recurrent event) the study period; 3) all patients registered as VTE with long term or indefinite treatment were identified and reviewed if they had a prior VTE event.

Medical records of all potential study patients were reviewed and in addition, questionnaires were sent to all patients who were alive at June 1st 2010. A second questionnaire was sent to the non-responders.

A recurrent episode of VTE, i.e. PE, DVT and/or arm vein thrombosis was defined as a recurrent thrombotic event requiring anticoagulant treatment according to the attending physician and proven by compression ultrasonography, CT-scan, ventilation perfusion scintigraphy or contrast venography. Patients who presented with both DVT and PE were classified as having PE. Patients were included in case of an objectively confirmed acute recurrent VTE during the 5 year study period and if they lived in the Leiden district on date of the recurrent VTE episode. The study was approved by the local Review Board.

Data collection

All potential study patients were evaluated in the civil registration system whether they were alive at time of sending the questionnaires and in addition the date of death. Medical records and questionnaires of all patients were reviewed for demographic characteristics, risk factors and information about the recurrent and previous VTE events (e.g. date of VTE events, type, location and duration of oral anticoagulant therapy) and if applicable the cause of death.

Recurrent VTE events were included, independent of the type of previous VTE event (e.g. also PE after a DVT episode). The database was checked for double entry and in case a patient had more recurrent events during the study period only the first episode was considered for inclusion.

Unprovoked VTE was defined in case of the absence of immobilization more than 3 days, surgery or a recent long flight, plaster cast of the lower extremity, active malignancy, pregnancy or postpartum period, use of oral contraceptive or hormone replacement therapy and the presence of a central venous catheter in case of arm vein thrombosis.[12]

Study outcomes and statistical analysis

The primary outcome of the study was the incidence of recurrent VTE (PE, DVT and arm vein thrombosis) in the Leiden region between January 1st 2003 and December 31st 2007. In addition, age and sex-specific incidence rates of recurrent VTE were calculated. Annual incidence rates (per 1000 inhabitants) were calculated as the number of patients with recurrent VTE occurring during the 5-year study period divided by the number of inhabitants of the Leiden District with corresponding 95% confidence intervals (CI). The Thrombosis Service Leiden covers a well described population of 513,143 inhabitants, estimated by the National Institute of Statistics, a national registry in which the age and gender of all inhabitants of the Netherlands are registered. All continuous variables are expressed as mean (standard deviation) and categorical data given in proportions and percentages. Mean values and frequencies were compared using Student's t-test and

Pearson's chi-square test, respectively. Analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, Ill).

RESULTS

Between January 1st 2003 and December 31st 2007, 640 potential patients were identified with recurrent VTE episode in the Leiden region and medical records were reviewed. Among these potential patients, 128 patients (23%) died and questionnaires were sent to the remaining 512 patients. Of these patients 59 declined participation and 67 did not respond after two sent questionnaires.

After review of the questionnaires and medical records of the 640 potential patients, 79 patients were excluded from further analysis because they did not live in the Leiden region at time of the recurrent event or because no recurrent event occurred during the study period. Finally, 561 patients were left for inclusion in the analysis.

Data to calculate the primary endpoint (presence of recurrent DVT, PE or arm vein thrombosis) were available in all 561 patients.

Clinical characteristics of patients with recurrent VTE.

In a total population of 513,143 inhabitants, 561 patients had a recurrent VTE event during 5 years, the total incidence of recurrent VTE was therefore 0.22 per 1000 inhabitants per year. The clinical characteristics of the 561 patients with recurrent VTE are summarized in Table 1. The mean age of the cohort was 59.79 ±16.6 years (range 15-95) with more males (53% versus 47%). In 346 patients (62%) the recurrent event was an isolated DVT, in 195 (35%) a PE (including 13 patients with also DVT of the lower limbs) and in 20 patients (3.6%) an arm vein thrombosis (including one patient with concomitant DVT of the lower extremity). The incidence of recurrent deep venous thrombosis, pulmonary embolism and arm vein thrombosis were therefore 0.13, 0.08 and 0.008 per 1000 inhabitants per year respectively.

The incidence rates increased steadily with age for both sexes (Figure 1). Overall the incidence was different between men and women; for men, 0.24 per 1000 male inhabitants per year (95% CI 0.236-0.244) and 0.20 per 1000 female inhabitants per year (95% CI 0.197 -0.204) for women. Men had higher incidence rates compared to women above 45 years of age (Figure 1). Deep vein thrombosis accounted for the majority (44-69%) of recurrent VTE in all age categories (Figure 2).

Presence of risk factors was known in 431 patients (77%). In these patients the recurrent event was provoked in 35%. The most frequent risk factor associated with recurrent VTE was malignancy (16% of 431), most commonly hematologic (20%), gastrointestinal (15%), breast (15%), lung (15%), gynecological (10%) and prostate (10%) malignancies.

Table 1. Patient characteristics of the 561 included patients.

Characteristic	Value
Male, n (%)	300 (53)
Recurrent event	
Age, mean (SD), y	60 (17)
Deep vein thrombosis	59 (16)
Pulmonary embolism	61 (17)
Arm vein thrombosis	54 (18)
Number of recurrent VTE events (%)	
One recurrent event	447 (80)
Two recurrent events	94 (17)
More than two recurrent events	20 (3.6)
Site of recurrent event	
Deep vein thrombosis, n (%)	346 (62)
Pulmonary embolism, n (%)	195 (35)*
Arm vein thrombosis, n (%)	20 (3.6)**
Years since previous event, mean (SD), y	5.0 (6.5)
Risk factors[#]	
Provoked event, n (%)	152 (35)
- recent surgery, n (%)	31 (20)
- immobilization, n (%)	30 (20)
- estrogen use, n (%)	26 (17)
- pregnancy, n (%)	5 (3.2)
- long flight, n (%)	8 (5.3)
- central venous catheter, n (%)	2 (1.3)
- active malignancy, n (%)	71 (47)
Idiopathic event	279 (65)
Mortality	
1 year after recurrent VTE event, n (%)	55 (9.8)
2 year after recurrent VTE event, n (%)	73 (13)
Previous event	
Age, mean (SD), y	55 (17)
Site of previous event	
Deep vein thrombosis, n (%)	360 (64)
Pulmonary embolism, n (%)	182 (32)***
Arm Vein thrombosis, n (%)	18 (3.2)
Risk factors[±]	
Provoked event, n (%)	128 (33)
Idiopathic event, n (%)	261 (67)

[#] presence of risk factors of the recurrent event known in 431 patients; [±] presence of risk factors of the previous event was known in 389 patients; * including 13 patients with concurrent DVT; ** including one patient with concurrent DVT of the leg; ***including 31 patients with concurrent DVT of the leg. n: number; SD: standard deviation; y: year; VTE: venous thromboembolism.

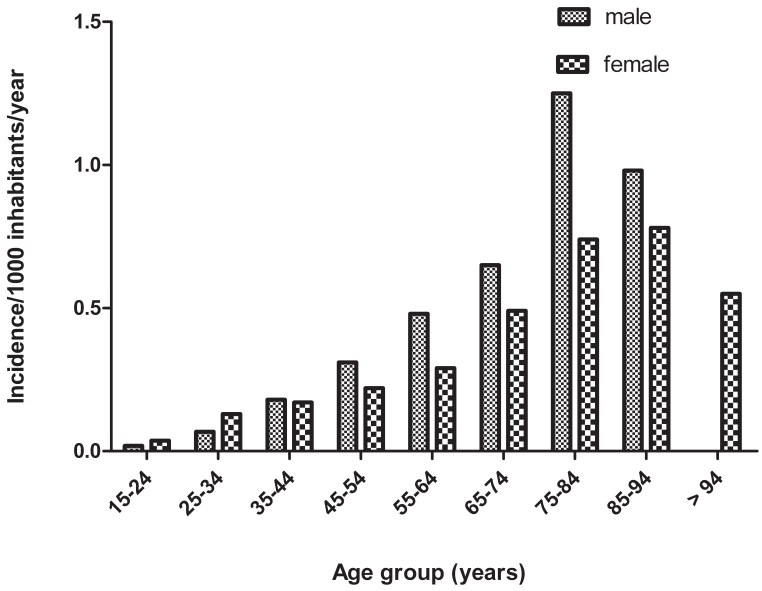


Figure 1. Age distribution stratified by gender (incidence).

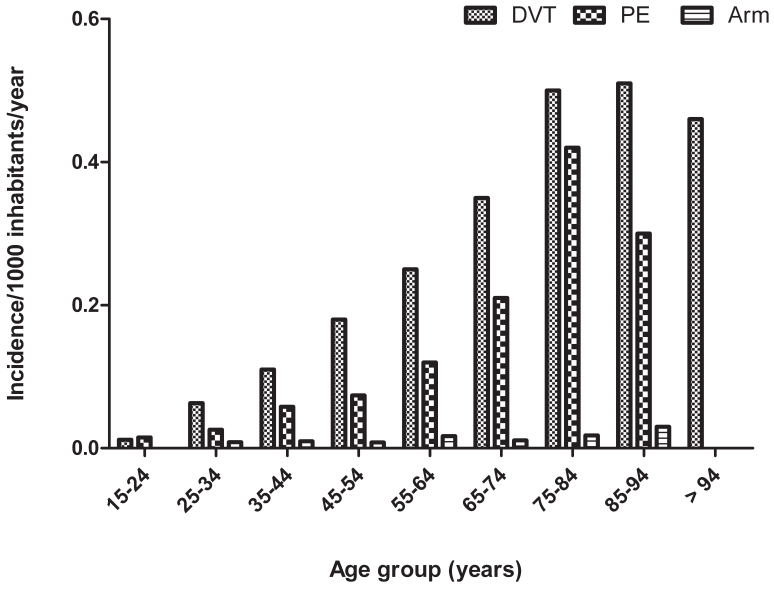


Figure 2. Age distribution stratified by type of recurrent venous thromboembolism (VTE) event (incidence).

The 1 and 2 year mortality rate were 9.8% and 13% respectively. (Table 1). The cause of death was registered by the Thrombosis Service Leiden in 81 patients (63%) None of the known causes of deaths were attributed to venous thromboembolic events, 43 (53%) died of malignancy, 14 (17%) patients due to cardiovascular causes and 3 patients died of a fatal bleeding during anticoagulant therapy.

The majority (80%) of the patients had one recurrent VTE episode, 17% had two recurrent events and 3% of the patients had more than two recurrent events (Table 1). In 38 patients (6.8%), the recurrent VTE event occurred during anticoagulant treatment, 47% of these patients had active malignancy.

Comparison to the previous VTE event

The recurrent VTE events occurred after a mean of 5.0 years (SD 6.5) after the previous VTE event. When stratified into years after the previous VTE event, a strong decline was found with the years, and 43% of the recurrent events occurred within two years (Figure 3). The percentage of patients with an active malignancy was higher during the first two years than after. The type of the previous event did not differ from the recurrent events; 64% had a DVT, 32% PE and 3.2% had arm vein thrombosis.

Data on the presence of risk factors of the previous thrombotic event were available in 389 patients (69%). The percentages of provoked versus idiopathic previous VTE event in these patients, were similar to the recurrent VTE events as well, 33 and 67% respectively.

In patients with a previous DVT, recurrent DVT occurred more often (80%) than PE (19%). The same effect was found after initial PE, the risk for recurrent PE was 69%, while 30% of the patients had a DVT (Figure 4).

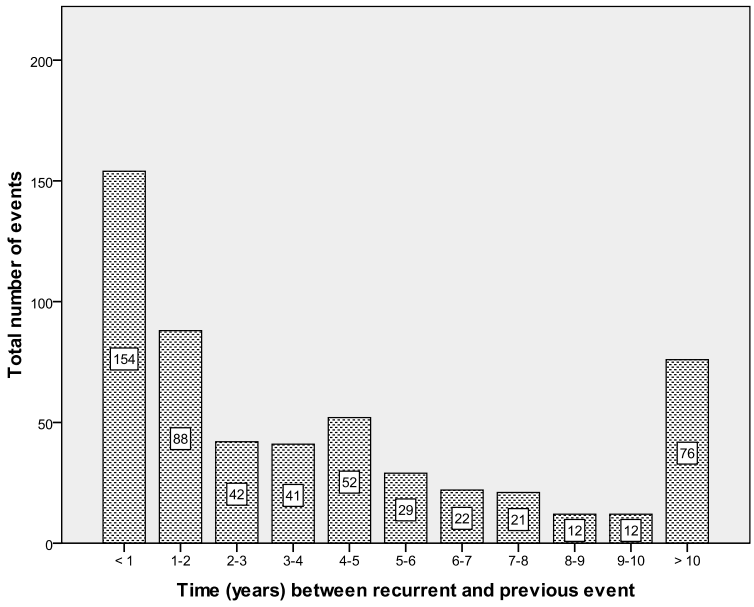


Figure 3. Time between recurrent and previous venous thromboembolism (VTE) event. The graph shows the times (years) between the recurrent and previous event in. The number in each column indicates the total number of events in time period. In 12 patients the time between previous and recurrent event was unknown.

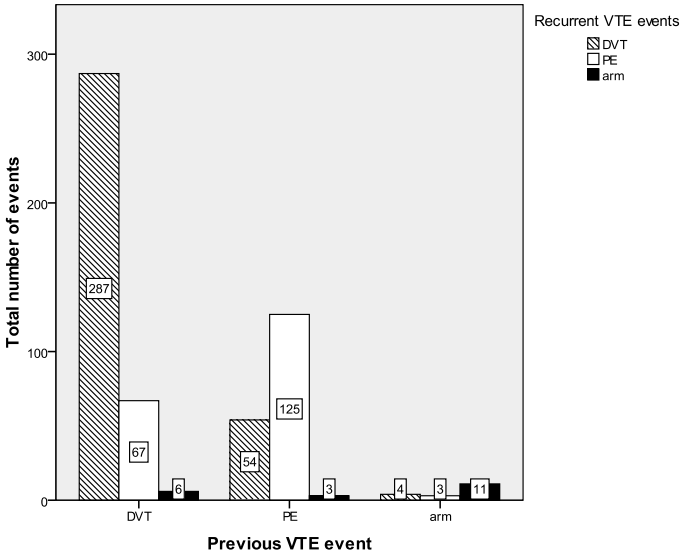


Figure 4. Type of recurrent venous thromboembolism (VTE) event versus type of previous VTE event. The graph shows the type of recurrent VTE event (deep vein thrombosis (DVT), pulmonary embolism (PE) or arm vein thrombosis) versus type of the previous VTE event (DVT, PE, arm vein thrombosis). The number in each column indicates the total number of events in each group. In 1 patient the type of previous event was not known.

DISCUSSION

This study was performed in a well-defined region and showed an overall annual incidence of recurrent VTE of 0.22 per 1000 inhabitants with significant more recurrent events occurring in male patients.

The results of our study are consistent with previous studies showing that the majority of recurrences occur in the first two years after the previous event and the incidence of recurrent DVT was one and half times higher than the incidence of recurrent PE and the incidence of recurrent arm vein thrombosis was rare with an incidence of 0.008 per 1000 inhabitants per year.[13]

We also confirmed earlier findings in that patients with a previous DVT were more likely to have a DVT as a recurrent event than PE, and patients with a previous PE were more likely to develop a recurrent PE.[14] An explanation could be that a residual thrombosis is regarded as a recurrent event. The diagnosis of recurrent VTE is often difficult, because of the presence of persistent thrombotic abnormalities after a first VTE event. In patients with a proximal DVT persistent vein abnormalities are present in 80% and 50% of patients at 3 months and 1 year.[15,16] Therefore, when a patient presents with a suspected recurrent event, it can be difficult to determine whether this represents

new disease or a residual abnormality. Furthermore, residual thrombosis might be a mechanical risk factor, which, by obstructing blood flow, facilitates recurrent thrombosis due to local stasis. However studies showed lower risk of recurrent ipsilateral DVT than contralateral recurrence.[16,17]

In our study we found an incidence rate increasing with age and a significantly higher incidence among men above 45 years of age. Similar as the results in population-based and autopsy studies which have shown that acute VTE occurs predominantly in the middle-aged and elderly people and showing exponential increase with age.[18] An explanation could be that women below 45 years of age are more exposed to risk factors like pregnancy and use of hormonal therapy (i.e. oral contraceptives and hormonal replacement therapy). Nevertheless the absolute recurrence numbers were low at younger age. Furthermore as mentioned in previous studies men have a higher risk for recurrent VTE events than women.[9,10]

This study contained a very large cohort of patients with recurrent VTE and is the first that reports on the absolute incidence of recurrent VTE in a defined population instead of cumulative incidence. This is of importance because patients with recurrent VTE receive prolonged anticoagulation, with associated risks and costs. Absolute incidence numbers reflect the impact of the disorder in the general population without the limitation of duration of follow-up to find recurrent events. The Dutch Thrombosis Service has a well described coverage area and patients with a (recurrent) VTE from the Leiden region are all (with only a few exceptions) registered at the Thrombosis Services. Both patients who received their diagnosis in hospital as patients who were diagnosed by their general practitioner were included in this analysis. Patients who developed a recurrent VTE during anticoagulant treatment were registered again and could therefore not be missed. Furthermore, all included cases were confirmed by objective tests.

This study has some limitations. We performed a retrospective analysis, which can be subject to various biases. Nevertheless, data to calculate our primary endpoint were available in all patients and information of the secondary endpoint, including the presence of risk factors, were available in 77% of the cohort.

Patients who died in the hospital after diagnosis and patients who receive only heparin treatment were not included. During the study period patients with malignancy were treated with oral anticoagulant therapy instead of low molecular weight heparin (LMWH) as is currently recommended in this group of patients. In our study 16% of the patients had a malignancy; this percentage does not indicate that patients with malignancy were missed.

The diagnostic management of recurrent VTE is difficult, because of the non-specific clinical symptoms of recurrent VTE, which could be attributed to chronic symptoms of a previous event and therefore underrecognized. Furthermore imaging of recurrent VTE has limitations. It is difficult to distinguish a residual from an acute new thrombosis

as mentioned above. Criteria for suspected ipsilateral recurrent DVT have been established[19], but these are lacking for patients with suspected recurrent PE or suspected recurrent arm vein thrombosis. Additionally a recent study showed that in 32% of the patients with a suspected ipsilateral recurrent DVT the diagnosis could not be established based on these criteria.[20]

Finally searching for isolated distal DVT was not routinely performed by all radiologists and could therefore have lead to an underestimation of the incidence of DVT. In our study we were not able to distinguish an isolated distal DVT from proximal DVT due to the lack of reported information about the location of DVT. However, the diagnostic value of isolated distal DVT is still a matter of debate.

In conclusion, this study identified an incidence of recurrent VTE of 0.22 per 1000 inhabitants per year with higher incidence in men than women and confirmed that the majority of recurrent events occurred within two years. These factors should be taken into account with risk stratification and knowledge of this figure is important because of the major consequences of prolonged anticoagulant therapy, morbidity and mortality for this group of patients.

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CHAPTER 7

Effectiveness of a simple diagnostic algorithm in patients with clinically suspected acute recurrent pulmonary embolism

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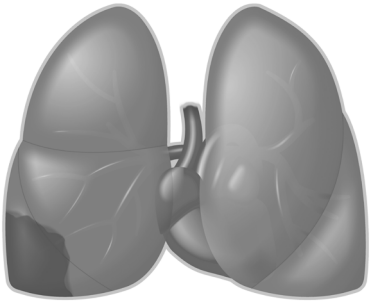
Submitted



ABSTRACT

Background

The value of diagnostic strategies in patients with clinically suspected acute recurrent pulmonary embolism (PE) has not been established. The objective was to determine the safety of a simple diagnostic strategy using the Wells clinical decision rule (CDR), quantitative D-dimer testing and computed tomography pulmonary angiography (CTPA) in patients with clinically suspected acute recurrent PE.

Methods and Results

This multicenter clinical outcome study included 516 consecutive patients with clinically suspected acute recurrent PE. An unlikely clinical probability (Wells rule 4 points or less) was found in 182 of 516 patients (35%), and the combination of an unlikely CDR-score and normal D-dimer result excluded PE in 88 of 516 patients (17%), without recurrent venous thromboembolism (VTE) during 3-month follow-up (0%; 95% CI 0.0-3.4%). CTPA was performed in all other patients and confirmed recurrent PE in 175 patients (overall prevalence of PE 33%) and excluded PE in the remaining 253 patients (49%). During follow-up, seven of these 253 patients returned with recurrent VTE (2.8%; 95% CI 1.2-5.5%), one of which was fatal (0.4%; 95% CI 0.02-1.9%). The diagnostic algorithm was feasible in 98% of patients.

Conclusions

An algorithm consisting of a clinical decision rule, D-dimer test and CTPA is effective in the diagnostic management of patients with clinically suspected acute recurrent PE and provides reasonable safety with a low risk for recurrent non-fatal and fatal VTE at follow-up.

INTRODUCTION

Pulmonary embolism (PE) is a frequent disease, occurring in 0.5-1.2 per 1000 persons per year.[1,2] The risk of recurrent PE is 10-20% in the first two years after discontinuation of anticoagulant therapy.[3,4] Little evidence is available regarding the best diagnostic strategy for patients presenting with suspected recurrent PE. The consequences of a false positive or false negative diagnosis of recurrent PE are substantial. An incorrect diagnosis of recurrent PE exposes the patient to prolonged and often life-long anticoagulation, with its costs, inconvenience, and bleeding risks, and on the other hand, a falsely negative diagnosis places the patient at high risk of – potential fatal – recurrent PE.

The safety of withholding anticoagulant therapy in patients with a first episode of clinically suspected PE in the presence of an unlikely score using a clinical decision rule (CDR) in combination with a normal D-dimer result, or a normal CTPA has been demonstrated in several prospective studies.[5,6,7] In case of suspected recurrent PE, there are several diagnostic challenges. Since all patients score at least 1.5 points due to the item "history of VTE", patients are more likely to be classified as 'PE likely' according to the Wells rule. And in case of a likely clinical probability it is not possible to exclude PE with D-dimer testing alone. Furthermore, the specificity of a D-dimer test has been shown to be less in case of a recurrent thrombotic disease.[8,9] Finally, interpreting the CTPA in patients with a previous PE is challenging because of the presence of residual thrombi, complicating the differentiation between old or a new PE.[10]

In two studies, a diagnostic algorithm was evaluated in patients presenting with clinically suspected recurrent PE.[9,11] In both studies no recurrent VTE (0% failure rate) was observed during 3-month follow-up in patients with a CDR indicating PE to be unlikely and a normal D-dimer test result. However, due to the modest sample sizes, the upper limits of the 95% confidence intervals (CI) were high (7.9 and 6.9%, respectively) in both studies. In the latter study, the VTE failure rate following a negative CTPA was 0.8% (95%CI 0.02-4.3)[11] The goal of the present study was to evaluate the safety of withholding anticoagulant treatment in patients in whom recurrent acute PE was excluded on the basis of a predefined diagnostic algorithm using the Wells clinical decision rule, quantitative D-dimer test and CTPA.

METHODS

This study was a prospective multicenter clinical outcome study in 7 hospitals in the Netherlands in patients with clinically suspected recurrent acute PE. The primary study goal was to establish the safety of withholding anticoagulant treatment in patients with

normal diagnostic tests using the predefined algorithm. The study was approved by the institutional review boards of all participating hospitals.

Patient population

Consecutive in- and outpatients with clinically suspected recurrent acute PE were eligible. Clinical suspicion for recurrent PE was defined as acute onset of shortness of breath, deterioration of existing shortness of breath or acute onset of pleuritic chest pain without another explicit explanation for these complaints. A previous PE had to be objectively diagnosed according to the following criteria: intraluminal filling defects on pulmonary angiography or CTPA, likely probability ventilation perfusion scintigraphy (VQ-scan) or intermediate probability VQ-scan in combination with objectively diagnosed deep venous thrombosis (DVT).

It was not known how many previous events the patients had in history, at least one event and more events are not likely because of the indication for life-long anticoagulation treatment.

The presence of one or more of the following criteria excluded potentially eligible patients from the study: age < 18 years, treatment with full-dose therapeutic low molecular weight or unfractionated heparin (LMWH) initiated 24 hours or more prior to eligibility assessment, treatment with vitamin K antagonists, contraindication to CTPA (i.e. allergy to intravenous iodinated contrast or renal dysfunction (creatinine clearance < 30 ml/min)), life expectancy less than 3-month, current pregnancy, or impossibility to return for follow-up.

Study Flow

The diagnostic workup scheme is illustrated in Figure 1. Information regarding risk factors for recurrent PE was gathered along with patients' presenting signs and symptoms. The

Table 1. Clinical Decision Rule according to Wells.

Items	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate > 100/min	1.5
Immobilization (>3 days) or surgery in the previous four weeks	1.5
PE or DVT in history	1.5
Hemoptysis	1.0
Malignancy (receiving treatment, treated in the last 6 months or palliative)	1.0
PE unlikely ≤ 4 points; PE likely > 4 points	

DVT: deep vein thrombosis; PE: pulmonary embolism.

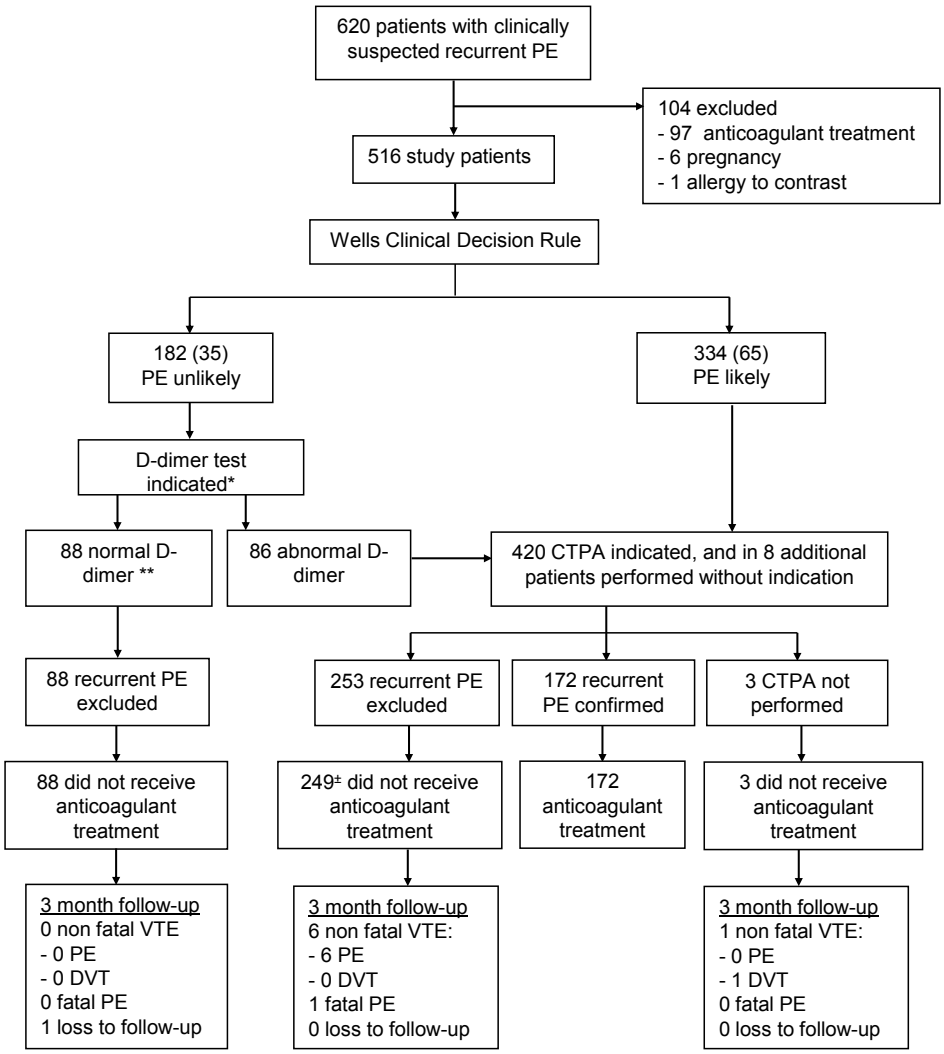


Figure 1. Flowchart and results of the diagnostic strategy. *8 patients did not undergo D-dimer testing, despite clinical decision rule indicating pulmonary embolism (PE) unlikely, protocol violation; **6 of these 88 patients underwent computed tomography pulmonary angiography (CTPA) (protocol violation), and did not show PE in any of these patients; ±3 patients received anticoagulant therapy for other reasons than PE, one patient was regarded as having PE despite negative CTPA test results. The numbers in parentheses represents percentages.

Wells clinical decision rule was calculated in all patients (Table 1).[8] In patients with a CDR score indicating an unlikely clinical probability defined by four points or less, a high sensitive D-dimer test was performed (Tinaquant, Roche Diagnostica, Mannheim, Germany; VIDAS, Biomerieux, Marcy Letiole, France; STA Lia, Diagnostica Stago, Asnieres, France or Innovance, Siemens, Marburg, Germany). In patients with an unlikely CDR score and a

normal D-dimer result (< 500 ng /mL) recurrent PE was considered to be excluded and anticoagulant treatment was withheld, without further diagnostic testing. In patients with a CDR score of more than four points (likely clinical probability), or an abnormal D-dimer test result, CTPA was performed within 24 hours of presentation. Anticoagulant treatment was withheld in patients with a CTPA negative for recurrent PE. Patients with a CTPA demonstrating recurrent PE were treated with standard anticoagulant therapy. All patients in whom recurrent PE was excluded were followed for a period of three months.

Imaging protocols

Standard contrast enhanced CTPA was performed using a 4-row, 16-row, or 64-row scanner with acquisition of 0.5-1mm sections of the entire chest. Acquisitions were done during single breath hold lasting 10-12 seconds. The rotation time was 0.4 sec. The tube current was 250-300 mA and the tube voltage was 100kV. 80-100 mL contrast material was injected in the antecubital vein at an injection rate of 4 mL/sec. The diagnosis of PE was confirmed by the presence of an intraluminal filling defect in the pulmonary artery tree in at least two projections. In those with a prior CTPA available for comparison, PE was diagnosed by the presence of a new intraluminal filling defect present on CTPA. Recurrent PE was considered to be excluded in the presence of an unchanged or normal CTPA. If no prior CTPA was available for comparison, the CTPA result was analyzed by comparing with the anatomical localization of the prior PE with the anatomical area of the prior PE on the pulmonary angiogram or ventilation perfusion scintigraphy or by comparing with the description of the prior PE on the radiology report. Trained radiologists judged the CTPAs to directly determine whether PE was present or excluded and the radiologist knew that a patient referred to CTPA either had a D-dimer level above 500 and/or a CDR score that was higher than 4 points, but had no knowledge of which of these items was the reason for performing a CTPA.

Follow-up

The primary outcome measure for this study was the 3-month VTE recurrence rate in patients with normal initial test results. Patients in whom PE was excluded by an 'unlikely' probability for PE and a normal D-dimer test result or by negative CTPA were followed for three months in order to ensure the correctness of the diagnosis. All patients were instructed to return to the hospital when they developed complaints, suggestive of VTE. If there was a suspicion of VTE during follow-up, objective tests were performed: CTPA, ventilation perfusion scintigraphy and/or compression ultrasonography. In case of death, information was obtained by reviewing hospital charts, results from autopsy or by contacting the general practitioner. Death was classified as due to PE in case of objective confirmation of PE prior to death or if PE could not be confidently excluded as the cause of death.

Sample size calculation and statistical analysis

For the primary study objective, we needed a sample size sufficiently large to provide reliable estimates of the negative predictive value (NPV) of both a CDR score of 4 points or less in combination with a normal D-dimer result, and the NPV of a negative CT for PE. Based on previous studies we expected that around 20% of the included patients would have a CDR of 4 points or less in combination with a normal D-dimer.[5] Of these, we assumed that at most 1% would return with symptomatic VTE during follow-up. We expected that approximately 80% of the total sample size would have an indication for CTPA, and of these, 66% would have a normal CTPA result. We assumed that 1.5% of the patients with a normal CTPA would have a symptomatic VTE during follow-up. Based on these estimates we expected an observed NPV in the group with unlikely clinical probability and normal D-dimer test results of at least 99% with a 95% CI of 95% to 100% and an observed NPV of the group with PE excluded by CT of at least 98.5% with a 95% CI of 96% to 100%. For this, a sample size of 500 patients was needed.

Exact 95% confidence intervals (CI) were calculated for the observed incidences.

RESULTS

Patients

During the study period from November 2002 to November 2009, a total of 620 patients were screened for eligibility, of whom 104 (18%) were excluded because of predefined exclusion criteria. The majority (93% of these 104 patients) was excluded due to treatment with anticoagulants prior to inclusion. The final study population consisted of 516 patients (Figure 1). Characteristics of these patients are shown in Table 2. The mean age was 55 years, 305 of the 516 (59%) were females, most patients (89%) were outpatients and 13% had active malignancy. A total of 172 patients (33%) were diagnosed with acute recurrent PE and the median time since first PE diagnosis was 3 years (25^{th} and 75^{th} percentiles 1-6 years). The mean age was approximately 10 years older in patients with recurrent PE present compared to patients in whom recurrent PE was excluded.

Diagnostic algorithm

CDR and D-dimer

Of the 516 patients with suspected recurrent PE, 182 (35%) had a CDR indicating recurrent PE unlikely, of whom 88 (17%) had a normal D-dimer test result. In six patients, CTPA was performed despite a normal CDR and D-dimer result (protocol violation). These CTPAs were negative for PE in all patients. During follow-up, one patient was lost to follow-up.

Table 2. Clinical characteristics of the included patients.

	All patients N = 516	Recurrent PE excluded N = 333	Recurrent PE present N = 183
Age, mean (SD), y	54.7 (17)	51.3 (17)	61.0 (16.4)
Female,%	59.2	64.6	50.0
Outpatient, %	88.8	90.0	85.1
Duration of complaints, median (25^{th}-7^{th} ‰), d	3 (1-9)	3 (1-9)	3 (1-9)
Time since prior PE, median (25^{th}-75^{th} ‰), y	3 (1-6)	3 (1-6)	2 (1-6)
Body mass index, mean (SD), kg/m2	27.3 (5.4)	27.2 (5.6)	27.4 (5.2)
Risk factors			
Immobilization or recent surgery, %	12.5	4.8	18.5
COPD with treatment, %	15.6	18.5	10.1
Heart failure with treatment, %	10.1	8.3	13.3
Active malignancy, %	13.3	9.6	20.0
Estrogen use, women, %	6.2	6.0	6.7
Body mass index ≥ 30 kg/m2, %	24.2	25.5	22.4
Symptoms and clinical presentation			
Clinical symptoms of deep vein thrombosis, %	8.3	5.4	13.5
Heart rate, mean (SD), bpm	83.4 (18.3)	81.4 (19.6)	86.5 (16.5)
Hemoptysis, %	5.9	3.8	9.7
Heart rate > 100 bpm,%	16.7	11.9	25.6

Bpm: beats per minute; COPD: chronic obstructive pulmonary disease; SD: standard deviation; VTE: venous thromboembolism. Complete information was not available on all patients, the n represents the number of patients in whom the information was present.

None of the remaining 87 patients received anticoagulant treatment during follow-up, and all of these patients had an uneventful follow-up, resulting in a failure rate of 0% (95% CI 0.0-3.4) and a NPV of 100% (95%CI 96.6-100). In case the patient who was lost to follow-up is counted for as a diagnostic failure, the failure rate increases to 1.1% (95%CI 0.05-5.8).

CTPA

CTPA was indicated in 420 patients (81%); 334 had a CDR indicating recurrent PE likely and 86 patients had a CDR indicating recurrent PE unlikely but an abnormal D-dimer test result. Protocol violations occurred in 11 patients. In eight patients CTPA was performed, despite an unlikely CDR result without D-dimer testing - and no PE was detected - and in three patients CTPA was indicated but not performed. In one of these latter patients, DVT was detected during follow-up (Table 3, patient 1). In total 425 patients underwent CTPA and recurrent PE was confirmed in 172 of these patients (prevalence of recurrent

Table 3. Characteristics of patients in whom venous thrombo-embolism was detected during 3-month follow-up, despite initial exclusion of the diagnosis.

Patient				Outcome of diagnostic tests at inclusion					Follow-up
Pt.	**Sex**	**Age**	**Duration of OAC discontinuation**	**Wells (points)**	**DD**	**CTPA at presentation**	**VTE**	**Day (d)**	**Brief description**
1	Male	60	unknown	9	-*	-*	DVT	54	Deep-vein thrombosis.
2	Male	80	15 years	6	600	Alternative diagnosis: pneumonia	PE	11	CTPA: extensive bilateral thrombi.
3	Female	38	2 months	6	200	Normal	PE	61	CTPA: extensive bilateral PE.
4	Female	43	2 weeks	5.5	-*	Alternative diagnosis: infection with bronchiectasis	PE	60	CTPA: PE in the artery of the left upper lobe.
5	Female	87	3 weeks	7	1744	Alternative diagnosis: pleural effusion	PE	24	CTPA: new bilateral filling defects.
6	Female	40	2 years	4 **	-*	Normal	PE	30	V/Q during follow-up showing mismatch, same localisation as previous PE. Considered as new recurrent PE and anticoagulant treatment given
7	Male	49	3 months	7	-*	Normal	PE	28	CTPA: extensive bilateral central PE.
8	Female	65	1month	5.5	-*	Normal	PE	44	CTPA: extensive PE, patient died 11 days later attributable to PE.

Pt.: patient; OAC: oral anticoagulant treatment; DD: D-dimer; CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism; DVT: deep vein thrombosis; V/Q: ventilation perfusion scintigraphy; *Test not performed. ** Patient 6. CTPA performed despite unlikely clinical probability; D-dimer test was not performed (protocol violation). During follow-up V/Q scintigraphy was performed showing a mismatch compatible with recurrent PE.

PE in patients with a PE likely probability was 43%; 143/334, 95% CI 38-48). PE was excluded by CTPA in 253 patients, of whom 207 had a normal CTPA. In 46 patients, an alternative diagnosis (e.g. pneumonia, pleural effusion or malignancy) was established. There were no non-diagnostic CTPA's in this cohort. None of the 253 patients with CTPA negative for recurrent PE were lost to follow-up. Three patients received vitamin K antagonists for other reasons than VTE and one patient was judged to have recurrent PE despite a negative baseline CTPA and received anticoagulant treatment. During 3-month follow-up, seven of the remaining 249 patients were diagnosed with recurrent VTE, according to the predefined criteria (Table 3, patient 2-8). The 3-month VTE failure

rate after negative CTPA was therefore 2.8% (7/249 patients; 95% CI 1.2-5.5), resulting in a NPV of 97% (95%CI 95-99). The majority of these failures occurred 1-2 months after initial investigations. In 6 patients recurrent PE was obvious with a new location or new extensive filling defects and in an additional patient PE was classified as recurrent PE (Table 3, patient 6). Five of the eight patients with recurrent VTE had active malignancy. Overall 22 patients died during follow-up of whom one patient of fatal PE (Table 3), 1/513, 0.2% (95% CI 0.01-1.0%). And 1/249 (0.4%; 95% CI 0.02-1.9%) of patients with negative CTPA died. Overall, the 3-month failure rate of the designated strategy including CDR, D-dimer and CTPA was 7/513 (1.4%; 95% CI 0.6-2.7), and 8/516 (1.6%; 95%CI 0.7-2.9) when considering all included patients, including three patients treated with anticoagulants during follow-up for other reasons than PE. The complete diagnostic algorithm could be completed in 505 patients (98%).

DISCUSSION

The present diagnostic strategy in patients with clinically suspected recurrent PE was effective. It was feasible in 98% of patients and excluded recurrent PE in 17% patients by an unlikely clinical probability combined with a normal D-dimer test, without recurrent VTE at follow-up. After a normal CTPA, patients with high risk of recurrent PE (patients had either likely probability by the CDR or an abnormal D-dimer test) had an absolute 2.8% recurrent VTE risk during 3-month follow-up. Of note, only one patient (0.4%) in whom recurrent PE developed had a fatal recurrent event. This figure is low and compares well with the 0.5% fatal PE, observed in an earlier study by our group involving a majority of patients presenting with a first episode of suspected acute PE.[5] Admittedly, the observed overall VTE recurrence rate is higher than the 1.2% (95% CI 0.6-2.0) after normal CTPA, described in a recent meta-analysis in patients with suspected PE. In that meta-analysis, the majority of patients had presented with a first episode of suspected PE.[12] There are likely several explanations for this difference. First, all patients who went for CTPA had a substantial risk of recurrent PE despite normal initial testing, since they already proved to be relatively thrombogenic by their first PE and had a likely clinical probability for a recurrent PE (high CDR or elevated D-dimer level). Second, six of eight recurrent events occurred at least 1-2 months after initial presentation and five of eight patients had active malignancy. Taken together, the observed VTE incidence is most likely the real risk in these patients, rather than a failure of the diagnostic strategy. It remains to be demonstrated whether the safety of excluding recurrent PE by alternative diagnostic algorithms, e.g. with performance of compression ultrasonography after normal CT, can be increased. Although ultrasonography will detect new DVT, the question remains if additional testing will avoid recurrent PE events and mortality. It should be

noted that ultrasonography had no additional value after a negative CTPA in an overall population suspected of PE including recurrent PE.[12]

This study confirms previous observations indicating that recurrent PE can be safely ruled out in case of an unlikely clinical probability assessed with the Wells rule and a normal D-dimer test result. Recurrent PE could be excluded in approximately one-fifth of our study population without the need for radiological imaging. This is slightly lower compared to patients with a first episode of PE, but still leads to the exclusion of PE without the need of additional imaging.[13]

The incidence of PE in patients with an unlikely or likely clinical probability for recurrent PE was 22% and 43% respectively, indicating that a CDR is of diagnostic value in the setting of suspected recurrent PE. The ability to distinguish patients with an unlikely and likely clinical probability was comparable to that in patients with a suspected first PE in which an incidence of 15% was seen in patients with an unlikely probability and 43% in patients with likely probability.[13]

Strengths of this study include the large cohort of patients suspected of recurrent PE. Also, the number of protocol violations was low (3%). We included patients from academic and non-academic hospitals and the baseline characteristics were comparable to other PE-outcome studies.[9,11,13] The diagnostic algorithm could be completed in 98%, which was similar in comparison with previous diagnostic outcome studies.[5] Some additional aspects require comment. First, the possibility of false-positive CTPAs, resulting in over diagnosis of recurrent PE, was not assessed. CTPA at time of stopping anticoagulant treatment after the first PE was not available as baseline-imaging test, and therefore old thrombi could have been judged to represent acute PE. It has been estimated that about 20-50% of patients have residual thrombus on CTPA, 6 months after diagnosis of PE.[10,14,15] However, the mean time since the prior PE in the present study was three years and importantly, the observed prevalence of objectively confirmed recurrent PE (33%) is in line with previous studies, this is in our view supportive of a true incidence of recurrent PE (27-40%).[9,11] Second, in spite of efforts, we have no recording of how many patients had a previous CTPA for comparison. Third, since the clinical decision rule includes the item "history of VTE", all patients scored at least 1.5 points. As a result, fewer patients could be classified as PE unlikely then is the case in patients suspected of a first PE (35 vs. 72%).[13] Despite this, the combination of CDR and a normal D-dimer test result was present in 17% compared to 23% in patients with suspicion of first PE.[13] Fourth, a large proportion of patients with suspected recurrent PE on anticoagulant treatment were excluded from this analysis. CDRs are not validated in these patients and sensitivity of D-dimer tests is decreased during anticoagulant treatment.[16,17] Therefore, direct imaging tests (CTPA) are recommended in these patients. The study mostly involved outpatients, therefore extrapolating the results to inpatients is difficult. And finally, despite the relatively large patient cohort, the upper limits of the CIs are still wide.

In conclusion, this study demonstrates that a diagnostic strategy, with a simple algorithm is effective in patients with clinically suspected recurrent acute PE. The diagnostic algorithm safely excluded recurrent PE based on a very low risk of fatal recurrent PE during follow-up and given the high a priori risk in these patients.

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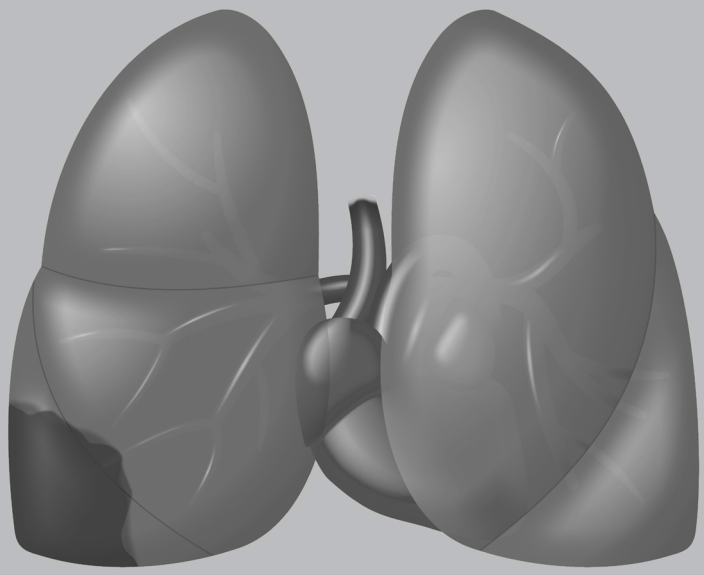
PART III

Outcome of Acute Pulmonary Embolism



CHAPTER 8

Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis.

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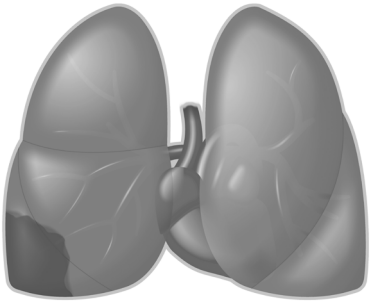
*Equally contributed

Am J Respir Crit Care Med 2008; 178:425-30



ABSTRACT

Rationale

The potential role of elevated brain-type natriuretic peptides in the differentiation of patients suffering from acute pulmonary embolism at risk for adverse clinical outcome has not been fully established.

Objectives

We evaluated the relation between elevated (NT-pro-)BNP levels and clinical outcome in patients with pulmonary embolism.

Methods

Articles reporting on studies that evaluated the risk of adverse outcome in patients with pulmonary embolism and elevated (NT-pro-)BNP levels were abstracted from Medline and EMBASE. Information on study design, patient- and assay characteristics and clinical outcome were extracted. Primary endpoints were overall mortality and pre-defined composite outcome of adverse clinical events.

Measurements and Main Results

Data from 13 studies were included. In 51% (576/1132) of the patients (NT-pro-)BNP levels were increased. The different analyses were performed in subpopulations. Elevated levels of (NT-pro-)BNP were significantly associated with right ventricular dysfunction ($p<0.001$). Patients with high (NT-pro-)BNP concentration were at higher risk of complicated in-hospital course (OR 6.8, 95%CI 4.4-10) and 30-day mortality (OR 7.6, 95%CI 3.4-17).Patients with a high (NT-pro-)BNP had a 10% risk of dying (68/671, 95%CI 8.0-13) while 23% (209/909, 95%CI 20-26) had an adverse clinical outcome.

Conclusions

High concentrations of BNP distinguish patients with pulmonary embolism at higher risk of complicated in-hospital course and death from those with low BNP levels. Increased (NT-pro-)BNP concentrations alone however do not justify more invasive treatment regimens.

INTRODUCTION

Right ventricular dysfunction on echocardiography is a common clinical finding in patients with acute pulmonary embolism (PE)[1-3] and predicts poor outcome in these patients. Prognostic stratification in acute PE patients may have consequences on management decisions. Patients identified with a low risk of complicated outcome may be eligible for outpatient management and high risk patients may benefit of more aggressive treatment.[1-2]

Several cardiac biomarkers have emerged as indicator of right ventricular dysfunction and predictor of clinical outcome in patients with acute PE. A recent meta-analysis demonstrated that elevated troponin levels identify patients with PE at high risk of short term death and adverse outcome.[4] Also, Brain-type natriuretic peptide (BNP) is a marker of ventricular dysfunction. This hormone is released in response to myocyte stretch. It is synthesized as an inactive prohormone (pro-BNP) that is split into the active hormone BNP and the inactive N-terminal fragment (NT-pro-BNP).[5] Several prospective studies have been performed to identify to potential role of either BNP or NT-pro-BNP in the risk stratification of patients with PE.[6-18] However, reported studies have limited patient numbers, used different cutoff points and involved different clinical endpoints. Therefore, we performed a meta-analysis of studies in patients with acute PE to evaluate the relation between elevated levels of BNP or NT-pro-BNP and clinical outcome.

METHODS

Data sources

A literature search was performed to identify all published prospective studies on BNP or NT-pro-BNP levels and clinical outcome in patients with PE. Medline and EMBASE were searched using pre-defined search terms, between January 1980 and October 2007. Search criteria included "Pulmonary Embolism" and "pro-brain natriuretic peptide" or "Brain Natriuretic Peptide" or "natriuretic peptide". Also, by searching the reference lists of all established studies, the researchers aimed to identify additional relevant papers. Papers were not limited to the English language. Only full papers were applicable for this analysis.

Study outcome

Objectively adjudicated short term adverse clinical events were used as primary outcome of this meta-analysis. These included mortality or an adverse clinical outcome defined as the occurrence of any of the following: death, cardiopulmonary resuscitation, mechanical ventilation, use of vasopressors, thrombolysis, thrombosuction, open surgi-

cal embolectomy or admission to the ICU. Right ventricular dysfunction was used as secondary endpoint.

Study selection and data extraction

Two independent researchers (F.K. and I.M., both MD) performed study selection. In case of disagreements a third researcher (M.H., MD, PhD) was consulted. Criteria for selection were a prospective design, consecutive inclusion, pre-defined endpoints, clear description of in- and exclusion criteria, objective criteria for diagnosis of PE, standardized treatment and the possibility of creating a 2 by 2 table based on BNP or NT-pro-BNP levels and clinical endpoints. Study sample size was not an eligibility criterion. Objective criteria for PE were positive CT findings, high probability VQ scan, positive pulmonary angiography or clinical suspicion of PE in combination with an ultrasonography proven deep vein thrombosis. Le Gal et al recently described that a positive compression ultrasonography of the lower limb veins is highly predictive of PE on computed tomography in suspected patients.[19] Data regarding patient characteristics, exclusion criteria, diagnostic criteria for PE, severity of PE (inclusion of hemodynamic instable patients and use of thrombolytic therapy), completeness of follow-up, immunoassay, timing of sampling, cutoff level, follow-up period and endpoints were abstracted.

Statistical analysis

Data were entered in Review Manager (Version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2003). Individual and pooled odds ratios were calculated to assess the relation between elevated BNP or NT-pro-BNP levels and clinical outcome. Mantel-Haenszel Methods for Combining Trials were used for weighting the studies. Cochran's chi-square test and the I^2 test for heterogeneity were used to assess inter study heterogeneity. The chi-square test assesses whether observed differences in results are compatible with chance alone. I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. Statistically significant heterogeneity was considered present at chi-square $p<0.10$ and $I^2 >50\%$.

RESULTS

Study selection

As a result of the literature search, 124 studies were revealed. Articles were excluded by review of title and abstract in case of review articles (n=48), animal studies (n=2), case reports (n=5), editorials, letters or author replies (n=13), studies not including the clinical course of PE (n=6) and if it concerned studies on other diseases than PE (n=17, Figure 1).

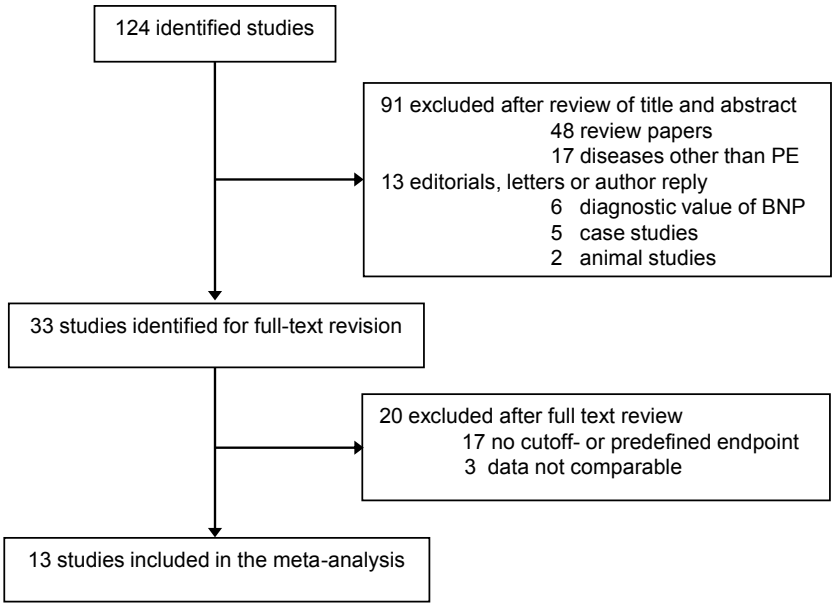


Figure 1. Flow diagram of study selection. PE: pulmonary embolism.

After full review, 20 more studies were excluded because our predefined endpoints were not reported (17) or no cutoff points were mentioned (3). We identified 13 studies that met our criteria.[6-18]

Characteristics of included studies

Demographic characteristics of the patients were comparable between all included studies (Table 1). Mean age of the patients varied between 53 and 75 years, the proportion of females ranged from 36-74%. In most patients, the diagnosis of PE was confirmed by CT-scan, high probability V/Q scan or pulmonary angiography. In three studies, hemodynamically unstable patients were excluded.[7,11,17] Noticeably, in two of these latter studies, some patients received thrombolytic therapy during their hospital stay.[7,11] Two included studies reported on partially overlapping patient cohorts.[16,18] Because one of them used BNP[16] and the other NT-pro-BNP[18] levels as outcome parameter, both studies could be incorporated into subgroup analyses based on type of BNP testing.

Assays and cutoff points

As shown in Table 1, all studies reporting NT-pro-BNP levels used a Roche analyzer (2 types), with 3 different cutoff levels, varying from 500 till 1000 pg/ml. In the BNP studies, two assays with 4 different cutoff levels varying between 75 and 100 pg/ml were used. In all included studies, the timing of sampling is comparable. Cutoff levels were not predefined in most studies. In these 10 papers, receiver operating characteristics

Table 1. Characteristics of included studies.

Marker	Ref	n	Female (%)	Age*	Assay†	Timing of sampling	Cut-off	Follow-up	PE diagnosis	Hemodynamic instability¥	Thrombolysis (n, %)
NT-pro-BNP	6	60	60	72 ±15	Roche, Elecsys 2010 analyzer	Admission	1000pg/ml§	In hospital	PA, V/Q, ultrasonography∂	Yes	1 (1.7)
	8	107	63	61 ±6	Roche, Elecsys 2010 analyzer	Admission, 4h, 8h, 24h	1000pg/ml	30 days	PA, V/Q, ultrasonography∂	Yes	–¤
	12	124	60	60 ±18	Roche, Elecsys 2010 analyzer	Admission, 4h, 8h, 24h	1000pg/ml	In hospital	PA, V/Q, ultrasonography∂	Yes	12 (11)
	13	100	65	63 ±18	Roche, ECLIA	Admission	600pg/ml	40 days	PA, V/Q	Yes	7 (7.0)
	15	79	63	63 ±17	Roche, Elecsys 2010 analyzer	Admission	600pg/ml	In hospital	PA, V/Q	Yes	8 (10)
	18	73	41	61 ±18	Roche, Elecsys 2010 analyzer	Admission	500pg/ml	In hospital	PA, V/Q	Yes	10 (14)
BNP	7	67	41	64 ±17	Biosite Diagnostics, Triage	Admission	100 pg/ml	NA‡	CT, V/Q	No	6 (9.0)
	9	181	58	53 ±17	Biosite Diagnostics, Triage	Admission	90pg/ml§	6 months	PA, V/Q	Yes	13 (22)
	10	51	65	79 ±9	Biosite Diagnostics, Triage	Admission	100 pg/ml	In hospital	PA, V/Q, ultrasonography∂	Yes	0 (0)
	11	61	74	75 ±14	Biosite Diagnostics, Triage	Admission	89 pg/ml	In hospital	PA, pulmonary angiography	No	7 (11)
	14	46	36	57 ±19	Biosite Diagnostics, Triage	Admission	90 pg/ml	In hospital	PA, V/Q, echocardiography∆	Yes	22 (48)
	16	73	41	61 ±18	Biosite Diagnostics, Triage	Within 4 hours	90pg/ml§	In hospital	PA, V/Q, embolectomy	Yes	6 (8.2)
	17	110	-¶	58 ±18	Immuno radiometric assay, Shionoria	Admission	75 pg/ml	3 months	PA, V/Q, ultrasonography	No	0 (0)

*Mean ±SD; †manufacturer and kind of assay (all were quantitative assays); ‡not applicable: endpoint was right ventricular dysfunction at time of diagnosis; ¶information was not provided; §predefined cut-off point; ∂typical clinical presentation and positive ultrasonography of lower limbs; ∆typical presentation and suggestive echocardiography; ¤specific information was not provided; ¥patients with hemodynamic instability were eligible for the study. PA: computed tomography or conventional pulmonary angiography; VQ: ventilation perfusion scintigraphy; n: number.

(ROC) analyses were performed to retrospectively determine optimal cutoff values with regard to complicated PE. Normal levels are defined as levels beneath or equal to the cutoff point.

Clinical outcome

Overall, in 51% (576/1132) of the patients the assays showed elevated plasma concentrations of (NT-pro-) BNP. Data on overall mortality were reported in 4 studies using BNP[10,11,14,17] and 4 studies using NT-pro-BNP.[8,12,13,15] In the BNP cohort, 17 of 123 patients (14%, 95%CI 8.3-21) with elevated BNP levels died compared to 3 of 138 (2.2%, 95%CI 0.45-6.2) with normal BNP levels. This resulted in an overall OR for death of 6.5 (95%CI 2.0-21, Figure 2). One study had a follow up of 3 months[17], as compared to the other 3 which had in-hospital follow-up. If this single study was left out of the analysis, overall OR decreased to 3.3 (95%CI 0.6-18). In the NT-pro-BNP cohort, 46 of 250 patients (18%, 95%CI 14-24) with elevated NT-pro-BNP levels died in comparison with 2 of 160 (1.3%, 95%CI 0.15-4.4) with normal NT-pro-BNP levels, OR for death was 8.7 (95%CI 2.8-27, Figure 2).

Numbers on PE-related mortality were only available in 3 studies.[11,13,17] Because follow-up time was dissimilar between these studies and not all mortality cases were adjudicated by an independent, blinded committee to determine the cause of death, we could not use PE-related mortality as an outcome of this analysis.

Ten studies provided data on adverse clinical outcome[6,8-13,15,16,18] of which 6 had NT-pro-BNP levels as outcome parameter.[6,8,12,13,15,18] Overall, criteria for adverse clinical outcome were comparable throughout all studies. In the BNP study group, 47 of 128 (37%, 95%CI 28-46) patients with elevated BNP levels had adverse advents during follow-up in comparison with 28 of 208 (13%, 95%CI 9.1-19) patients with normal plasma concentrations. High BNP levels were associated with a higher risk of occurrence of adverse clinical events (OR 6.3, 95%CI 3.6-11, Figure 3). This OR was even higher (9.5, 95%CI 3.5-25) after exclusion of 1 study with 6 months of follow-up,[9] thereby limiting the outcome to in hospital clinical course. Of the 318 patients with elevated NT-pro-BNP levels, 102 experienced short term adverse events (32%, 95%CI 27-38) as compared to 12 of 225 (5.3%, 95%CI 2.8-9.1) patients with normal NT-pro-BNP levels. Patients with high NT-pro-BNP serum concentration were at higher risk of complicated in-hospital course compared to patients with normal levels (OR 7.5, 95%CI 3.8-15, Figure 3). Pooled data of all assays showed elevated (NT-pro-) BNP levels in 52% of the patients with a risk of 23% (209/909, 95%CI 20-26) and an OR of 6.8 (95%CI 4.4-10) towards complicated clinical course.

Right ventricular dysfunction

Data on right ventricular dysfunction were reported in 6 studies (Figure 4). Four studies were evaluating BNP (243 patients)[7,11,14,16] and 2 studies evaluated NT-pro-BNP levels

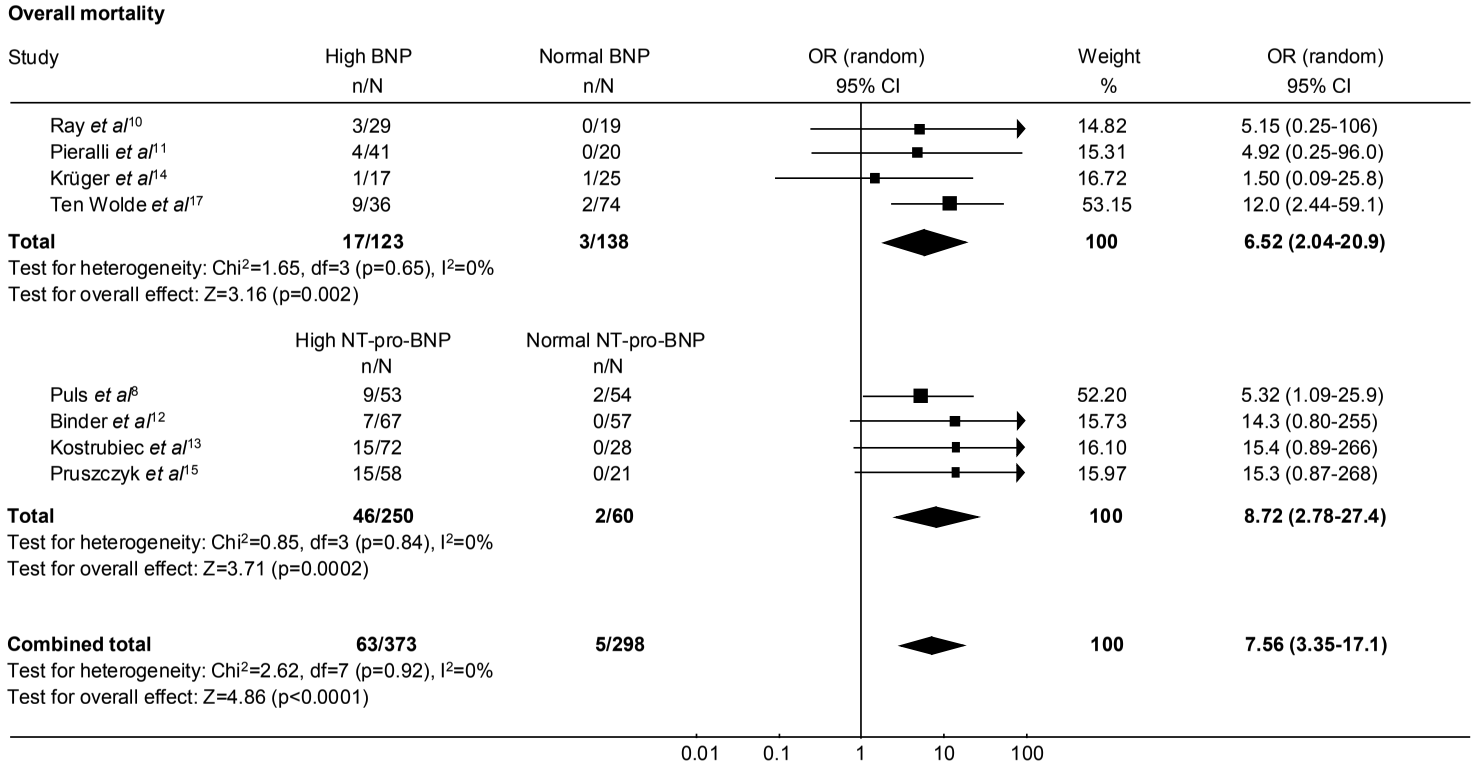


Figure 2. Odds ratio (OR) for overall mortality based on elevated (NT-pro-) BNP levels. Different cutoffs were used for different studies; Mantel-Haenszel methods for combining trials were used for weighting the studies. CI: confidence interval.

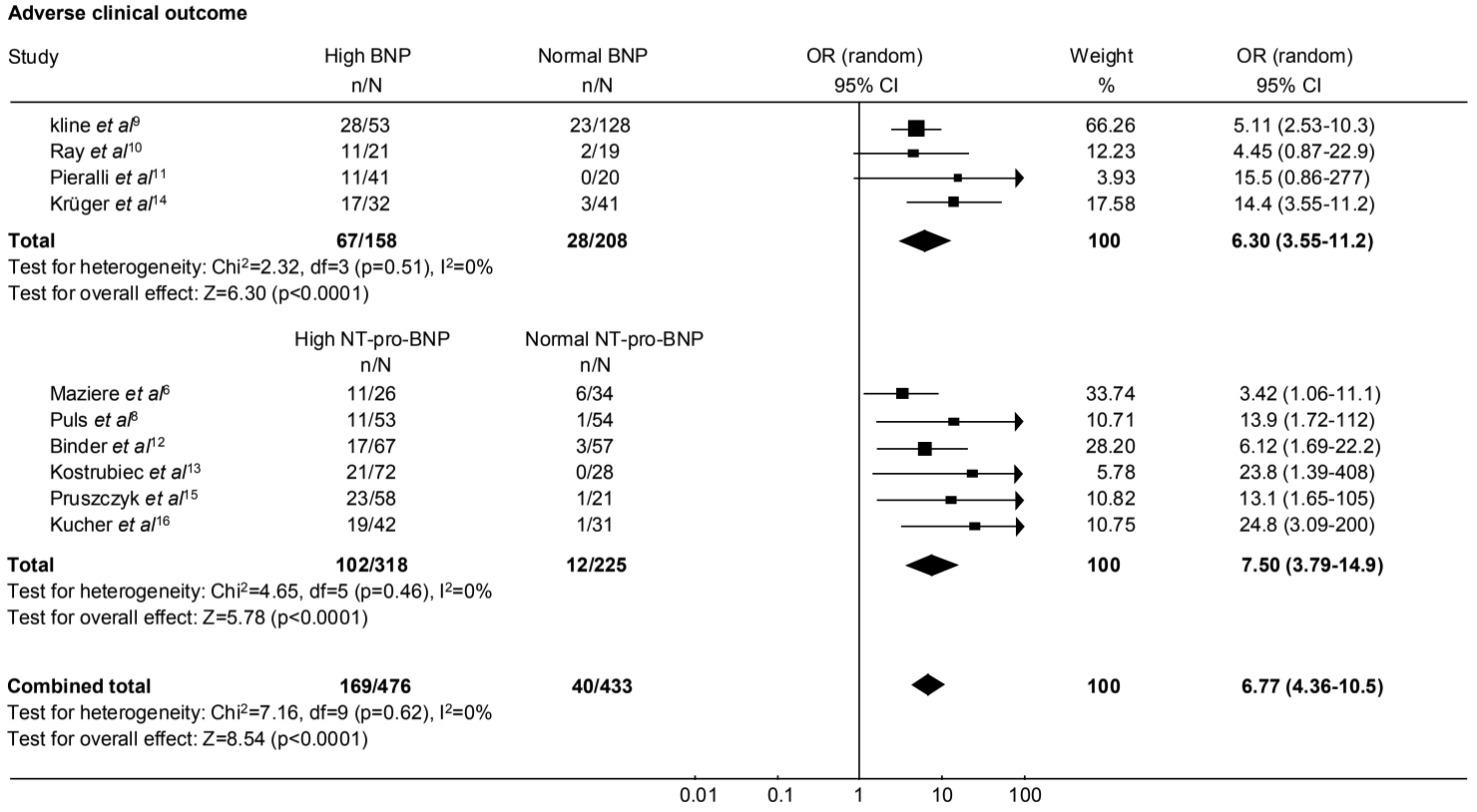


Figure 3. Odds ratio (OR) for adverse clinical outcome based on elevated (NT-pro-) BNP levels. Different cutoffs were used for different studies; Mantel-Haenszel methods for combining trials were used for weighting the studies. CI: confidence interval.

(197 patients).[12,18] The incidence of right ventricular dysfunction was 85% (116 of 137 patients; 95%CI 78-90) and 12% (13 of 106 patients; 95%CI 6.7-20) in patients with and without elevated BNP levels respectively (p<0.0001). A positive association was found between increased concentration of BNP and the presence of right ventricular dysfunction (OR 81; 95%CI 27-238). In NT-pro-BNP studies, the incidence of right ventricular dysfunction was 45% (49 of 109 patients; 95%CI 35-55) in patients with elevated NT-pro-BNP levels compared with 4.5% (4 of 88 patients; 95%CI 1.3-11) in patients with normal NT-pro-BNP levels. Elevated NT-pro-BNP levels were associated with the presence of right ventricular dysfunction (OR, 16.81; 95% CI 5.73 to 49.37). Pooled data of all assays revealed a combined OR of 39 (95%CI 17-89).

DISCUSSION

This meta-analysis demonstrates a significant relation between high levels of (NT-pro-) BNP and deterioration of clinical condition in patients with acute PE. This is physiologically plausible since BNP is released as a reaction to right ventricular stress, which has been shown to predict a non-benign course in patients with PE.[1-3] This relation is also demonstrated in this analysis: we found a very strong correlation between increased levels of (NT-pro-) BNP and right ventricular dysfunction on echocardiography (Figure 4).

There are some points for discussion if (NT-pro-) BNP levels would be incorporated in clinical treatment strategies for patients with acute PE. First, timing of blood sampling has consequences for the established BNP-concentration. The BNP prohormone (pro-BNP) in normal ventricular myocytes is not stored to a significant amount. As a consequence, it takes several hours for the plasma natriuretic peptide levels to increase significantly after the onset of acute myocardial stretch.[20] A very recent onset of complaints could therefore result in false-negative (NT-pro-) BNP test results. Second, many different cutoff levels for (NT-pro-) BNP are proposed in the literature.[21,22] The variation may be related to patient selection, different gender and age.[22] Despite the different cutoff levels and different assays, the prognostic value of both NT-pro- BNP and BNP was consistent in all included studies.

What are the potential implications of our findings? First, normal levels of BNP have a high negative predictive value for unfavorable outcome. Patients with normal levels of (NT-pro-) BNP have low risks for death as well as hemodynamic deterioration resulting in any adverse events. Conversely, elevated concentrations of B-type natriuretic peptides are a nonspecific finding. An explanation for this phenomenon is the elevation of natriuretic peptides in a multitude of other conditions, including preexisting left ventricular dysfunction, higher age, renal impairment and chronic lung disease.[23] The combination of BNP with other clinical risk factors for adverse outcome may improve

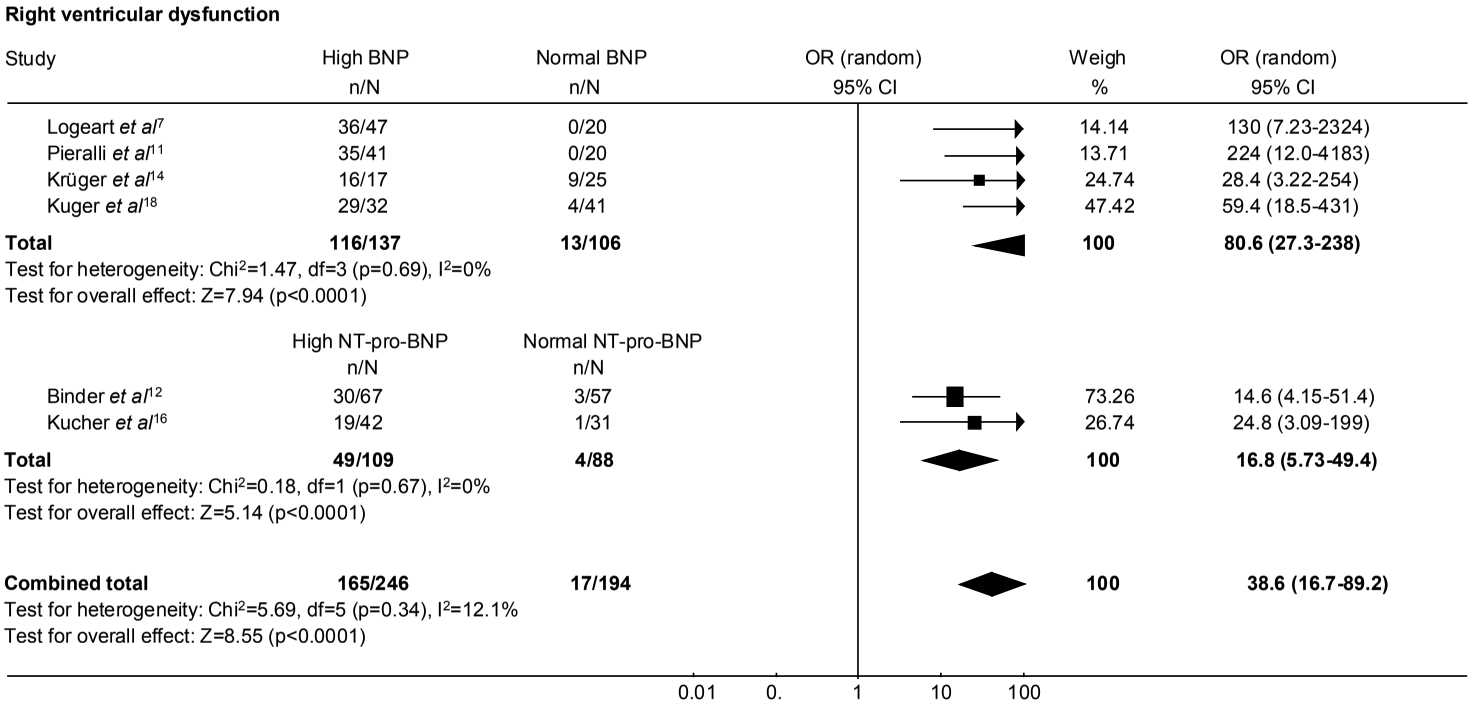


Figure 4. Odds ratio (OR) for right ventricular dysfunction on echocardiography based on elevated (NT-pro-) BNP levels. Different cutoffs were used for different studies; Mantel-Haenszel methods for combining trials were used for weighting the studies. CI: confidence interval.

sensitivity and positive predictive value for clinical deterioration. Such algorithms for risk stratification would be clinically useful if they were able to identify patients eligible for outpatient management, for standard or intensive in-hospital treatment. Proposals for such algorithms including (bio)markers of right ventricular function, e.g. (NT-pro-) BNP, troponin[4] or heart-type fatty acid-binding protein,[24,25] have been made but not validated prospectively in clinical outcome studies yet.[12,13,26] Future studies are required to determine the clinical benefits of more aggressive treatments in patients with adverse prognosis as identified by these risk stratifications and less intensive treatment including out of hospital treatment in patients with normal values of BNP.

This meta-analysis has limitations. First, included studies used different assays with different retrospectively calculated cutoff points. Second, duration of follow-up and definitions of endpoints varied among the studies. In addition, most studies did not mention completeness of follow-up. Nonetheless, we have included a large cohort of prospectively followed patients (n=1128) and our analysis showed no evidence of heterogeneity between the outcomes of the incorporated studies. Third, the relative risk for mortality is not adjusted for confounding factors, thus part of the effect ascribed to high BNP values may be related to clinical conditions associated with PE. Fourth, we could not determine the ideal cutoff for the two BNP tests because we did not have the raw data to do ROC curves and other analyses. Finally, in the included studies it is not stated whether thrombolytic therapy or ICU admission were the result of the clinical condition or a high (NT-pro-)BNP value.

In summary, an elevated level of (NT-pro-)BNP is a risk factor for short-term mortality, overall short term complicated clinical outcome and an indicator of right ventricular dysfunction in patients with acute PE. It remains to be demonstrated whether it could play a role in risk stratification algorithms identifying patients that could benefit from differentiated forms of therapy, of which thrombolytic therapy and home treatment are two poles of the spectrum.

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CHAPTER 9

Efficacy and safety of outpatient treatment with LMWH in patients with acute pulmonary embolism: The Hestia Study

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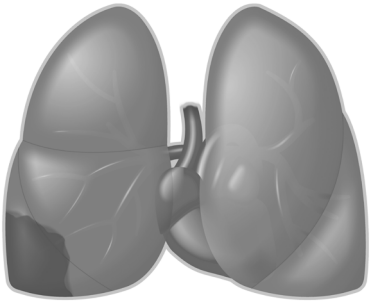

ABSTRACT

Background

Traditionally, patients with pulmonary embolism (PE) are initially treated in the hospital with low molecular weight heparin (LMWH). The results of a few small nonrandomized studies suggest that in selected patients with proven PE outpatient treatment is potentially feasible and safe.

Objective

To evaluate the efficacy and safety of outpatient treatment according to predefined criteria in patients with acute PE.

Patients and Methods

Prospective cohort study of patients with objectively proven acute pulmonary embolism, conducted in twelve hospitals in the Netherlands between 2008 and 2010. Patients with acute PE were triaged with the predefined criteria for eligibility for outpatient treatment starting with LMWH (Nadroparin), followed by vitamin K antagonists. All patients eligible for outpatient treatment were sent home either immediately or within 24 hours after PE was objectively diagnosed. Outpatient treatment was evaluated with respect to recurrent venous thromboembolism (VTE), including PE or deep venous thrombosis (DVT), major haemorrhage and total mortality during 3-month follow up.

Results

Of 297 included patients, who all completed follow-up, 6 patients (2.0%; 95% confidence interval [CI], 0.8-4.3) had recurrent VTE (5 PE (1.7%), 1 DVT (0.3%)).

Three patients (1.0%, 95% CI 0.2-2.9) died during 3-month follow-up, none of fatal PE. Two patients had a major bleeding event, of which one fatal intracranial bleeding (0.7%, 95% CI 0.08%-2.4%).

Conclusion

Patients with pulmonary embolism selected for outpatient treatment with predefined criteria can be treated with anticoagulants on outpatient basis.

INTRODUCTION

Pulmonary embolism (PE) is a common condition with a variable clinical presentation ranging from patients with minor thoracic pain to patients with fatal PE.[1] The risk for mortality and other serious events differs. Patients presenting with symptoms of shock have a high risk for short-term mortality of approximately 30%, while patients who maintain a normal blood pressure have a risk of PE-attributable mortality of 2-6%.[2-4] Patients with a risk of short-term mortality of less than 1% are typically considered to be low-risk patients[4] and these patients may potentially be amenable for outpatient treatment. In patients with deep vein thrombosis (DVT) treatment out of the hospital with lowmolecular-weight heparin (LMWH) followed by vitamin K antagonists (VKA) is commonly accepted.[5,6] Since these patients have a low risk of developing (fatal) PE, outpatient treatment of patients with DVT has become worldwide standard of care.[7] In the last decade, several small observational studies on outpatient treatment in PE have been published.[8-21] These studies on outpatient treatment include 9 prospective and 5 retrospective studies with the largest prospective study containing 152 patients entirely treated at home. The majority of the prospective studies used simple bedside criteria for selection of patients for outpatient treatment.[9,10,12,19-21] In these studies no PE related mortality occurred, only one patient died of major bleeding and non-fatal recurrence rates of venous thromboembolism (VTE) varied from 0% - 6.2%.[22] The objective of the Hestia Study was to confirm the results of these small cohort studies in a large study and provide proof that incidences of VTE recurrence, major bleeding and mortality are very low in patients selected by a simple set of exclusion criteria.

METHODS

Design Overview

The Hestia study was a multicenter prospective cohort study in patients with acute PE who were selected for outpatient treatment if they did not apply to a predefined set of exclusion criteria. We evaluated the efficacy and safety of out of hospital anticoagulant treatment with LMWH followed by vitamin K antagonists for at least three months. The protocol was approved by the institutional review board of each participating hospital. The data were collected and stored in the database by the investigators. All suspected outcome events were classified by an independent central adjudication committee, whose members were not participating in the study. It was predefined that an independent data and safety monitoring board periodically reviewed the studies' outcomes after every 50 included patients and advised the investigators. The manuscript was written by the investigators and they vouch for the accuracy and completeness of the reported data.

Setting and Participants

Patients were recruited from 12 hospitals in the Netherlands (three academic and nine non-academic hospitals). Consecutive patients, applying to the following inclusion criteria, were potentially eligible: over 18 years of age with objectively proven acute PE presenting to the Emergency Department or outpatient clinic. Patients with asymptomatic or chronic PE, defined as duration of symptoms existing longer than 14 days and no acute worsening within the last 14 days, were not included. Patients were triaged according to predefined exclusion criteria (Exclusion criteria; Table 1). This checklist with 11 items can be used as a bedside test and can be completed within five minutes. Patients could not be treated at home if one of the exclusion criteria (Table 1) were fulfilled; otherwise patients were eligible for outpatient treatment. For study reasons additional exclusion criteria were the following: impossibility for the required 3-month follow-up (e.g. no fixed address, foreign citizen) or life expectancy less than three months. After giving written informed consent and starting treatment with LMWH, patients were sent home either immediately, or within 24 hours after the diagnosis of PE for out-of-hospital treatment.

Table 1. Exclusion criteria for outpatient treatment.

Is the patient hemodynamically instable?*
Is thrombolysis or embolectomy necessary?
Active bleeding or high risk for bleeding?**
More than 24 hours of oxygen supply to maintain oxygen saturation > 90%?
Is pulmonary embolism diagnosed during anticoagulant treatment?
Severe pain needing intravenous pain medication for more than 24 hours?
Medical or social reason for treatment in the hospital for more than 24 hours? (infection, malignancy, no support system ie)
Does the patient have a creatinine clearance of less than 30 ml/min?***
Does the patient have severe liver impairment?****
Is the patient pregnant?
Does the patient have a documented history of heparin-induced thrombocytopenia?

*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.

Interventions

Patients were treated with standard anticoagulant therapy according to international guidelines.[7] Initial treatment consisted of once daily subcutaneous LMWH Nadroparin

corrected for body weight (11400 IU for body weight < 70 kg.; 15200 IU for body weight ≥ 70 kg). The first dose of LMWH was given at the emergency department under supervision of a nurse. The patient or a family member was instructed how to administer LMWH at home. On the same day vitamin K antagonists (phenprocoumon or acenocoumarol) were started and titrated to an INR between 2.0 and 3.0. The INR was monitored and VKA was titrated by the Dutch Thrombosis Services. LMWH was continued for at least five days and was stopped by the Thrombosis Services if the INR was in the target range for two consecutive days. Patients with active malignancy could be treated with LMWH alone during a 6-month period, according to the guidelines.[7] This treatment decision was left to the treating physician.

Outcomes and Follow-up

All patients were seen at the outpatient clinic at one week and three months after initial presentation. After six weeks follow-up an additional telephone contact was planned. At each contact the presence of clinical signs and symptoms suggestive of recurrent VTE or bleeding were assessed. Patients were instructed to contact their specialist before the fixed appointments for objective testing whenever clinical signs or symptoms suggestive of recurrent PE, DVT or if a bleeding complication occurred. The primary endpoint was objectively proven recurrent VTE during 3-months follow-up. Major bleeding and death within three months were defined as secondary endpoints. Symptomatic recurrent VTE was the main efficacy parameter. Recurrent VTE was considered present if recurrent PE or DVT were documented objectively, or in case of death in which PE could not be confidently ruled out as a contributing cause. The objective criterion for the diagnosis of recurrent PE was a new intraluminal filling defect on spiral CT or pulmonary angiography; cut-off of contrast material in a vessel > 2.5 mm in diameter on pulmonary angiography; a new perfusion defect involving at least 75% of a segment, with corresponding normal ventilation (i.e. a high probability lung scan); a new non-diagnostic lung scan accompanied by documentation of DVT by ultrasonography or venography; or confirmation of a new PE at autopsy. The objective criterion of a new DVT was a –new-, non-compressible venous segment or a substantial increase (≥ 4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on contrast venography. Major bleeding was the main safety outcome and was defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of more than 2.0 g/dL (1.3 mmol/L), or leading to transfusion of more than two units of whole blood or red cells.[23] Clinically relevant bleeding episodes, not qualifying as major bleeding, were classified as clinically relevant non-major bleeding (e.g. epistaxis that required intervention,

large hematoma visible on the skin, or spontaneous macroscopic hematuria). Mortality was defined as death due to recurrent PE (fatal PE), fatal bleeding, cancer, or another established diagnosis. Information about the cause of death was obtained from autopsy reports or from a clinical report. An independent adjudication committee consisting of two physicians not involved in the study evaluated all possible endpoints i.e. recurrent VTE, major bleeding or death. Any dispute was resolved by a third opinion. If no objective imaging of a suspected event was obtained, the event was evaluated on clinical grounds by the adjudication committee.

Statistical analysis

The primary endpoint is symptomatic recurrent VTE during 3 months of follow-up. We considered outpatient treatment to be effective if the upper limit of the 95% confidence interval of the incidence of recurrent VTE did not exceed a predefined margin. This predefined margin was based on incidences reported in literature.[6,24] It was stated that VTE recurrence rates of patients treated at home should not be higher than rates found in patients treated in the hospital. Incidences of recurrent VTE in the literature are reported up to 7%.[6,25] We therefore defined outpatient treatment according to the predefined criteria to be effective if the upper limit of the 95% confidence interval did not exceed the 7%. A power calculation was performed assuming an observed VTE recurrence in the study population of 3%.[24] To obtain an estimate of the incidence with a confidence interval below 7% a sample size of 257 patients was needed to achieve a power of 0.91 (one-sided binomial test). Allowing for a drop-out rate of 10%, a total of 280 patients with PE eligible for outpatient treatment had to be included. Exact 95% confidence intervals (CI) were calculated around the observed incidences with Fisher's Exact Test. SPSS software version 17.0 (SPSS Inc, Chicago, IL) was used for all analysis. The analysis was performed according to the intention to treat principle.

RESULTS

Study patients

Between May 2008 and April 2010 a total of 581 consecutive patients with acute PE were screened with the exclusion criteria for outpatient treatment, of which 243 were not eligible for outpatient treatment according to the criteria described in Table 1.

A total of 338 patients were eligible for outpatient treatment, of which 41 patients were excluded for study reasons. This resulted in a total study population of 297 (51%) patients treated as outpatients (Figure 1). Some of the patients (23%) were admitted to the hospital for less than 24 hours, mainly because CT scanning was not available at night. The mean duration of hospital admission in these patients was 19 hours. The

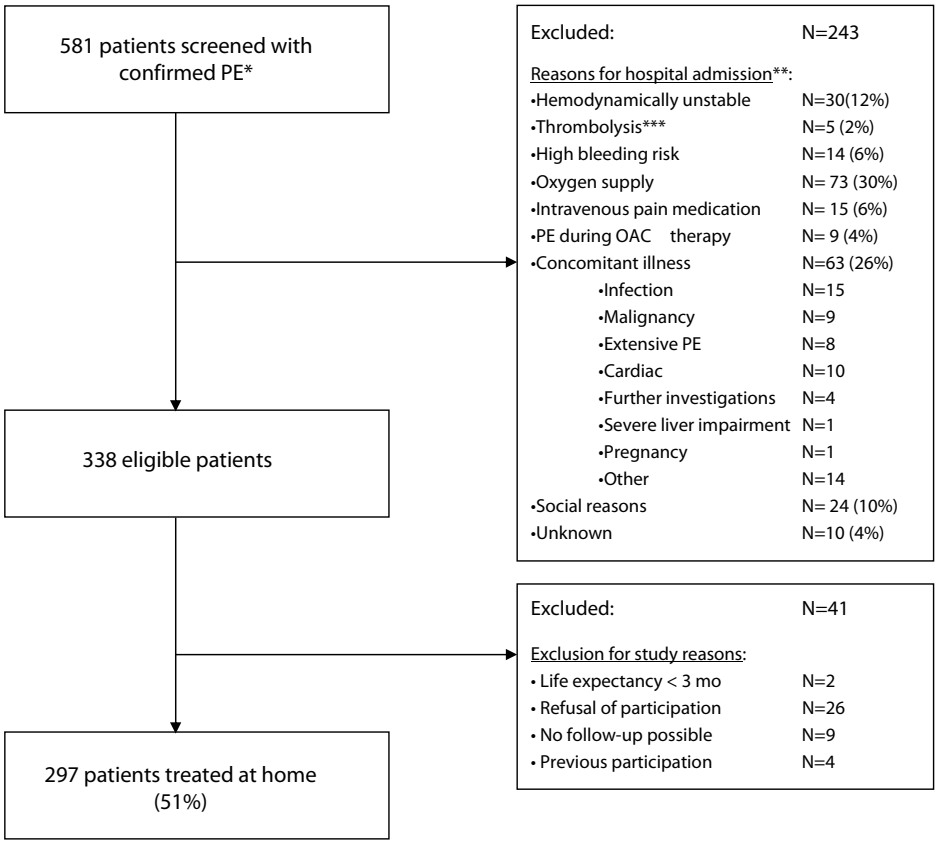

Figure 1. Flow-chart. *Meeting inclusion criteria: outpatients older than 18 years with acute symptomatic objectively confirmed pulmonary embolism (PE). **Most important exclusion criterion. ***Thrombolysis for other reasons than hemodynamic instability. OAC: oral anticoagulants.

clinical baseline characteristics of these patients are shown in Table 2. The mean age was 55 years and 26% of patients were older than 65 years, 58% of the patients were male and 9% had an active malignancy.

Treatment and follow-up

All patients were treated with LMWH for at least five days, except for one patient, who only received four days of LMWH treatment because of hemoptysis. In another patient the LMWH treatment protocol was violated. This patient received the first dose of LWMH on the emergency department, but he did not continue the treatment at home. Although he finally received LMWH for at least five days, the LMWH treatment was interrupted for 48 hours during the second and third day after the index event. In the majority of patients, initial LMWH therapy was followed by VKA treatment (Table 2). 6.1% of patients were treated with long term LMWH treatment alone because of malignancies or known

Table 2. Baseline characteristics of study patients (n=297).

Characteristics	
Age (years)	55 (15)
Age ≥ 65 yr	78 (26)
Male gender	172 (58)
BMI (kg/m^2)	27 (5)
Duration of complaints (days)	4 (3)
Risk factors for VTE	
Immobilization > 3 days or surgery < 4 weeks	27 (9.1)
Paralysis, paresis or plaster cast lower limbs	10 (3.4)
Estrogen use	47 (16)
Active malignancy	28 (9.4)
Heart failure with therapy	1 (0.3)
COPD with therapy	11 (3.7)
History of VTE	74 (25)
Unprovoked VTE*	207 (70)
Treatment**	
LMWH + VKA	276 (93)
Duration of LMWH usage (days)	9 (3)
LMWH continued	18 (6.1)

Categorical data are displayed as N° (%). Numerical data are displayed as means (standard deviation). *Unprovoked VTE is defined as venous thromboembolism without presence of one of the following provoking factors: estrogen use, immobilization more than 3 days or operation in the last month or active malignancy. No thrombophilia testing was done. LMWH: low molecular weight heparin; VKA: vitamin K antagonists; VTE: venous thromboembolism; COPD: chronic obstructive pulmonary disease. **Data on treatment were missing in N=3 (1.0%).

allergy to VKA. In 3 patients (1.0%) information about the type and duration of anticoagulant treatment was missing. The 3-month follow-up period was completed in all patients.

Outcome events

Efficacy during the first week of treatment

One patient had recurrent PE during the first week (0.3% 95% CI 0.008-1.9%; Table 3). In this patient the LMWH treatment protocol had been violated (described above), because he did not use LMWH at home. He returned to the hospital at day three with increasing dyspnea; although no repeat CT scan was performed, it was adjudicated as an extension of the initial PE. He was admitted to the hospital for adequate anticoagulant therapy with therapeutic doses of LWMH and vitamin K antagonists (Table 4). None of the patients, receiving adequate anticoagulant treatment, experienced a recurrent VTE event within seven days of the initial event. No patient died of fatal PE during this period.

Table 3. Adverse clinical outcome during 3-month follow-up (N=297).

Clinical outcome	Number	Percentage (95% CI)
Total recurrences	6	2.0 (0.75 – 4.3)
Fatal recurrent PE	0	0 (0-1.2)
Non-fatal recurrent PE	5	1.7 (0.55-3.9)
Non-fatal recurrent DVT	1	0.34 (0.0082-1.9)
Major bleeding complications	2	0.67 (0.082-2.4)
Fatal bleeding	1	0.34 (0.0082-1.9)
Non-fatal major bleeding	1	0.34 (0.0082-1.9)
Clinically relevant non-major bleeding	15	5.1 (2.9-8.2)
All cause mortality	3	1.0 (0.21-2.9)

PE: pulmonary embolism; DVT: deep vein thrombosis.

Efficacy during further follow-up

Between the second week and 3-month follow-up, another five patients had recurrent VTE: recurrent PE in four patients and DVT in one patient (Table 3).

During the whole study period of 3-month follow-up six patients (2.0%; 95% CI 0.8-4.3%) had a recurrent VTE of which one patient (0.3%; 95% CI 0.008.-1.9%) had an objectively proven recurrent DVT and five patients (1.7%; 95% CI 0.5-3.9%) had recurrent PE, adjudicated on clinical grounds. In five of six patients adjudicated as having recurrent VTE anticoagulant treatment was altered. Details are described in Table 4. None of the recurrent VTE events were fatal and all patients recovered completely (Table 4).

Safety

Two patients (0.7%; 95% CI 0.08-2.4%) had a major bleeding episode (Table 3). One patient had a fatal intracranial bleeding at day seven. This intracranial bleeding started while she was in the outpatient clinic for a predefined appointment; she died within 24 hours. The second patient had a large abdominal muscle hematoma accompanied with a drop in hemoglobin level of 2.5 mmol/L at day 14, for which a short observation on the intensive care unit was needed; this patient recovered completely. Clinically relevant non-major bleeding occurred in 15 patients (5.1%; 95% CI 2.9-8.2%). These non–major clinically relevant bleeds occurred between day one and day 66 (median day 24) and consisted of five patients with large skin hematomas, six patients with macroscopic hematuria, three patients with hemoptysis and one patient with an ovary bleeding without significant drop in haemoglobin. In three patients with clinically relevant non-major bleeding anticoagulant treatment was interrupted for one day: in one patient with hemoptysis, in one patient with a large skin hematoma and in the patient with the ovary bleeding.

Table 4. Description of adverse clinical outcome during 3 months of follow-up.

Recurrent VTE (n=6)						
Gender	**Age**	**Complaints**	**Day**	**Imaging**	**Adverse event**	**Brief description**
Male	80	Increasing dyspnea	3	No extra CT scanning performed	Clinically adjudicated recurrent PE	Patient did not administer LMWH at home, complaints of dyspnea increased and he was admitted for administration of LMWH until INR was in target range
Male	78	Chest pain	8	No extra CT scanning performed	Clinically adjudicated recurrent PE	Admission for observation. Acenocoumarol was switched to Phenprocoumon to achieve increased stability of INR levels.
Female	38	New thoracic pain	10	No extra CT scanning performed	Clinically adjudicated recurrent PE	LMWH dosage was increased from 15200 IU once daily to 22800 IU once daily (BMI 40 kg/m^2). Admission until INR was stable in target range.
Female	37	Increasing dyspnea	28	No extra CT scanning performed	Clinically adjudicated recurrent PE	Admission for recurrent PE during inadequate INR level (1.5), LMWH treatment until INR was in target range
Female	55	Recurrent DVT	48	US: extension of thrombus from calf vein to iliac vein level	Objectively proven recurrent DVT	Admission for recurrent DVT in patient with malignancy, increasing dosage of LMWH from 11400 IU once daily to 19000 IU once daily.
Male	45	New thoracic pain	60	No extra CT scanning performed	Clinically adjudicated recurrent PE	Recurrent PE during inadequate VKA therapy (INR 1.4), LMWH therapy until INR was in target range
Major bleeding (n=2)						
Gender	**Age**	**Adverse event**	**Day**	**Imaging**	**Brief description**	
Female	54	Fatal intracranial bleeding	7	Cerebral CT scan: central bleeding right basal ganglion area	Admission for intracranial bleeding in patient treated with Nadroparin combined with VKA, INR of 4.0 and concomitant uncontrolled hypertension, died the same day, autopsy confirmed diagnosis. Hypertension existed at index PE event, but was controlled by medication before discharge.	
Female	74	Abdominal hematoma	14	Large hematoma in abdominal muscle sheet (volume 1.7 L)	One day ICU admission for large hematoma of abdominal rectal sheet, INR of 5.3 while still on Nadroparin therapy with hypotension, drop in hemoglobin of 2.5 mmol/L, fully recovered	

Table 4. (continued)

Mortality (n=3*)					
Gender	**Age**	**Adverse event**	**Day**	**Autopsy**	**Brief description**
Male	67	Died	29	No	Died of metastatic pancreatic cancer, diagnosed before index PE
Female	59	Died	59	No	Died of metastatic pancreatic cancer, diagnosed before index PE

CT: computed tomography; DVT: deep vein thrombosis; ICU: intensive care unit; IU: international units; LMWH: low molecular weight heparin; PE: pulmonary embolism; US: ultrasonography; VKA: vitamin K antagonist; VTE: venous thromboembolism

*Including one patient that died of fatal intracranial bleeding, mentioned in section "major bleeding".

Mortality

Three patients (1.0%; 95% CI 0.2-2.9%) died during the study (Table 3). One patient died of fatal intracranial bleeding at day seven, confirmed by autopsy. The cause of mortality in the two other patients was progressive metastatic pancreatic cancer (at day 29 and 59). The cause of death in the two patients with malignancy was clinically adjudicated by the treating physician. None of the patients died of fatal PE.

DISCUSSION

This study evaluated the efficacy and safety of outpatient treatment of patients presenting with acute PE. Patients with acute PE were triaged in a standardized way and eligible patients were treated as outpatients. The present study shows that outpatient anticoagulant treatment of patients selected by the exclusion criteria has a low risk for recurrent VTE: VTE recurred in 2% of patients, with the upper limit of the confidence interval reaching 4.3%, which is lower than the predefined limit of 7%. None of the recurrences were fatal. None of the patients in the present study, receiving adequate anticoagulant treatment, experienced a recurrent VTE event within seven days of the initial event, a period which equals the average duration of hospital admission for PE.[26] Comparison of the recurrence rate of 2.0% (95% CI 0.8 – 4.3%) found in the present study to the VTE recurrence rate of 3.0% (95% CI 1.8-4.6%) in a historical cohort of patients with PE treated in the hospital[24] demonstrates almost identical rates, suggesting the efficacy of the LMWH treatment at home may be at least as good as the efficacy in the hospital. Moreover, our results are similar to outcomes in small prospective studies summarized in a systematic review,[22] a recently performed prospective cohort study[8] and results of a large retrospective cohort[13] on outpatient treatment of PE. Of note, our rate is considerably lower than the 6.2% found in the study of Kovacs et al.[12] This discrepancy might be explained by the higher proportion of patients with malignancies

(25% vs. 9%) in that study. The rate of bleeding with the outpatient treatment was low in comparison to bleeding rates reported in the literature. In the present study major bleeding occurred in 0.7% and 5.1% of patients had non-major clinically relevant bleeding. In studies with comparable groups of patients major bleeding rates in patients with PE treated at home varied between 0 and 2.8%.[22] Moreover, fatal bleeding occurred in only one patient (0.3%) in the present study. This is well comparable to the fatal bleeding rates of 0.3% to 0.6% in unselected patients with PE treated in the hospital.[24,27] In this study a simple set of exclusion criteria was used to select patients for outpatient treatment. The choice for these criteria was reinforced by former research.[12] The criteria are pragmatic, easy to use at the bedside, fast-to-perform and cheap. This study, where predefined exclusion criteria were used, 51% of patients with PE could be treated out of the hospital, which is comparable to the 51-55% found in two large retrospective studies, using comparable criteria.[11,12] In the literature the use of "subjective items" has been criticized.[28] However this study shows that physicians guided by the simple bedside criteria are well able to distinguish low risk patients eligible for outpatient treatment. In addition, comparable sets of criteria have been used safely in different cohorts from different countries.[9,10,12,19-21] Two other approaches have recently been suggested for selecting patients for outpatient treatment: the Pulmonary Embolism Severity Index (PESI)[29] and NTproBNP.[8] The predictive values of PESI and NT-proBNP have been derived from unselected cohorts of patients with PE treated in the hospital.[30,31] A large cohort study with unselected patients treated for PE in the hospital demonstrated that patients with PE and low PESI scores (class I and II) have a risk for 90-day mortality of 1.2%.[29] A recent meta-analysis showed that unselected patients with low NT-proBNP levels have a 30-day mortality of 1.3%.[32] The predictive value of the PESI and NT-proBNP in patients preselected with pragmatic exclusion criteria is currently unknown. In addition, these two selection methods are validated on short term mortality, but our data showed that short term mortality in preselected groups potentially eligible for outpatient treatment is very low (1.0%). This study had strengths and limitations that should be addressed. To our knowledge this is the largest trial in patients with acute pulmonary embolism who were treated as outpatients within 24 hours after the diagnosis of pulmonary embolism. The inclusion of consecutive patients as well as the absence of loss to follow-up make that selection bias is no issue in the present study.[33] One limitation of the study is that the endpoint ascertainment could not be blinded due to the single-arm design of the study. However, ascertainment of both the exposure (pulmonary embolism) and the outcome (recurrent VTE) was performed according to predefined criteria, which minimizes the risk of information bias. The reported recurrence rate of 2% could be an overestimation, because in the five patients who were centrally judged as having recurrent PE, no objective imaging was done. These five patients were centrally adjudicated as recurrent PE because of the clinical signs suggestive of recurrent PE and/or the local decision to

change anticoagulant therapy. The central adjudication committee was conservative on this to avoid an underestimation of the recurrence rate. Another limitation is that 23% of patients had to stay in the hospital for up to 24 hours for logistic reasons. Finally, we initially considered a randomized study design with random allocation to in or outpatient treatment, but concluded this was not feasible due to the very large sample size that would have been needed. Instead, a single-arm clinical trial was performed with predefined triaging of patients and careful standardized follow-up in all patients using predefined criteria for assessing and adjudicating recurrent events and bleeding. Such a single-arm trial is a valid instrument to evaluate treatment in a population provided that consecutive patients are included and all patients get standardized triaging, to avoid investigator bias.

In conclusion, outpatient treatment of acute PE may be effective and safe in patients selected with the predefined and easy-to-perform criteria, based on the observed low recurrence, mortality and bleeding rates. In view of the single arm trial design these results have to be confirmed in a randomized controlled trial.

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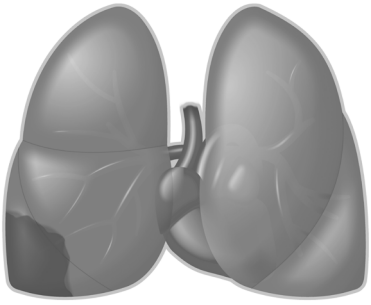
CHAPTER 10

General discussion and summary



In patients with a suspected pulmonary embolism (PE), multiple diagnostic strategies are available to confirm or exclude this diagnosis. The objectives of this thesis are to simplify, to validate and compare diagnostic strategies in patients with clinical suspicion of acute PE, with special focus on suspected recurrent PE. Subsequently, diagnostic outcomes of these strategies in patients with proven PE were studied and the possibility of home-treatment was evaluated. **Chapter 1** provides a general introduction to the diagnostic methodologies for patients with suspected acute PE and highlights some subjects for further related research.

PART I. DIAGNOSTICS IN ACUTE PULMONARY EMBOLISM

Chapter 2 provides a general overview of current diagnostic methods to confirm or rule out acute PE, focusing on different clinical decision rules, D-dimer tests and additional imaging techniques. In addition, diagnostic strategies will be evaluated that combine the preceding diagnostic tools.

In the available literature, several clinical decision rules are described. One of the best validated and widely used clinical decision rules is the Wells clinical decision rule. However, the merits of this rule are often debated, mainly because the rule includes one subjective item by which the physician must consider the possibility of an alternative diagnosis. A clinical decision rule as a well as a D-dimer test do not generate reliable clinical outcomes when executed as single tests, but an unlikely score of the decision rule combined with a normal D-dimer test result safely excludes a PE. In all other cases, additional imaging is necessary with CTPA as first choice modality.

In **chapter 3** the revised Geneva score was simplified and validated, which is a clinical decision rule with only objective variables. The revised Geneva score was simplified by attributing one point to each of the variables, which makes it easier to remember and helps to avoid miscalculations. In 1049 patients with suspected PE the proportion of patients classified as low clinical probability was 36% with a 7.7% prevalence of PE, this was comparable with the originally revised Geneva score. The area under the receiver operating characteristics curves (AUC of ROC) was similar, 0.74 (95% CI 0.70-0.77) versus 0.75 (95% CI 0.71-0.78), which shows that the diagnostic accuracy is not diminished by applying simplification. Furthermore, it appeared to be safe to withhold anticoagulation to patients with a low, intermediate (using a 3-part rule) or unlikely (in a 2-part rule) clinical probability on PE combined with a normal D-dimer test. During a 3-month follow-up period, none of these patients was diagnosed with VTE.

In addition to this simplification, prospective validation is described in **chapter 4**. Four clinical decision rules (the Wells rule, the revised Geneva score, the simplified Wells rule and the simplified revised Geneva score) were directly compared in excluding PE in

combination with D-dimer testing. Different variables of the four CDRs were collected and D-dimer test were performed in all 807 included patients. A computer program calculated all scores and indicated whether PE could be excluded (PE unlikely according to all four CDRs and a normal D-dimer test), or a CTPA should be performed (at least one CDR indicating PE likely or an elevated D-dimer level). Additionally, we evaluated the results of the individual CDRs for each patient. The number of patients categorized as "PE unlikely" ranged from 62% (simplified Wells) to 72% (Wells rule), the prevalence of PE in group of patients categorized as PE unlikely was similar (13-16%) for all CDRs. Combined with a normal D-dimer level, PE could be excluded in similar proportion of patients in 22 to 24% of the cases. The incidence of VTE during the 3-month follow-up period was comparable, 0.5-0.6% (upper limit 95% CI 2.9-3.1). Despite the discordant results in 30% of patients, PE was missed in none of these patients with a normal D-dimer level. It was concluded that the four CDRs in combination with a D-dimer test performed similarly in the exclusion of acute PE. In addition the prospective validation indicated that the simplified CDRs may be used in clinical practice.

A CTPA scan is currently the preferred imaging test to confirm or exclude PE. Nonetheless, the safety of withholding anticoagulant therapy in especially patients with a high clinical pretest probability and a negative CTPA is being debated. In **chapter 5**, a meta-analysis was performed to determine the safety of ruling out PE by normal CTPA in a specific group of patients with a strict indication for CTPA, i.e. likely or high clinical probability of PE, an elevated D-dimer level, or both. The pooled negative predictive value of CTPA as sole imaging test was 98.8% (95% CI 98.2-99.2), and the pooled NPV based on a normal CTPA followed by negative compression ultrasonography of the legs was 98.9% (95% CI 98.0-99.4). These numbers are comparable with those after a normal pulmonary angiography, historically the gold standard methodology for the diagnosis of PE. The 3-month risk of fatal PE after a negative CTPA was very small (0.6%), complementing this test with normal compression ultrasonography had no additional value (0.5%). In conclusion, it can be stated that a normal CTPA alone can safely exclude PE in all patients in whom CTPA is required to rule out VTE in these patients.

PART II. RECURRENT ACUTE PULMONARY EMBOLISM

Part II focuses on patients with suspected recurrent PE. In **chapter 6** the incidence of recurrent thrombosis in a well defined population, the Leiden region, was studied. The study estimated an overall annual incidence of recurrent VTE of 0.22 per 1000 inhabitants, the incidence of recurrent PE was 0.08 per 1000 inhabitants per year. The incidence of recurrent events was higher in male patients and the majority of recurrences occurred

in the first two years after the previous event. Malignancy was the most prevalent risk factor associated with recurrent VTE.

Chapter 7 describes the performance of a simple diagnostic strategy in patients with clinically suspected recurrent PE, using the Wells CDR, a D-dimer test and CTPA. 17% of the 516 included patients with suspected recurrent PE had a low clinical probability and normal D-dimer test result. A recurrent PE could be excluded safely, none of these patients had a recurrent VTE during the 3-month follow-up period. CTPA excluded recurrent PE in 253 patients, however, during follow-up seven patients had a recurrent VTE event (2.8%; 95% CI 1.2-5.5%), of which one was fatal (0.4%; 95% CI 0.02-1.9%). This analysis showed that the algorithm is effective in the management of patients with clinically suspected recurrent acute PE. CTPA provides reasonable safety in excluding acute recurrent PE in patients with high clinical probability for recurrent PE, with a low risk for fatal PE at follow-up.

PART III. CLINICAL OUTCOMES OF ACUTE PULMONARY EMBOLISM

The stratification of hemodynamically stable patients with proven PE, in a group with high and a group with low probability at adverse clinical outcome, can be important for diagnostic and therapeutic management. Right ventricular dysfunction predicts complicated outcome in patients with acute PE. Brain-type natriuretic peptide (BNP) is a hormone released in response to myocyte stretch and thereby a marker of ventricular dysfunction. It is synthesized as an inactive pro-hormone (pro-BNP) that is split into the active hormone BNP and the inactive N-terminal fragment (NT-pro-BNP) In **chapter 8** a meta analysis is described in which the role of (NT-pro-) BNP has been evaluated for the risk assessment for adverse clinical outcome for patients with proven acute PE. This study shows the ability to distinguish an increased risk with elevated (NT-pro-) BNP values for complications during the hospital stay (odds ratio 6.8%, 95% CI 4.4–10) and 30-day mortality (odds ratio 7.6, 95% CI 3.4 -17) and it is an indicator for right ventricular dysfunction in patients with acute PE. Whether a high (NT-pro-) BNP value by itself can stratify patients for more or less intensive treatment is yet to be proven.

In **chapter 9** patients with a proven PE and a low suspicion at complications according to predefined criteria were treated at home with the standard treatment of anticoagulants. In total 297 patients, 51% of screened patients, were treated at home. During a 3-month follow-up period, 6 patients developed a recurrent VTE (2.0%;95% CI: 0.8-4.3%); one patient a DVT and five patients PE. In total three patients died during the follow up period, one patient as a result of an intracranial bleeding, the two other patients as a

result of progressive malignancy. Besides the patient with an intracranial bleeding one other patient developed a major bleeding (total 0.7%;95% CI:0.1-2.4%). It is concluded that home treatment with anticoagulant seems effective and safe in patients with acute PE, when selected according to pre defined criteria.

FUTURE PERSPECTIVE

The goal of the diagnostic process at suspicion of PE is to develop a standardized, accurate and simple strategy that can be easily applied for the majority of patients with suspicion on PE. With the current diagnostic methodologies, consisting of clinical decision rules, D-dimer tests and imaging with CTPA as first choice, we have well validated, safe and efficient strategies for patients with suspected PE. Challenges remain to further optimize this strategy. In clinical practice, the clinical decision rules are not always applied in the correct and optimal manner. This can be improved by implementing the simplified decision rules, as described earlier, in clinical practice. Also further optimization can take place in several subgroups of patients. Research can hereby focus on elderly patients, D-dimer tests get less reliable with increasing age. A current study, the Adjust study, is focusing on a age adjusted D-dimer cut-off level. The D-dimer cut off level is defined as patient's age x 10 in patients above 50 years of age, potentially increasing the proportion of older patients in whom PE safely could be excluded. In patients with a decreasing kidney function the reduced usage of contrast is desirable and for women in the age of fertility reduction of radiation by CT scans is reason for further research. Finally, data are scarce for pregnant women, with increased risks of radiation exposure to the fetus. Magnetic resonance angiography (MRA) has potential to be an alternative to CTPE in these patients. The less nephrotoxic gadolinium contrast-enhanced acquisitions can be used for thrombus imaging with the advantage of avoiding ionizing radiation and iodinated contrast material. But accuracy is currently insufficient for implementation in routine clinical care. With further development of CTPA with higher resolutions, more and smaller emboli will be detected. Further research needs to be done to understand the clinical relevance of these smaller clots.

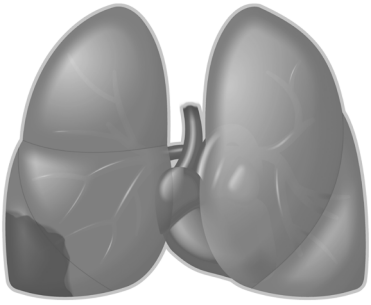
Specific algorithms or cutoff values can help to get a better prediction of the probability on PE for the individual patient, implementation in daily practice is however more difficult with the usage of different values in different patient groups. With electronic assistance a more individually generated risk stratification based on the unique features of the patient may become feasible.

According to the current guidelines, a patient with proven PE needs to be hospitalized. The Hestia study, described in this thesis, has shown however, that home treatment seems to be a good alternative for a carefully selected group of patients. Randomized

trials are necessary to further optimize this evidence. Finally, the added value of markers such as NT- pro BNP have to be evaluated, with the goal to optimally, clearly and simply select patients with a low risk for acute complications.

CHAPTER 11

Nederlandse samenvatting



Bij patiënten met een verdenking acute longembolie zijn diverse diagnostische strategieën mogelijk om deze diagnose aan te tonen, danwel uit te sluiten. Het doel van dit proefschrift was het vereenvoudigen, het valideren en vergelijken van diagnostische strategieën bij patiënten met verdenking acute longembolie, met specifieke aandacht voor verdenking recidief longembolie. Vervolgens werd gekeken naar uitkomsten bij patiënten met een bewezen longembolie en werd de mogelijkheid van thuisbehandeling geëvalueerd. **Hoofdstuk 1** geeft een algemene introductie over de diagnostiek bij patiënten met een verdenking acute longembolie en de geeft punten weer waar verder onderzoek naar verricht moet worden.

DEEL I. DIAGNOSTIEK BIJ ACUTE LONGEMBOLIE

Hoofdstuk 2 beschrijft een uitgebreide stand van zaken wat betreft diagnostische methoden om een longembolie aan te tonen of uit te sluiten. Hierbij is er aandacht voor verschillende klinische beslisregels, de D-dimeer test en voor aanvullend radiologisch onderzoek. Tevens worden de mogelijke algoritmes besproken waarbij voorgaand genoemde onderzoeken worden gecombineerd. In de literatuur zijn verschillende beslisregels beschreven, een van de best gevalideerde en meest gebruikte regels is de Wells klinische beslisregel. Echter er blijft discussie bestaan doordat deze beslisregel een subjectieve variabele bevat waarbij de waarschijnlijkheid van de diagnose longembolie wordt beoordeeld en afgezet tegen de waarschijnlijkheid van een alternatieve diagnose. Zowel een beslisregel als D-dimeer test kunnen niet als enige test gebruikt worden, maar de combinatie van een lage score met een beslisregel met een normale D-dimeer test sluit een longembolie veilig uit. In alle andere gevallen is aanvullende beeldvorming aangewezen met CTPA als eerste keus. In **hoofdstuk 3** wordt de vereenvoudigde gereviseerde geneva score geëvalueerd, een klinische beslisregel met alleen objectieve variabelen. De originele gereviseerde score en de vereenvoudigde versie bevatten dezelfde variabelen, maar bij de vereenvoudigde versie wordt slechts één punt aan iedere variabele toegekend. Dit is gemakkelijker te onthouden en eenvoudiger toe te passen met minder risico op fouten met uitrekenen van de score. Bij 1049 patiënten met verdenking longembolie was het aantal patiënten dat als 'longembolie onwaarschijnlijk' werd geclassificeerd 36% met een 7.7% prevalentie van longembolieën in deze groep, dit was goed vergelijkbaar met de originele gereviseerde Geneva score. Ook het oppervlak onder de ROC curves was gelijk met 0.74 (95% BI 0.70-0.77) versus 0.75 (95% BI 0.71-0.78) wat laat zien dat de diagnostische accuraatheid niet verminderd door de simplificatie toe te passen. In dit cohort bleek te veilig om antistolling te onthouden aan patiënten met een lage, intermediaire (bij 3-delige regel) of onwaarschijnlijke (bij 2-delige regel) voorafkans op longembolie en een normale D-dimeer test. Tevens werd bij geen van deze patiënten met een lage

of intermediaire gereviseerde score en een normale D-dimeer uitslag, gedurende de 3-maanden follow-up een veneuze trombo-embolie gediagnosticeerd. Deze resultaten suggereren dat de gesimplificeerde regel toegepast kan worden in de klinische praktijk. In aansluiting hierop werd deze vereenvoudigde regel prospectief gevalideerd in **hoofdstuk 4**. In dit hoofdstuk worden vier klinische beslisregels (de Wells beslisregel, de gereviseerde Geneva score, de gesimplificeerde Wells beslisregel en de gesimplificeerde gereviseerde geneva score) direct met elkaar vergeleken voor het uitsluiten van een longembolie, in combinatie met de D-dimeer test. Verschillende variabelen die nodig zijn voor het berekenen van de vier scores werden verzameld en de D-dimeer test werd bij alle 807 geïncludeerde patiënten verricht. Een computer programma berekende of de diagnose kon worden uitgesloten (onwaarschijnlijke volgens alle 4 de regels en een normale D-dimeer test) of dat een CT-scan nodig was (indien ten minste 1 regel longembolie waarschijnlijk aangaf of de D-dimeer waarde verhoogd was). Vervolgens werd voor iedere patiënt gekeken naar de uitkomst van de individuele beslisregels. Afhankelijk van de beslisregel varieerde het aantal patiënten met uitkomst 'longembolie onwaarschijnlijk' van 62% (vereenvoudigde Wells regel) tot 72% (Wells regel), de prevalentie van longembolie in de groep met longembolie onwaarschijnlijk waren vergelijkbaar (13-16%). Gecombineerd met een normale D-dimeer waarde kon de diagnose worden uitgesloten in 22-24% van de patiënten. De incidentie van VTE tijdens 3 maanden follow-up was vergelijkbaar, 0.5-0.6% (bovenste grens 95% BI 2.9-3.1). Ondanks het feit dat de uitkomst van de beslisregels in 30% van de patiënten met elkaar verschilde, werd in geen van deze patiënten met een discrepante regel en een normale D-dimeer waarde een longembolie gevonden. Geconcludeerd werd dat de vier beslisregels vergelijkbaar waren wat betreft veiligheid en klinische toepasbaarheid in het uitsluiten van een longembolie in combinatie met de D-dimeertest. De vereenvoudigde regels zijn hiermee ook prospectief getoetst en gevalideerd en kunnen in de klinische praktijk worden gebruikt.

Een CT-scan is meest gebruikte diagnostische test voor aantonen of uitsluiten van longembolie. De vraag was of bij een patiënt met hoge voorafkans een negatieve scan niet afdoende is om een longembolie uit te sluiten. In **hoofdstuk 5** hebben we de negatief voorspellende waarde van een CTPA voor longembolie onderzocht door een meta-analyse uit te voeren van studies die een longembolie uitsloten middels CTPA bij patiënten met een hoge of waarschijnlijke voorafkans en/of hoge D-dimeer waarde en studies waarbij CTPA nog door een compressie-echografie van de benen werd gevolgd. De negatief voorspellende waarde van CTPA alleen was 98.8% (95% BI 98.2-99.2), bij CTPA gevolgd door negatieve compressie-echografie van de benen was dit 98.9% (95% BI 98.0-99.4). dit komt overeen met de cijfers na negatieve pulmonalis angiografie, wat lange tijd de gouden standaard geweest. Het risico op een dodelijke longembolie in drie maanden na een negatieve CTPA was laag (0.6%) en toevoeging van compressie-echografie had hierbij geen meerwaarde (0.5%). Concluderend is een negatieve CTPA

alleen afdoende om een longembolie uit te sluiten bij patiënten met een indicatie voor CTPA om een longembolie uit te sluiten. Er is geen reden om na een negatieve CTPA aanvullend een echografie te verrichten bij deze patiënten.

DEEL II. RECIDIEF ACUTE LONGEMBOLIE

In deel II werd specifiek ingegaan op patiënten met een verdenking op recidief longembolie. In **hoofdstuk 6** werd gekeken naar de incidentie naar recidief trombose in de regio Leiden. Er werd een incidentie van recidief trombose gevonden van 0.22 per 1000 inwoners per jaar, van recidief longembolie bedroeg de incidentie 0.08 per 1000 inwoners per jaar. De incidentie van was hoger bij mannen dan vrouwen en de meerderheid van de recidieven treden op binnen 2 jaar na de vorige episode. Maligniteit was de meest frequent aanwezige risicofactor.

Hoofdstuk 7 beschrijft de evaluatie van het diagnostisch proces bij patiënten met verdenking recidief longembolie, hierbij gebruikmakend van de Wells klinische beslisregel, D-dimeer test en CTPA. Bij 17% van de 516 geïncludeerde patiënten met een verdenking recidief longembolie was sprake van een lage klinische verdenking in combinatie met een lage D-dimeer waarde en kon een recidief longembolie veilig uitgesloten worden zonder optreden van recidief trombose gedurende 3 maand follow-up. CTPA sloot een longembolie uit bij 253 patiënten, echter zeven van deze patiënten presenteerden zich binnen 3 maanden met een recidief trombose (2.8%; 95% CI 1.2-5.5%), waarvan één fataal (0.4%; 95% CI 0.02-1.9%). Geconcludeerd werd dat dit onderzoek aantoont dat het gebruikte algoritme effectief is bij patiënten met een verdenking op een recidief acute longembolie. Gegeven het lage risico op een fatale longembolie gedurende de follow-up en het hoge a priori risico in deze patiëntengroep het sluit veilig een longembolie uit.

DEEL III. UITKOMST BIJ ACUTE LONGEMBOLIE

Het stratificeren van patiënten met een bewezen longembolie die wel hemodynamisch stabiel zijn in een groep met een hoge en een groep met een lagere kans op complicaties kan van belang zijn voor het maken van keuzes bij de behandeling. In **hoofdstuk 8** wordt een meta-analyse beschreven waarin we de rol van (NT-pro-)BNP hebben geëvalueerd voor het maken van een risicoschatting voor klinische uitkomsten bij patiënten met bewezen een longembolie. Deze studie laat een onderscheidend vermogen zien met een verhoogd risico bij verhoogde (NT-pro)BNP waarden voor complicaties tijdens de ziekenhuisopname (odds ratio 6.8, 95% BI 4.4-10) en mortaliteit binnen 30 dagen na de diagnose (odds ratio 7.6, 95% BI 3.4-17) en het is een indicator voor rechter ventrikel

disfunctie bij patiënten met een acute longembolie. Of een hoge (NT-pro) BNP waarde op zichzelf aanleiding kan zijn om meer of minder intensieve behandeling te starten zal nog moeten worden aangetoond. In **Hoofdstuk 9** werden patiënten met een bewezen acute longembolie en een lage verdenking op complicaties volgens vooraf vastgestelde criteria thuis behandeld met de standaard behandeling met antistolling. In totaal werden 297 patiënten, 51% van de gescreende patiënten, thuis behandeld. Gedurende een 3 maanden follow-up ontwikkelden 6 patiënten een recidief VTE (2,0%; 95%-BI: 0,8-4,3%); 1 patiënt een DVT en vijf patiënten een longembolie. In totaal zijn tijdens de follow-up drie patiënten overleden, geen van dezen als gevolg van een longembolie; één patiënt door een intracraniële bloeding en twee anderen als gevolg van progressie van een maligniteit. Naast de patiënt met de intracraniële bloeding ontwikkelde één andere patiënt een ernstige bloeding (totaal 0,7%; 95%-BI: 0,1-2,4%). Concluderend lijkt thuisbehandeling met antistolling van patiënten met een acute longembolie, geselecteerd volgens de vastgestelde criteria, effectief en veilig te zijn.

TOEKOMSTPERSPECTIEF

Het doel van het diagnostisch proces bij een verdenking longembolie is een gestandaardiseerd, accuraat en eenvoudige strategie die eenvoudig bij de grote meerderheid van de patiënten met een verdenking longembolie toegepast kan worden. Met de huidige diagnostiek bestaande uit beslisregels, D-dimeer testen en beeldvorming met de CTPA als eerste keus, hebben we een goed gevalideerde veilige en efficiënte strategie voor patiënten die zich presenteren met een verdenking longembolie. Er zijn echter nog steeds uitdagingen om deze strategie verder te optimaliseren. In de praktijk wordt nog niet optimaal en correct gebruik gemaakt van klinische beslisregels, dit kan verbeterd worden door het implementeren van de eerder beschreven gesimplificeerde beslisregels in de klinische praktijk. Tevens kan verdere optimalisatie plaatsvinden in verschillende subgroepen. Onderzoek kan zich hierbij richten op oudere patiënten waarbij de D-dimeer waarde minder accuraat wordt met het stijgen van de leeftijd, bij patiënten met verminderde nierfunctie is het beperken van het contrastmiddel wenselijk, en bij vrouwen in de fertiele leeftijd is vermindering van de stralingbelasting door de CT-scans reden voor verder onderzoek. Tot slot zijn data schaars voor diagnostiek bij vrouwen tijdens de zwangerschap, met risico van straling voor de foetus. Gespecificeerde algoritmes of afkapwaarden kunnen helpen bij een betere voorspelling van de kans op een longembolie voor een individu, implementatie in de dagelijkse praktijk is echter moeilijker bij gebruik van verschillende afkapwaarden bij verschillende subgroepen. Met behulp van elektronische ondersteuning is hierbij verbetering mogelijk van op een individu gebaseerde risicostratificatie en management.

Met verdere ontwikkeling van de CTPA met hogere resoluties zullen meer kleinere embolieën gedetecteerd worden. Er zal verder onderzoek gedaan moeten worden naar de klinische relevantie hiervan, deze is vooralsnog onduidelijk. Mogelijk dat andere beeldvormende technieken als de MRI scan een alternatief gaan vormen voor de CTPA scan, de MRI scan is nu nog onvoldoende van kwaliteit voor implementatie in de klinische praktijk.

Volgende de huidige richtlijnen dient een patiënt met een bewezen longembolie opgenomen te worden, thuisbehandeling lijkt nu echter een reële mogelijkheid voor een groep goed geselecteerde patiënten. Er is verder – gerandomiseerd - onderzoek nodig om dit te optimaliseren, hierbij moet ook de toegevoegde waarde van markers als NT-proBNP of de pulmonary embolism severity index (PESI) moet worden geëvalueerd, met als doel om zo optimaal, eenduidig en op een simpele manier patiënten met laag risico op complicaties te selecteren.

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Mos ICM, Tan M, van der Meer F, Klinkenberg M, Huisman MV. Incidentie recidief VTE - The incidence of recurrent venous thromboembolism in a defined population. Submitted

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Mos ICM, Tan M, Klok FA, Kroft LJM, de Roos A, Oudkerk M, Kamphuisen PW, Huisman MV. Beeldvormende technieken bij diagnostiek van Diepe Veneuze Trombose en Longembolie. Submitted

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NAWOORD

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CURRICULUM VITAE

Inge Christina Maria Mos werd geboren op 31 augustus 1982 te Zoetermeer. In juni 2000 behaalde zij haar VWO diploma aan het Staring College te Lochem. In afwachting van inloting voor de studie geneeskunde studeerde zij een jaar gezondheidswetenschappen aan de Universiteit Maastricht. Na een jaar kon de overstap naar de studie geneeskunde worden gemaakt aan dezelfde universiteit. De eerste ervaringen met onderzoek werden opgedaan tijdens de wetenschapsstage op de afdeling Interne Geneeskunde en Biochemie onder leiding van prof. dr. H. ten Cate. In oktober 2007 behaalde zij haar artsexamen. Naar haar artsexamen maakte ze de overstap naar Leiden waar ze tot en met december 2010 werkzaam was als arts-onderzoeker op de afdeling Algemene Interne Geneeskunde en Endocrinologie van het Leids Universitair Medisch Centrum. Tijdens deze periode werd het in dit proefschrift beschreven onderzoek uitgevoerd onder begeleiding van dr. M.V. Huisman. In januari 2011 is ze begonnen met de opleiding tot internist in het Medisch Centrum Haaglanden te 's-Gravenhage (opleiders dr. P.H.L.M. Geelhoed Duijvestijn en dr. A.H. Bootsma).