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The diagnostic management of suspected pulmonary embolism

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The Diagnostic Management of Suspected Pulmonary Embolism

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Step into this room and dance
hoose, loose
Pull out your arsenal
And Dance
This is the floor, these are the rules, these are the moves
This is the room in which we dance
Close the floor, say you will

Dance

Madrugada, "The Nightly Disease"

Aan mijn moeder

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A pulmonary embolism (PE) comprises a sudden lodgement of a blood clot in a pulmonary artery with subsequent obstruction of blood supply to the lung parenchyma. Depending on the size and length of the embolic mass, it may occlude the main pulmonary artery, impact astride the bifurcation (a saddle embolus) or pass out into the progressively smaller branching pulmonary arteries. These pulmonary blood clots arise for more than 95% from thrombi within the large deep veins of the lower legs (popliteal, femoral or iliac veins). Hence, deep vein thrombosis (DVT) and PE are regarded as different expressions of a single clinical entity called venous thrombo-embolism (VTE).
The first description of PE is attributed to Laennec in 1819 but in 1846, Virchow, a well known pathologist, was the first to recognize that blood clots in the pulmonary artery originate as venous thrombi[1]. He stated: "The detachment of larger or smaller fragments from the end of the softening thrombus which are carried along by the current of blood and driven into remote vessels. This gives rise to the very frequent process on which I have bestowed the name of Embolia". The term "pulmonary emboli" was born.

Pulmonary embolism is a potentially fatal disease of which early recognition and institution of anticoagulant treatment can prevent mortality. Due to the diversity and aspecificity of signs and symptoms of pulmonary embolism, varying from asymptomatic pulmonary embolism to haemodynamic instability and shock, clinical recognition is notoriously inaccurate. Post-mortem studies have shown that the majority of cases of pulmonary embolism detected were not diagnosed prior to deatz[2]. Therefore, to demonstrate or refute the diagnosis, objective diagnostic tests are mandatory in patients with a clinical suspicion of PE.

It has only been since forty years that a diagnosis of PE can be objectively diagnosed and physicians need not rely solely on their clinical judgement of the presence or absence of PE. In 1963, Williams and Sasahara published a landmark study of pulmonary angiography as a diagnostic tool in diagnosing PE[3;4]. The armamentarium has been expanded with the introduction of perfusion scintigraphy in 1964 and ventilation scintigraphy in 1968[5;6]. The major concerns leading to a continued search for better diagnostic tools were the invasiveness and consequently complications of pulmonary angiography as well as the high percentage (40-60%) of non-conclusive ventilation perfusion (VQ) scans.

A promising diagnostic tool, of which the first clinical report appeared in 1992, is helical computed tomography (CT)[7]. This method provides a series of images of the thorax in the transverse plane enabling to view all intra-thoracic structures. In order to visualize the pulmonary arteries, it requires intravenous injection of iodinated contrast agent via an antecubital vein during scanning. Helical CT has clear advantages, i.e. direct visualisation of thrombus as an intra-luminal filling defect, the possibility of making an alternative diagnosis, a rapid scanning time (less than 30 seconds), wide availability and excellent inter-observer agreement[8;9]. The percentage of inconclusive CT scans is low, but radiation exposure is higher compared to ventilation-perfusion scintigraphy. Moreover, allergic reactions to contrast agents occur in a small percentage of patients as well as contrast medium-induced nephropathy[10].

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General introduction



Basilica di San Petronio, Bologna, Italia

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A diagnostic algorithm based on helical CT has gained widespread interest due to the common availability of helical CT. These algorithms have however often been implemented without appropriate assessment in clinical practice[11].

Another step forward was the development of clinical prediction rules and D-dimer tests in the nineties. They're advantageous because of the possibility of limiting the requirement for objective diagnostic tests such as ventilation-perfusion scintigraphy or helical CT. Clinical prediction rules categorize patients with a clinical suspicion of pulmonary embolism into a low, intermediate and high pre-test probability of pulmonary embolism. Although implicit clinical assessment empirically has been shown to be reasonably accurate, the advantage of a clinical prediction rule is the rapid bedside stratification of likelihood of PE by a more standardized approach.
D-dimers are degradation products of cross-linked fibrin that are released when a thrombus is degraded by fibrinolysis. D-dimer tests are rapid and widely available tests with high sensitivity and negative predictive value (97-100%). However, D-dimer tests are not specific (specificity of approximately 35 - 45%) due to enhanced fibrinolysis in several other conditions (malignancy, infection, high age, postoperative state, pregnancy).
Several studies have demonstrated that it is safe to exclude pulmonary embolism in patients with a low pre-test probability of pulmonary embolism combined with a normal D-dimer test[12-14]. Using such an approach, more invasive radiological imaging tests are obviated in 15-47% of patients suspected of PE.
An overview of the diagnostic tools available to diagnose or exclude pulmonary embolism in patients with clinically suspected PE is given in Chapter 2.

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Aims of the studies and outline of the thesis

Several questions remain regarding the clinical utility of the combination of a clinical prediction rule and D-dimer as well as regarding helical CT. A retrospective analysis suggested that the clinical utility of the Wells score could be further increased by using two, instead of three categories of clinical probability, dichotomising patients either into 'unlikely' or 'likely' to have pulmonary embolism. However, no large, prospective studies have been carried out to evaluate this dichotomization. Furthermore, it is currently unknown whether the diagnosis of pulmonary embolism can be excluded, and anticoagulant treatment withheld, on the basis of a negative helical CT alone, without performing additional tests.

Our **first aim** was to investigate whether patients with a clinical suspicion of PE could be safely left untreated on the basis of a clinical decision rule indicating 'PE unlikely' combined with a normal D-dimer test. Our **second aim** was to evaluate whether helical CT could be used as a sole test to exclude PE in patients with a clinical suspicion of PE with either a clinical decision rule indicating 'PE likely' or an abnormal D-dimer test in patients indicated as 'PE unlikely'. To answer these questions, the Christopher-study was designed, a prospective management-study performed in 12 hospitals in the Netherlands between November 2002 and September 2004. It evaluated a diagnostic algorithm of sequential application of clinical decision rule, D-dimer tests and helical CT. The results of the Christopher-study are described in Chapter 3.

Due to the non-specificity of clinical signs and symptoms of PE, only 20-30% of patients with clinically suspected PE do have the disease. Ideally, a simple non-invasive test without radiation exposure and with low costs excludes a diagnosis of PE in the 70-80% of patients with a clinical suspicion of PE who do not have the disease. Excluding PE by non-invasive tests has been simplified by the introduction of the Wells clinical decision rules and quantitative D-dimer assays. These tests use fixed cut-off levels, i.e. a score of 4 to categorize patients into 'PE unlikely' or 'PE likely' and a cut-off level of 500 ng/ml to categorize a D-dimer test as 'normal' or 'abnormal'. Our **third aim** was to analyse whether the cut-off levels of the clinical decision rule as well as the D-dimer test could be varied to increase the clinical utility in excluding pulmonary embolism (Chapter 4).

The safety of excluding PE on the basis of a normal helical CT has been the subject of debate over the past years since the accuracy of CT has been reported to be only 70%. The reason for the low accuracy is believed to be the limited reliability of detecting small emboli in subsegmental arteries. The advent of multi-row detector CT (MDCT) is thought to increase the detection rate at the subsegmental artery level. In the Christopher-study, we used single (SDCT)- as well as multi-row detector systems and therefore, our **fourth aim** was to analyse whether the prevalence of subsegmental PE differed between the two CT systems (Chapter 5).

Patients diagnosed with PE are treated with oral anticoagulants for a period of at least three months. Despite treatment, some patients experience a recurrent thrombo-embolic

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event, while others experience side effects from treatment, i.e. major or minor bleeding events. Our **fifth aim** was to evaluate within the Christopher-study the natural course of hemodynamically stable patients diagnosed with PE and to assess the incidences of recurrent venous thrombo-embolism, bleeding and mortality. Our **sixth aim** was to identify risk factors for these events as well as the time course of these events (Chapter 6).

In many diagnostic studies of pulmonary embolism, patients with a clinical suspicion of PE are eligible, without discriminating patients with or without a prior history of PE. No study has reported on the safety of withholding anticoagulant therapy on the basis of normal diagnostic tests in patients with a clinical suspicion of recurrent PE. The consequences of misdiagnosis of recurrent PE are major. Incorrectly concluding that recurrent PE is present exposes the patient to prolonged - and often life-long- anticoagulation with its attendant costs, inconvenience, and bleeding risks. Incorrectly concluding that recurrent PE is absent puts the patient at high risk of ongoing PE, which may be fatal. Our **seventh aim** was to analyse the safety of the diagnostic algorithm used in the Christopher-study to exclude clinically suspected recurrent PE in patients with a history of PE (Chapter 7).

Patients diagnosed with a first episode of pulmonary embolism are usually treated for six months with anticoagulant therapy. It is unknown whether all pulmonary clots have resolved by the end of treatment. Our **eighth aim** was to review the literature to establish evidence concerning rate of resolution of pulmonary clots six months after diagnosis of PE (Chapter 8).

Pregnancy is a common exclusion criterion for studies on diagnostic tests in patients with a suspicion of PE. It is generally thought that helical CT exposes the fetus to more radiation exposure than VQ scintigraphy. Our **nineth aim** was to investigate whether fetal radiation exposure is indeed higher in helical CT compared to VQ scintigraphy (Chapter 9). Moreover, our **tenth aim** was to scrutiny the literature in order to evaluate the evidence concerning performance of diagnostic tests in pregnancy for a clinical suspicion of DVT and PE (Chapter 10).

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Diagnostic methods in pulmonary embolism

M. Nijkeuter, M.V. Huisman

European Journal of Internal Medicine 2005; 16: 247- 256



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Abstract

Diagnosing pulmonary embolism is challenging since clinical signs and symptoms are non-specific. The diagnostic tests available for demonstrating pulmonary embolism all have their drawbacks and are often costly and consume considerable amounts of resources. Simple tools that have become available in the last several years include clinical prediction rules and D-dimer testing. Assessment of the clinical probability, combined with a D-dimer test can limit the need for additional diagnostic tests by 30%. For outpatients with a normal, sensitive ELISA D- dimer test and a low to moderate clinical probability, PE can safely be ruled out. Pulmonary angiography, though still the gold standard, is rarely used nowadays because of its invasiveness, its high costs and limited availability, and the declining experience of radiologists with the technique. Two imaging techniques, i.e. lung scintigraphy and helical CT are the diagnostic methods of choice. A normal perfusion lung scan can safely exclude PE. However, 55-65 % of patients have indeterminate lung scan results, making additional imaging tests necessary. Helical CT is increasingly being used as the first-line test because it can directly visualise a thrombo-embolus, it can suggest an alternative diagnosis, and there is excellent inter-observer agreement. A normal helical CT, followed by compression ultrasonography of the leg veins, can safely rule out PE. Finally, the safety of withholding anticoagulant treatment from patients with a normal multi-row detector helical CT as the sole test has not yet been demonstrated.

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Introduction

Diagnosing pulmonary embolism (PE) is challenging. Because a wide spectrum of symptoms is possible, the clinical diagnosis is non-specific. There is a clinical suspicion of PE in 1-2 per 1000 inhabitants but in only 20-30% of patients the diagnosis can be confirmed[1;2]. Because pulmonary emboli are potentially fatal, a proper diagnosis is essential and sensitive diagnostic testing is, therefore, mandatory. If PE is diagnosed, anticoagulant therapy should be started although this is associated with a chance of serious bleeding complications. It has been estimated that 3-4% of patients face major bleeding during heparin therapy[3;4]. In observational studies, the use of warfarin with an INR 2.0-3.0 has been associated with an annual incidence of major bleeding ranging from 5 to 9%[5]. In a recent randomised trial, an annual incidence of major bleeding of 3.8% was observed in patients receiving full dose warfarin therapy, despite careful on-site monitoring[6]. It has been estimated that less than 5% of patients will present with massive PE with circulatory instability. In this situation, echocardiography is generally the most appropriate and fast approach and treatment will consist of intravenous thrombolytic therapy[7]. The diagnostic tests available for demonstrating pulmonary embolism in hemodynamically stable patients all have their drawbacks and are often costly and consume considerable resources. The aim of this article is to give an overview of the diagnostic tools used in patients with a clinical suspicion of non-massive PE.

Clinical diagnosis

A clinical suspicion of PE is raised when a patient complains of acute dyspnea without an apparent cause. Other symptoms are acute (pleuritic) chest pain worsening with breathing and less frequently cough, hemoptysis or fainting. "Classic" signs of PE on physical examination are tachycardia, pleuritic rub, an accentuated pulmonic component of the second heart sound and neck vein distention. However, all these symptoms and signs are non-specific and inconsistently found in patients with PE, necessitating further diagnostic work-up[8].

Measuring arterial blood gases to demonstrate hypoxaemia is of little diagnostic use in PE. Blood gases are normal in 15% of patients with proven PE[9]. Classic abnormalities found on an electrocardiogram include sinus tachycardia, an S wave in lead I, a Q wave and an inverted T wave in lead III and T-wave inversion in leads V1 to V4 indicating right ventricular strain. These signs are, however, also non-specific for PE. A chest X-ray is only useful in demonstrating an alternative diagnosis (pneumonia, pneumothorax, heart failure) to explain the patient's complaints. Signs found on chest x-ray in patients with PE that are suggestive, but not specific, include focal oligemia (Westermarks's sign), a peripheral wedged-shaped density above the diaphragm indicating lung infarction (Hampton's hump) or an enlarged right descending pulmonary artery (Palla's sign).

Clinical prediction rule

The assessment of pre-test probability of PE allows categorization of patients suspected of PE in low, intermediate and high clinical probability corresponding to a prevalence of PE

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of 10% (low clinical probability), 30-40% (intermediate probability) and 70-80% (high clinical probability)[10]. Assessment of the clinical probability, combined with a D-dimer test, can limit the need for additional diagnostic tests by 30%[2]. Until recently, grouping patients into low, intermediate and high clinical probability of PE had been done with implicit assessment empirically. An implicit assessment of clinical probability was used in seven studies. In the low, moderate and high pre-test categories, the rates of PE ranged from 8-19%, 26 to 47% and 46 to 91%, respectively (Table 1)[11].

Table 1

Accuracy of Pretest Probability Assessment for PE using implicit diagnosis

Source	No.	%PE	Category	Est.Prob	No	Act.Prob%
PIOPED (1)	887	28	Low	0-19	228	9
			Interm	20-79	569	30
			High	80-100	90	68
Miniati et al. (73)	783	44	Unlikely	10	349	8
			Possible	50	179	47
			Very likely	90	225	91
Perrier et al. (13,14) (74)	985	27	Low	≤20	368	9
			Moderate	21-79	523	33
			High	≥80	94	66
Sanson et al. (18)	413	31	Low	0-19	58	19
			Moderate	20-80	278	29
			High	>80	77	46
Musset et al. (57)	1041	34	Low	0-19	231	12
			Moderate	20-79	525	26
			High	80-100	285	68

Est.Prob=Estimated probability, Act.Prob=Actual probability

Although implicit evaluation yield a reasonably good accuracy, this way of categorizing patients is subject to inter-observer variability[12;13;14]. A more standardized approach to scoring clinical probability is the Wells' score[15]. This prediction rule was derived from a cohort of 1260 in- and outpatients with suspected PE. Of 40 variables assessed as potential predictors, only 7 were found to be independently associated with the presence of PE (Table 2). Points for the clinical prediction rule were assigned by doubling the value of the regression coefficients and rounding to the nearest 0.5. Subsequently, cut-off points were created to classify patients into low, moderate and high probability of PE with corresponding rates of PE of 3%, 28% and 78%, respectively[15]. In the validation study, the corresponding rates of PE were 2%, 18.8% and 50% respectively[15].

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Table 2

Simplified Wells score

Condition	Points
Cancer	1
Hemoptysis	1
Heart rate > 100/min	1.5
Previous PE or DVT	1.5
Recent surgery or immobilization	1.5
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3

Clinical probability: low 0-1, intermediate 2-6, high ≥ 7 points
PE unlikely: 0-4, PE likely >4

In addition, a cut-off score was determined to be designated 'PE unlikely' such that a negative D-dimer in these patients would result in a rate of PE close to 2%. A score of ≤4 or less in combination with a negative D-dimer resulted in a rate of PE of 1.7% (95%CI: 0.2-6.0%)[15].

Another prediction rule, the Geneva score, was developed from a database of 1090 consecutive patients admitted to the emergency ward with suspected PE[16]. Logistic regression identified 7 variables independently associated with PE (Table 3). Patients with a low clinical probability (score 0-4) had a prevalence of PE of 10%, while those with an intermediate probability (score 5-8) had a prevalence of 38% and patients with a high probability (score ≥ 9) had a prevalence of PE of 81%[16].

Table 3

The Geneva Score

Condition	Points
Previous PE or DVT	2
Heart rate > 100/min	1
Recent surgery	3
Age, y	
60-79	1
≥ 80	2
PaCO2*	
< 4.8 kPa	2
4.8-5.19 kPa	1
PaO2*	
< 6.5 kPa	4
6.5-7.99 kPa	3
8-9.49 kPa	2
9.5-10.99 kPa	1
Atelectasis	1
Elevated hemidiaphragm	1

Clinical probability: low 0-4, intermediate 5-8, high ≥9, * by room air

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In general, accuracy studies of the Wells and Geneva scores have confirmed their validity with 1.3 to 13%, 16 to 40% and 38 to 91% of the low, intermediate and high pretest probability groups, respectively, having pulmonary embolism (Table 4)[12;15-19]. Only one study had results that were in disagreement with these findings[18]. In that study, there was no clear discrimination between the low, moderate and high probabilities of PE[18].
The simplified Wells score is suited for out- and inpatients. An important drawback of this score is the highly subjective judgement of the item 'alternative diagnosis less likely than PE'. The Geneva score is completely objective but it requires analysis of arterial blood gas by room air, which may not always be possible for patients with severe hypoxia.

Table 4
Accuracy of pretest probability assessement of PE using Wells and Geneva rules

Source	No.	%PE	Category	Act.Prob%
Wells et al. (17)[a]	1239	17.5	Low	3
			Moderate	28
			High	78
Sanson et al. (18)°	414	29	Low	28
			Intermed	30
			High	38
Wells et al. (15)°	252	17.6	Low	2
			Moderate	18.8
			High	66.7
Wicki et al. (16)*	986	27	Low	10
			Moderate	38
			High	81
Wells et al. (24)°	930	9.5	Low	1.3
			Intermed	16.2
			High	37.5
Chagnon et al. (12)°	277	26	Low	12
			Moderate	40
			High	91
Chagnon et al. (12)*	277	26	Low	13
			Moderate	38
			High	67

[a] Wells Extended Score, ° Simplified Wells score, *Geneva Score

Wells et al studied inter-observer variability for the pretest probability using the initial extended score but not in the simplified score. The coefficient Kappa was excellent (K=0.86)[17]. Chagnon et al. did not document inter-observer agreement for the Geneva score or for the simplified Wells score, but reported that 83 patients (30%) were classified differently by the two scores (K=0.43)[12]. Extreme disagreement, defined as patients classified as low clinical probability by one score and high probability by the other, occurred in only 2 of 277 patients. Leclerq et al. studied the observer variability in the assessment of clinical probability for patients with suspected PE[20]. Using the simplified Wells score, duplicate assessment in the categories unlikely/likely PE, resulted in a different category in 6 of 45

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patients (K=0.66) mainly due to the subjective item "alternative diagnosis less likely than PE". It is concluded that reproducibility of clinical probability is moderate but comparable to the disagreement of clinicians in daily medical practice over patients' histories, physical examination and diagnostic tests, including X-rays and ECG. Clinicians should be aware of this when using a clinical prediction rule.

D-dimer tests

D-dimers are degradation products of cross-linked fibrin released when a thrombus is degraded by fibrinolysis. For patients with acute venous thrombo-embolism, levels of D-dimers are typically increased up to eightfold. The sensitivity of D-dimer for detecting venous thromboembolism is reported to be 97 to 100% at a cut-off value of 500 ng/ml[21;22]. However, D-dimer tests have a low specificity of approximately 35 to 45% since they are also produced in various other conditions, including malignancy, inflammation and infection[23]. D-dimer tests are therefore only useful in ruling out thrombosis. Because the negative predictive value lowers with increasing likelihood of PE, it is generally recommended to use D-dimer tests in combination with a priori assessed clinical decision rule and never be used as a sole diagnostic test in patients with pulmonary embolism. For patients with a high clinical probability of PE, the negative predictive value of D-dimer is too low to safely rule out PE (88.5%, 95%CI: 69.9–97.6) and additional testing is required[13;19].

It has been reported that the use of D-dimer testing in combination with a clinical prediction rule can obviate the need for objective imaging tests by 15-47% (Table 5)[19;24].

Measurement of D-dimer has become feasible with the development of monoclonal antibodies that bind to epitopes on D-dimer fragments. The resulting complexes are detected by enzyme-linked immunosorbent assay (ELISA) or agglutination techniques. The classic microplate ELISA-technique is considered the gold standard but this test is not suitable for quick diagnosis. There are quicker tests that combine the ELISA method with a final fluorescence (VIDAS test, result within 35 minutes(22;25)) or that make use of the immunofiltration (membrane ELISA) technique (Instant IA D-dimer, Nycocard D-dimer, test result within 2-8 minutes[26;27]). These have the highest sensitivity and negative predictive value (98-100%)[22;28]. These ELISA D-dimer tests can safely exclude thromboembolism but they do so at the expense of a relatively low diagnostic utility. Other techniques involve agglutination of latex beads or red blood cells and provide a semi-quantitative or qualitative result within a few minutes (Simpli-RED). More recently, immunoturbidimetric techniques have been developed that allow a quantitative estimation (TinaQuant, Liatest, MDA D-dimer). SimpliRed, a D-dimer test with relatively low sensitivity and high specificity is diagnostically useful in a great proportion of patients but should be combined with a low clinical probability in order to safely rule out PE[29]. Finally, disadvantages of the visual reading may lead to inter-observer variability(30).

Van der Graaf et al. compared 13 D-dimer methods in 99 outpatients suspected of deep venous thrombosis[31]. Venography was used as a reference standard and revealed DVT in 50.5% of patients. Of the novel quantitative D-dimer assays, VIDAS and Tinaquant

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appeared the most sensitive (sensitivity 100%, specificity 40%). De Monye et al. compared the diagnostic accuracy of these same two rapid quantitative D-dimers (Tinaquant and VIDAS) for patients with suspected PE and validated the test results using a combination of objective reference tests[30]. Using the manufacturer's advised cutoff values, the sensitivity and specificity were 88% and 52% for VIDAS and 82% and 61% for Tinaquant, respectively. When the sensitivities of these assays were set at 95% in order to safely replace perfusion scintigraphy as an initial test, the corresponding specificities then dropped to 24% for Tinaquant and 29% for VIDAS. Another study also evaluated two D-dimer tests (VIDAS and SimplyRED) to exclude PE and validated the results using pulmonary angiography[32]. VIDAS D-dimer showed a sensitivity of 97% (95%CI: 83-100%) and a specificity of 26% (95%CI: 18-36%) at a cut-off value of 500 ng/ml and a prevalence of PE of 25%. SimplyRED showed a sensitivity of 73% (95%CI: 55-87%) and a specificity of 76% (68-85%).

Three studies have used a normal result on the D-dimer test alone to exclude PE. In the first study, of 444 outpatients suspected of PE, 159 (36%) had a normal result on a rapid ELISA D-dimer test (VIDAS) and none of these patients had a venous thromboembolic event in the three-month follow-up[13]. The prevalence of PE in this study was 23%. Another study showed that of 141 outpatients, 67 (47.5%) had normal results on a rapid ELISA D-dimer test (Vidas), of whom 42 patients had suspected PE. No false-negative D-dimer level was found at three months follow-up[33]. The prevalence of VTE in this study was however only 10%. A recent management-study excluded PE by a normal D-dimer result (VIDAS) in 268 of 965 patients (29%) and none experienced a thromboembolic event during 3 months of follow-up (failure rate 0%, 95%CI:0-1.4%)[2]. The prevalence of PE in this study was 23%. From these studies it can be concluded that ruling out PE in outpatients with a rapid and sensitive ELISA d-dimer test seems safe (failure rate 0%, 95%CI:0-1.8%).

Four studies have combined normal D-dimer results with a low clinical probability of PE(Table 5). Wells et al. demonstrated a negative predictive value of 99.5% (1 VTE of 437 patients, 95%CI: 99.1-100%) with the SimplyRED D-dimer test[19]. Ten Wolde et al. excluded PE by a low clinical probability and a normal D-dimer result (Tinaquant) in 95 of 631 patients (15%) and none had a thromboembolic event during three months of follow-up (failure rate 0%, 95%CI:0-3.8%)[34]. Another study showed also a failure rate of 0% in patients with a low clinical probability and normal D-dimer results(95%CI: 0-6%)[35]. A fourth study excluded PE in 306 of 653 patients (47%) and 1 patient developed non-fatal PE during follow-up (failure rate 0.3%, 95%CI: 0-1.8%) with the prevalence of PE being 17%[36].

Table 5
Studies combining low clinical probability with normal D-dimer for exclusion of PE

Author	D-dimer assay	%PE	n	Failure rate
Wells et al.(19)	SimplyRED	9.5%	437/930 (47%)	0.5% (0-0.9)
Ten Wolde et al.(34)	Tinaquant	20%	95/631 (15%)	0 (0-3.8%)
Kruip et al.(35)	VIDAS	22%	60/234 (26%)	0 (0-6%)
Anderson et al.(36)	Agglutination assay	17%	306/653 (47%)	0.3% (0-1.8%)

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Only one study combined normal D-dimer levels with a low to moderate clinical probability of PE and no thromboembolic event was observed during follow up of 64 patients (failure rate 0%, 95%CI: 0-5.6%)[37].

One disadvantage of the D-dimer test is the lower sensitivity when complaints are present for more than 10 days, while specificity is compromised in certain patient groups, i.e. elderly patients, or patients with infections, malignancy, sepsis, pregnancy or those in the postoperative state[38]. D-dimer tests should therefore be used by clinicians who are aware of the different test characteristics of the various D-dimer assays available. Moreover, knowledge of performance of d-dimer assays in different subgroups of patients is essential and should be applied to patients on an individual case-to-case basis.

Compression ultrasonography

The prevalence of (a)symptomatic deep vein thrombosis in patients with suspected and objectively proven PE differs in the literature varying in a meta-analysis from 18% (95%CI: 15-20%) in suspected PE to 36-45% in proven PE[39]. Demonstrating a deep vein thrombosis by compression ultrasonography of the legs justifies treatment with anticoagulants in a patient with a clinical suspicion of PE. However, the sensitivity of compression ultrasonography for patients without clinical symptoms of a DVT is only 23 % (95%CI: 19-26)[40]. Moreover, when pulmonary embolism is not objectively diagnosed at a first episode, the diagnosis may become problematic when a patient returns with clinically suspected recurrent PE.

Compression ultrasonography may be used for patients with suspected PE: 1) when they also have clinically suspected DVT; 2) in order to reduce the number of lung scans by demonstrating a DVT in patients with no symptoms of DVT and 3) after objective diagnostic testing (helical CT or lung scan) prove inconclusive.

Pulmonary angiography

The traditional gold standard for diagnosing PE is contrast pulmonary angiography. However, this diagnostic test is rarely used nowadays because of its invasiveness, its high costs and limited availability, and the declining experience of radiologists with the technique. Because pulmonary angiography is the reference method, no formal evaluation of sensitivity or specificity can take place. The clinical validity of a normal pulmonary angiography has been studied and revealed a thromboembolic risk of 1.6% (95%CI: 0.3-2.9) with most events occurring in the first month[41]. Pulmonary angiography should still be available when other imaging tests are inconclusive.

Ventilation/ perfusion lung scintigraphy

Perfusion scintigraphy is a non-invasive indirect method of visualising pulmonary perfusion by intravenous albumin aggregates labelled with technetium 99 m. Pulmonary hypoperfusion is not highly specific for PE since any disease that narrows the airways or fills the alveoli with fluid will result in hypoxic pulmonary vasoconstriction. A perfusion defect corresponding to a segment is more specific for PE. The main purpose of ventilation

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scanning, as an adjunct to perfusion lung scintigraphy in acute PE, is to allow for the classification of segmental perfusion defects as mismatched (perfusion defect with normal ventilation), which is generally accepted as proof for the presence of pulmonary embolism. Before scintigraphy, a chest X-ray needs to be performed to rule out abnormalities, since these disturb the interpretation of perfusion defects. Further, there is evidence suggesting that the ventilation scan may be validly replaced by chest X- ray with an overall agreement of 88% and a positive predictive value of 86% for a scintigraphic mismatch[42].

Lung scintigraphy is one of the methods of choice since anticoagulant therapy can be safely withheld from patients with a normal perfusion scan (VTE incidence 0% in 6 months, 95%CI: 0-3.2%)[43]. The positive predictive value of a high-probability VQ scan is approximately 90% and most physicians consider such a test result sufficient to rule in PE. One disadvantage of perfusion scintigraphy is that in most patients (55-65%) the diagnosis of PE cannot be confirmed or ruled out due to indeterminate lung scan results and additional imaging tests need to be performed[1]. Two large studies have attempted to combine clinical probability to lung scanning to increase the diagnostic yield. In 175 patients with suspected PE who were not treated on ground of a low empiric clinical probability and a non-diagnostic lung scan, provided that ultrasonography did not show a proximal DVT, the 3-month thromboembolic risk was 1,7% (95%CI: 0.4-4.9%)[44]. However, this combination was found in only 21% of patients. In another study, anticoagulant treatment was withheld from 665 of 1239 (54%) patients who had a non-diagnostic scan, a low or intermediate clinical probability of PE and normal serial CUS and the 3-month thromboembolic risk was only 0.5% (95%CI: 0.1-1.3%)[17].

Table 6
Early studies evaluating helical CT for a suspicion of PE

	Year	Patients(n)	PE(%)	Sensitivity(%)	Specificity(%)
Remy-Jardin(48)	1992	42	45	95	96
Teigen(49)	1995	60	39	65	97
Goodman(50)	1995	20	55	64	89
Remy-Jardin(51)	1996	75	57	91	78
van Rossum(52)	1996	249	17	95	97
Mayo(53)	1997	139	33	89	98
Garg(54)	1998	24	25	67	100
Weighted average		609	31	86(81-91)	96(93-97)

Helical CT

Helical CT is increasingly being used as the first-line test for a clinical suspicion of pulmonary embolism (PE). Helical CT has clear advantages over perfusion scintigraphy, i.e. direct visualisation of thrombus, the possibility of providing an alternative diagnosis, cost effectiveness and excellent inter-observer agreement[45;46]. A diagnostic algorithm based on helical CT has gained widespread interest due to the availability of helical CT. These algorithms have however often been implemented without appropriate assessment in clinical practice. Early studies evaluating the accuracy of helical CT for a clinical

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suspicion of PE demonstrated a sensitivity ranging from 64 to 95% with a specificity ranging from 78 to 100%(Table 6). These studies however did not all meet the rigorous methodological criteria for defining the accuracy of a diagnostic test[47]. Two large studies have been carried out evaluating single-row helical CT versus a reference method[55;56]. The first one included 299 consecutive patients at the emergency department with a clinical suspicion of PE and an elevated D-dimer level. PE was established by using a validated algorithm that included clinical assessment, lower-limb compression ultrasonography, lung scanning and pulmonary angiography, in comparison with single-row helical CT scans. Among patients with conclusive results, sensitivity of helical CT was 70% (95%CI: 62-78%) and specificity 91% (95%CI: 86-95%)[55].

In the second study, a different algorithm was studied with all patients starting with perfusion scintigraphy[56]. All abnormal scans were followed by pulmonary angiography and single-row helical CT was performed in all patients with perfusion defects. Among the 517 patients studied, helical CT showed a sensitivity of 69% (95 CI: 63-75%) and a specificity of 84% (95% CI: 80-89%). Moreover, the sensitivity of helical CT was calculated to be 86% (95%CI: 80-92%) for detecting segmental or larger PE and only 21% (95%CI: 14-29%) for subsegmental PE. Both studies conclude that single-row helical CT should not be used as the sole diagnostic test for patients with clinically suspected PE.

To demonstrate the validity of withholding anticoagulant treatment from patients with a normal helical CT, three large outcome studies with comparable algorithms, have appeared recently in the literature[2;57;58].

In the first study, 1041 consecutive in- and outpatients with suspected PE were included and underwent helical CT and ultrasonography of the legs[57]. PE was diagnosed in 360 (34.6%) patients. Of 601 patients with negative helical CT and ultrasonography, 76 were clinically assessed as having a high probability of PE and lung scanning or pulmonary angiography followed, which showed PE in 4 (5.3%, 95%CI: 1.5-13.1). Of the 507 patients with negative helical CT and ultrasonography that were not treated, 9 experienced venous thromboembolism during the 3-month follow up period (1.8%, 95%CI: 0.8-3.3). It was concluded that anticoagulants could be safely withheld from patients with a low or intermediate probability of PE and negative findings on helical CT and compression ultrasonography.

Van Strijen et al. evaluated single-row detector helical CT as the primary diagnostic test in suspected pulmonary embolism[58]. In this prospective, clinical outcome study, 510 consecutive in- and outpatients with a clinical suspicion of PE underwent helical CT. If CT scan results were normal or inconclusive, compression ultrasonography was performed on the same day and if normal, again at days 4 and 7. Anticoagulation was only started when helical CT was positive for the presence of PE or when compression ultrasonography was positive for the presence of deep vein thrombosis. Helical CT identified PE in 125 of 510 patients (24.3%), an alternative diagnosis in 130 patients (25.3%) and CT scans were normal in 248 patients (48.6%). Compression ultrasonography revealed DVT in 2 patients, both on the initial examination. In the group with normal CT scans or with an alternative diagnosis 3 patients had a PE or DVT (0.8 %, 95 % CI 0.2-2.3 %). This study shows that single-row detector helical CT can be used safely as the primary diagnostic test for a clinical suspicion of PE.

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Finally, Perrier et al evaluated a diagnostic strategy for pulmonary embolism starting with a prediction rule combined with implicit judgement, followed by D-dimer testing, venous ultrasound and helical CT[2]. PE was considered ruled out either by a normal D-dimer test or in patients with a negative ultrasound and CT scan and a low to intermediate clinical probability. All 7 thromboembolic events occurred in the 406 patients with a low-to-intermediate clinical probability of PE, a negative ultrasound and a negative helical CT scan, yielding a 3-month thromboembolic risk of 1.7% (95%CI: 0.8-3.5%) It can be concluded that in patients with elevated D-dimer levels, a strategy based on a clinical prediction rule and ultrasound combined with helical CT appears safe and effective.

As is summarised in Table 7, the recurrence rate of VTE in negative helical CT varies considerably. This is largely due to differences in design of the studies, patient selection and follow up. Taking into account the three largest and best designed studies, it can be concluded that recurrence of VTE is 0.8-1.8% in an algorithm using helical CT combined with ultrasonography.

Table 7
Outcome studies in validating helical CT

Author	Year	N	Recurrence
Ferretti(59)	1997	164	5.4%
Garg(60)	1999	126	1.3%
Lomis(61)	1999	143	0%
Goodman(62)	2000	198	1.0%
Ost(63)	2001	103	4.2%
Gottsater(64)	2001	305	1.4%
Musset(57)	2002	525	1.8% (0.8-3.3)
van Strijen(58)	2003	512	0.8% (0.8-3.5)
Perrier(2)	2004	450	1.7% (0.8-3.5)

An issue often debated is the limitation of helical CT to accurately detect small peripheral emboli. Results of early studies in which single-row detector CT was compared with selective pulmonary angiography demonstrated the high accuracy of CT for detection of PE to the segmental arterial level but suggested that subsegmental pulmonary emboli may be overlooked on CT scans. Sensitivity of single-row detector CT for detecting subsegmental PE in a large accuracy study was only 21% (95%CI: 14-29%) compared to 86% (95%CI: 80-92%) for segmental or larger PE[56]. CT technology is rapidly developing and has, in recent years, brought the advent of multi-row detector CT allowing coverage of the entire chest with 1-mm or submillimeter resolution within a short single breath-hold. Use of multi-row detector CT significantly improves pulmonary arterial visualization in the middle and peripheral lung zones and increases the detection rate of subsegmental emboli[65;66]. However, no clinical outcome studies have evaluated multi-row detector helical CT in diagnosing PE.

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Another problem relating to the detection rate of small peripheral emboli, is the unknown relevance of these small clots that might have gone unnoticed in the past. The percentage of these small peripheral emboli in subsegmental arteries has been reported to range from 6% to 30%[1;67]. It is not yet known whether treatment of these small emboli results in a better clinical outcome for the patient. From the three outcome-studies discussed above, in which patients with a normal single-row detector helical CT and normal repeated ultrasonography did not receive anticoagulation, it may indirectly be concluded that small emboli that cannot be detected by CT do not need anticoagulant treatment in patients in stable cardiopulmonary condition at presentation, in view of the low thromboembolic rate at 3-month follow-up (0.8- 1.8 %, 95 % CI 0.2-2.3 %). A large, clinical outcome study involving more than 3000 patients is currently under way in the Netherlands. In this study, called Christopher study, consecutive patients with clinically suspected PE are being diagnosed in 12 participating hospitals, according to an algorithm involving clinical decision rule and D-dimer to exclude PE and multi-row helical CT to assess the presence of PE in patients with a high clinical probability or an abnormal D-dimertest. The primary endpoint is the occurrence of VTE during 3-month follow up after normal initial tests. Results of this study are expected in 2005.

Magnetic Resonance Angiography (MRA)

MRA is a new, rapidly evolving technique with the advantage of noninvasiveness, non-ionizing radiation requirement, the use of safer (gadolinium) or no contrast agent and the versatile sequences employed to assess various tissues in the chest. The first study to compare MRA with pulmonary angiography obtained a sensitivity of 70% and a specificity of 100% in a group of 23 patients with PE[68]. A pioneering study investigated the performance of a coronal gadolinium-enhanced three-dimensional time-of-flight sequence during a single-breath hold in 30 patients with suspected PE[69]. Eight patients had PE demonstrated by angiography. In 10% of patients the images were of insufficient quality and the sensitivity and specificity in the remaining patients varied between 75% and 100%, and 95% and 100% respectively[69]. Another study in 36 consecutive patients with intermediate- or low-probability lung scan results and a high clinical suspicion, MRA was compared to pulmonary angiography[70]. A total of 19 emboli were demonstrated in 13 patients by angiography and MRA diagnosed 12 patients as PE (one false positive, specificity of 96%) and missed two cases (sensitivity of 85%). Both missed PE's were isolated and subsegmental. A more recent methodologically sound study compared contrast-enhanced pulmonary three-dimensional MRA with pulmonary angiography in 141 consecutive patients with an abnormal perfusion scintigraphy[71]. MRA was contraindicated in 13 patients (9%) and not interpretable in 8 patients (6%). The prevalence of PE was 30%. MRA demonstrated 27 of 35 patients with confirmed emboli for an overall sensitivity of 77%. The sensitivities for isolated subsegmental, segmental, and central/lobar PE were 40%, 84%, and 100% respectively. MRA demonstrated emboli in 2 patients with normal angiogram for a specificity of 98%.

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Several techniques of magnetic resonance imaging that can be applied to venous thromboembolic disease are rapidly evolving, i.e. MR angiography (non-gadolinium-enhanced or gadolinium-enhanced 3D MRA), MR direct thrombus imaging, MR perfusion imaging and MR perfusion-ventilation imaging. A promising fairly simple technique is direct thrombus imaging that uses methemoglobin, a clot product, as an endogenous contrast. It has the advantage of potentially being able to differentiate between old and new clots[72]. However, additional prospective studies evaluating both accuracy and feasibility of the various MRA techniques are required before MRA can be introduced as a routine procedure for the diagnosis of PE. The limited availability of MRA remains problematic in most hospitals.

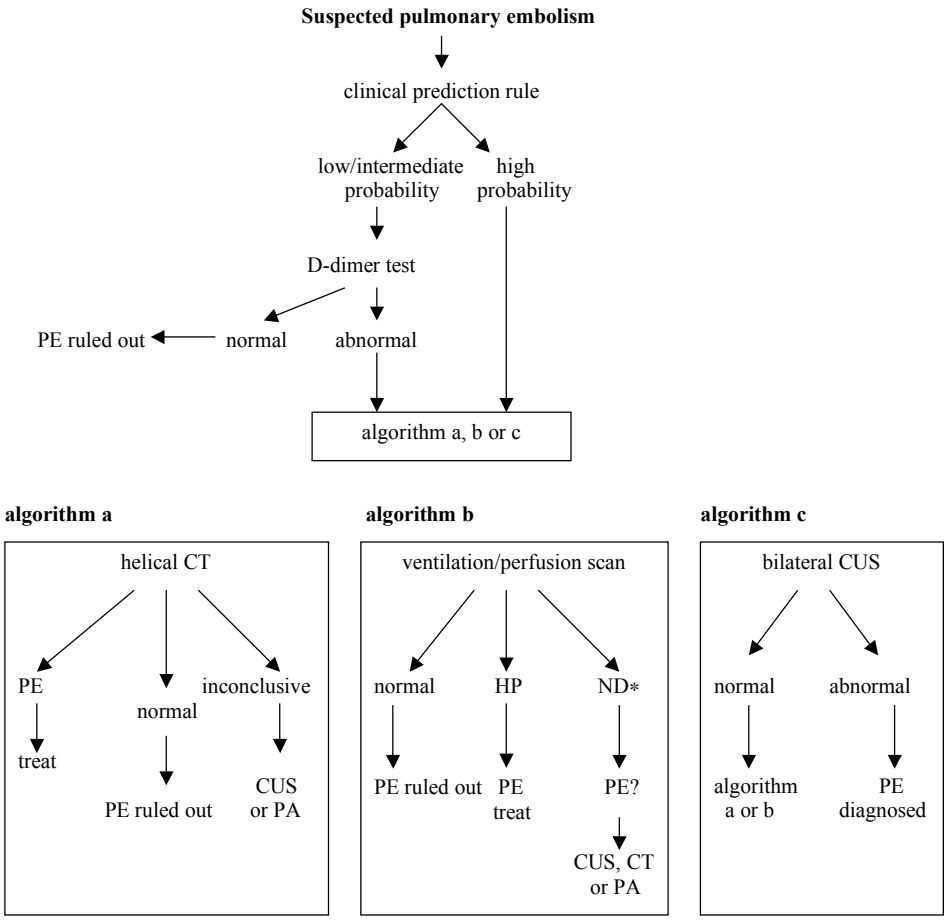
Practical advises for diagnostic approach

In patients with clinically suspected PE, the diagnostic algorithm could start with assessing pre-test probability according to one of the two established rules. When there is a low or intermediate probability, D-dimer testing should follow. PE can be excluded when clinical probability is low/intermediate and quantitative D-dimer testing is normal. In case of a high clinical probability of PE or an abnormal D-dimer result, several algorithms (Figure 1) are optional in ruling out PE, depending on the logistics of the hospital.

Compression ultrasound can be performed and when positive, treatment with anticoagulants is started. When compression ultrasound is negative, either helical CT or lung scanning should be performed. In case of an abnormal chest X-ray, helical CT is to be preferred since the likelihood of an indeterminate lung scan is high. If helical CT shows an intravascular filling defect, PE is diagnosed and treatment with anticoagulants is started. If helical CT is negative, PE can be considered ruled out and anticoagulants are withheld. In case of a normal chest X-ray, lung scanning can be performed. If the result is a normal scan, PE can be considered ruled out. In case of a high-probability scan, PE is considered ruled in and anticoagulants are started. When an inconclusive result is obtained, further diagnostic testing with either helical CT or pulmonary angiography should be performed.

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Figure 1
An approach to patients with clinically suspected pulmonary embolism



PE: pulmonary embolism; CT: computed tomography; PA: pulmonary angiography; HP high probability; CUS: compression ultrasonography
* ND=non-diagnostic result. Non-diagnostic results are those that indicate an intermediate or low-probability of pulmonary embolism, or that do not indicate a high probability.

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Effectiveness of Managing Suspected Pulmonary Embolism using an Algorithm combining Clinical Probability, D-dimer Testing and Computed Tomography

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Abstract

Context
Previous studies have evaluated the safety of relatively complex combinations of clinical decision rules and diagnostic tests in patients with suspected pulmonary embolism.

Objective
To assess the clinical effectiveness of a simplified algorithm using a dichotomised clinical decision rule, D-dimer testing and computed tomography (CT) in patients with suspected pulmonary embolism.

Design, setting and patients
Prospective cohort study of consecutive patients with clinically suspected acute pulmonary embolism, conducted in 12 centres in The Netherlands from November 2002 through December 2004. The study population of 3306 patients included 82% outpatients and 57% women.

Interventions
Patients were categorized as "pulmonary embolism unlikely" or "pulmonary embolism likely" using a dichotomised version of the Wells clinical decision rule. Patients classified as unlikely had D-dimer testing and pulmonary embolism was considered excluded if the D-dimer test result was normal. All other patients underwent CT, and pulmonary embolism was considered present or excluded based on the results. Anticoagulants were withheld from patients classified as excluded and all patients were followed up for three months.

Main outcome measure
Symptomatic or fatal venous thromboembolism (VTE) during the 3-month follow-up.

Results
Pulmonary embolism was classified as unlikely in 2206 patients (66.7%). The combination of pulmonary embolism unlikely and a normal D-dimer test occurred in 1057 patients (32.0%), of whom 1028 were not treated with anticoagulants; subsequent non-fatal VTE occurred in 5 patients (0.5 % [95% confidence interval {CI}, 0.2-1.1%]). Computed tomography showed pulmonary embolism in 674 patients (20.4%). Computed tomography excluded pulmonary embolism in 1505 patients of whom 1436 patients were not treated with anticoagulants; in these patients the 3-month incidence of VTE was 1.3 % (95% CI: 0.7-2.0%). Pulmonary embolism was considered a possible cause of death in 7 patients after a negative CT scan (0.5%; 95% CI: 0.2-1.0%). The algorithm was completed and allowed a management decision in 97.9 % of patients.

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Conclusion
A diagnostic management strategy using a simple clinical decision rule, D-dimer testing and CT is effective in the evaluation and management of patients with clinically suspected pulmonary embolism. Its use is associated with low risk for subsequent fatal and non-fatal VTE.

Introduction

The main challenge in the diagnostic work up of patients with clinically suspected pulmonary embolism (PE) is to accurately and rapidly distinguish the approximately 25 percent of patients who have the disease and require anticoagulant treatment from the 75 percent who do not [1;2]. A number of new approaches have improved the diagnostic process for pulmonary embolism. The first is the combination of a clinical decision rule, such as the Wells score[3], which categorizes patients as low, intermediate or high clinical probability of PE, with a D-dimer test. Several management studies have shown that pulmonary embolism can be safely ruled out without the need for additional imaging in patients with low clinical probability and a normal D-dimer test result, occurring in 20 to 40% of patients[3-5]. In these studies 3 categories of likelihood were used. However, a retrospective analysis suggested that the clinical utility of the Wells score could be further increased by using 2 instead of 3 categories of clinical probability, dichotomizing patients as either likely or unlikely to have had a pulmonary embolism, but no large prospective studies evaluating this dichotomization have been carried out[3].
Another advancement is computed tomography (CT), which has emerged as a prominent imaging technique for the exclusion or confirmation of PE, as well as the detection of alternative diagnoses [6-10]. However, a critical missing piece of information has been whether it is safe to withhold anticoagulation treatment after a CT that is negative for pulmonary embolism[11;12]. In a recent study[13], recurrent venous thromboembolism (VTE) occurred in 1.7 % of patients who initially had a low or intermediate probability for pulmonary embolism using the Geneva score[14], abnormal D-dimer test, normal bilateral compression ultrasound (CUS) of the leg veins and a normal multidetector-row CT. In that study, all patients with high probability for pulmonary embolism had to undergo pulmonary angiography after normal CT and normal CUS. A more efficient strategy would consist of an algorithm with a dichotomized decision rule, D-dimer testing and CT, in which pulmonary embolism is considered excluded in patients with an unlikely clinical probability score and a normal D-dimer test result, while CT is used in all other patients as the sole imaging method to make management decisions. Therefore, we performed a prospective study in a large cohort of consecutive patients with clinically suspected PE to evaluate the effectiveness of this novel management strategy.

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Methods

Study design

The Christopher Study was a prospective cohort study evaluating a diagnostic algorithm consisting of sequential application of a clinical decision rule, D-dimer testing and CT within 24 hours of presentation (Figure). All patients were followed up for a period of 3 months after presentation to document the occurrence of subsequent symptomatic VTE.

Patients

Consecutive patients with clinically suspected pulmonary embolism, defined as a sudden onset of dyspnea, sudden deterioration of existing dyspnea, or sudden onset of pleuritic chest pain without another apparent cause, were potentially eligible for the study. Patients presenting to the emergency ward (outpatients) and inpatients were eligible. Patients presenting to an outpatient office were directly sent to the emergency department for evaluation. Patients were recruited between November 2002 and September 2004.

Exclusion criteria were treatment with therapeutic doses of unfractionated or low-molecular-weight-heparin for more than 24 hours, life expectancy less than 3 months, pregnancy, geographic inaccessibility precluding follow-up, age younger than 18 years, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance less than 30 ml/min [<0.5 mL/s]), logistic reasons (eg, unavailability of CT, patient too ill to undergo CT scanning), or hemodynamic instability. Five academic and 7 general urban hospitals in the Netherlands participated. The Institutional Review Boards of all participating hospitals approved the study protocol and written or oral informed consent was obtained from all participants.

Clinical decision rule and D-dimer assay

Patients with clinically suspected PE were evaluated by an attending physician using a validated clinical decision rule (Table 1)[3]. Pulmonary embolism was classified as "unlikely" with a clinical decision rule score of 4 or less points, and "likely" with a score of more than 4 points. This cut-off was chosen because it has been shown to give an acceptable VTE diagnostic failure rate of 1.7 to 2.2% in combination with a normal D-dimer test result[3]. An estimated 300 attending physicians in the participating hospitals used the clinical decision rule with the study participants.

In patients with a clinical decision rule indicating pulmonary embolism unlikely, a D-dimer concentration was measured, using either the VIDAS D-Dimer assay (Biomerieux, Marcy L'Etoile, France) or the Tinaquant assay (Roche Diagnostica, Mannheim, Germany). A D-dimer concentration of 500 ng/ml or less was defined as normal. In patients with pulmonary embolism unlikely and a normal D-dimer test result, the diagnosis of pulmonary embolism was considered excluded and anticoagulant treatment was withheld. Those patients who had a combination of clinical decision rule indicating pulmonary embolism with an abnormal D-dimer test result or who had a clinical decision rule indicating pulmonary embolism likely, underwent CT.

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Table 1

Clinical decision rule according to Wells et al. [3]

	points
Clinical signs and symptoms of deep vein thrombosis (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/minute	1.5
mmobilisation (> 3 days) or surgery in the previous 4 weeks	1.5
Previous PE or DVT	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the last 6 months or palliative)	1.0

Clinical probability of PE unlikely ≤ 4 points, clinical probability of PE likely > 4 points.

Radiological evaluation

Computed tomography was performed using either single-detector row or multi-detector row systems. Patients were examined during suspended inspiration. The single-detector row CT parameters were 3 mm slice thickness with a 2 mm reconstruction interval at 120 kV/140 mAs, 120-140 mL of non-ionic contrast material containing 350 mg of iodide per mL with an injection speed of 3.0 mL/s and an injection delay of 16 s. Multi-detector row CT parameters were 1.25 mm slice thickness with a 1.2 mm reconstruction interval at 120 kV/120 mAs, 80-100 mL of non-ionic contrast material containing 350 mg of iodide per mL with an injection speed of 4.0 mL/s and bolus-tracking in the common pulmonary artery to get optimal contrast opacification of the pulmonary arteries. The pulmonary arteries were evaluated up to and including the subsegmental vessels from the level of the aortic arch to the lowest hemidiaphragm. Pulmonary embolism was diagnosed if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least two adjacent slices. These patients received low molecular weight heparin or unfractionated heparin, followed by vitamin K antagonists, according to local practice. In patients without pulmonary embolism, the presence or absence of an alternative diagnosis was recorded and anticoagulant treatment was withheld. The CT was considered inconclusive if the images could not be interpreted because of motion artefacts due to movements of the patient or the heart or if there was insufficient contrast enhancement of the pulmonary arteries. The management of patients in whom the CT could not be performed or who had an inconclusive CT scan was left to the discretion of the attending physician.

The decision of the presence or absence of pulmonary embolism was made by trained attending radiologists, who were blinded to any specific patient clinical information. By protocol design they knew that a patient referred for CT either had a D-dimer level that was above 500 ng/ml or a clinical decision rule score that was higher than 4 points, but did not know which of these items was the reason for performing a CT-scan.

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Outcome measures

The primary outcome of the study was the incidence of symptomatic VTE events during three months follow-up, defined as fatal PE, non-fatal PE or deep vein thrombosis (DVT). An independent adjudication committee, whose members were unaware of the patient's allocation within the diagnostic algorithm, evaluated all suspected VTE events and deaths. A diagnosis of PE or DVT was made based on a priori defined and generally accepted criteria[15]. Deaths were classified as due to pulmonary embolism in case of confirmation by autopsy, in case of an objective test positive for pulmonary embolism prior to death or if pulmonary embolism could not be confidently excluded as the cause of death. Follow-up consisted of a scheduled outpatient visit or telephone interview at 3 months. Patients were additionally instructed to contact the study centre or their general practitioner immediately in the event of symptoms suggestive of DVT or pulmonary embolism. At each visit, information was obtained on complaints suggestive of VTE, including acute onset of dyspnea, acute worsening of existing dyspnea, acute onset of chest pain, unilateral leg swelling and leg pain, as well as interval initiation of anticoagulants. In case of clinically suspected DVT or PE, objective diagnostic tests were required, including CUS for suspected DVT, and ventilation-perfusion scintigraphy or CT for suspected pulmonary embolism. In case of death, information was obtained from the general practitioner, from the hospital records or from autopsy.

Statistical analysis

The 2 primary analyses were incidence of symptomatic VTE during follow-up, confirmed by objective testing, in [1] the group of patients in whom anticoagulant treatment was withheld based on a classification of pulmonary embolism unlikely by clinical decision rule and a normal D-dimer test result, and 2) the group of patients in whom anticoagulant treatment was withheld based on a CT scan that excluded pulmonary embolism. Additional analyses were performed for fatal pulmonary embolism in these groups, as well as among the patients with a normal CT scan and an alternative diagnosis on CT separately. Sample size was based on an assumption of a 1% incidence of VTE in both patient groups and a goal to keep the upper limit of the 95% confidence interval below 2.7%[5,9], which has been reported as the upper limit of the range of recurrent VTE after a normal angiogram[16]. We calculated that approximately 1000 patients would have to be included in each group, using a 2-sided type I error of 0.05, and a type II error of 0.20. Since we expected that approximately 30% of patients would have a classification of pulmonary embolism unlikely by clinical decision rule and a normal D-dimer test result[5], a total study population of 3300 patients was needed.

Exact 95% confidence intervals (CI) were calculated around the observed incidences using StatXact software, version 5 (Sytel Software corp, Cambridge, Mass). Descriptive parameters were calculated using SPSS software, version 11.5 (SPSS, Inc., Chicago, Ill). For statistical differences, the Fisher exact test was used; statistical significance was set at $P<0.05$.

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Results

Study patients

A total of 3503 consecutive patients with clinically suspected pulmonary embolism were screened, of whom 184 (5.3%) were excluded because of predefined exclusion criteria: more than 24 hours of low molecular weight heparin (n=50), life expectancy less than 3 months (n=47), pregnancy (n=26), geographic inaccessibility precluding follow up (n=20), renal insufficiency (n=26), logistic reasons (n=10), age younger than 18 years (n=4), and allergy to intravenous contrast agents (n=1). In addition, 13 patients refused consent (Figure). The final study population of 3306 participants included 2701 (81.7 %) outpatients and 605 (18.3 %) inpatients; the baseline demographic and clinical characteristics of the 3306 study patients are shown in Table 2.

Table 2
Baseline demographic and clinical characteristics of the 3306 study patients

Characteristic	Value
Age in years, mean (SD+)	53.0 (18.4)
Female sex, n (%)	1897 (57.3)
Outpatients, n (%)	2701 (81.7)
Duration of complaints in days, median (IQR^)	2 (1-5)
Paralysis, n (%)	91 (2.8)
Immobilisation or recent surgery, n (%)	610 (18.4)
Previous VTE, n (%)	480 (14.5)
COPD with treatment, n (%)	341 (10.3)
Heart failure with treatment, n (%)	243 (7.3)
Malignancy, n (%)	476 (14.4)
Oestrogen use, n (%)*	438 (23.1)
Clinical symptoms of DVT, n (%)	190 (5.7)
Heart rate (beats per minute >100), n (%)	867 (26.2)
Hemoptysis, n (%)	176 (5.3)

+SD= standard deviation, ^IQR= interquartile range, *of females only

Results of diagnostic algorithm

Of the 3306 included patients, 2206 (66.7 %) had a clinical decision rule indicating PE unlikely and were tested for D-dimer concentrations (Figure). The prevalence of pulmonary embolism in these patients was 12.1% (266/2206; 95 % CI: 10.7-13.5%) versus 37.1% (408/1100 patients; 95%CI: 34.2-40.0 %)) in those with a clinical decision rule indicating PE likely (p<0.001). Among the 1149 patients classified as unlikely but with an abnormal D-dimer test result, the prevalence of pulmonary embolism was 23.2% (266/1149). D-dimer test results were normal in 1057 (32.0%) patients and in these patients pulmonary embolism was considered excluded. Of the 2206 patients undergoing D-dimer testing, 968 (44 %) had a VIDAS D-dimer test performed; 1238 patients (56 %) a Tinaquant D-dimer test.

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Of the 2249 patients with either abnormal D-dimer concentrations (n= 1149) or a clinical decision rule indicating pulmonary embolism likely (n=1100), 2199 underwent CT. In the other 50 patients a CT was indicated but not performed because of lack of venous access, extreme obesity, DVT confirmed by CUS prior to CT, or a deteriorating clinical condition prior to CT. Multidetector-row CT was performed in 1939 patients and single-detector-row CT in 260 patients. Computed tomography excluded pulmonary embolism in 1505 (45.5% of the total study population). In these patients, 702 had additional diagnostic information visualized on CT: pneumonia (n=212), pleural effusion (n=163), malignancy (n=50) and other diagnoses (n=277). Pulmonary embolism was confirmed in 674 patients (20.4 % of the study population). Computed tomography was inconclusive in 20 patients (0.9%). Hence, the diagnostic algorithm could be completed according to the protocol in 3256 patients (98.5 %) and allowed a management decision in 3236 patients (97.9 %).

Patients with pulmonary embolism unlikely and normal D-dimer test result

Of the 1057 patients with the combination of a clinical decision rule indicating pulmonary embolism unlikely and normal D-dimer test result, 29 patients (2.7 %) were treated with oral anticoagulants during follow-up for various reasons other than VTE. Three of the 1028 remaining patients returned with symptomatic VTE events (2 non-fatal PE, 1 DVT) during the 3-month follow-up. In 25 patients the protocol was violated and a CT or a ventilation-perfusion scan was performed while not indicated. Pulmonary embolism was diagnosed in 2 of these 25 patients. Therefore, the incidence of VTE was 5 of 1028 (0.5 %; 95% CI: 0.2 to 1.1%) (Table 3). Two patients were lost to follow-up (0.2%). In a 'worst case' scenario, in which these two patients would have developed VTE, the incidence of VTE would have been 7 of 1028 (0.7 %; 95% CI: 0.3 to 1.4 %). There were no fatal pulmonary embolisms. Eight (0.8 %) of the 1057 patients died of other causes.
Of the study population, 605 were inpatients and 56 of these had a decision rule indicating pulmonary embolism unlikely and a normal D-dimer test result (9.3%). No VTE was observed at follow-up in these patients (VTE rate, 0%;95% CI: 0-6.4%). The results for inpatients and outpatients were comparable (VTE rate 0% (95% CI: 0-6.4%) versus 0.5% (95% CI: 0.2-1.2%)). The VIDAS D-dimer test had a true negative rate of 44.2 % (428/968 patients) and the Tinaquant D-dimer assay had a true-negative rate of 50.8 % (629/1238 patients) (p< 0.002). The negative predictive values for the VIDAS and Tinaquant assays were 100% (95%CI: 99.1-100%) and 99.2% (95%CI: 98.1-99.7%), respectively.

Patients with CT excluding pulmonary embolism

Of the 1505 patients in whom CT excluded pulmonary embolism, 69 (4.6%) received anticoagulants during follow-up for various reasons other than VTE. Of the 1436 patients who did not receive anticoagulant treatment, 18 experienced VTE events during the 3-month follow-up (1.3 %; 95% CI: 0.7 to 2.0%). Eleven of these had non-fatal symptomatic thromboembolic events (3 pulmonary embolism and 8 DVT). Fatal pulmonary embolism was presumed to have occurred in the other 7 patients (0.5%, 95%CI: 0.2-1.0%); it was proven by autopsy in 2 and attributed as the cause of death in 5 (Table 4). Follow-up was

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incomplete in one of the 1436 patients (0.1%). In a "worst-case" scenario in which this patient would have developed VTE, the incidence of VTE would have been 19 of 1436 (1.3%; 95% CI: 0.8 to 2.1%).

Rates of VTE during follow-up were comparable for inpatients and outpatients (VTE rate 1.4%(95 % CI 0.4 to 3.1 %) versus 1.2% (0.7-2.1%), respectively). Among the patients who did not receive anticoagulants, similar incidences of VTE were observed in those with a normal CT (9/764; 1.2% [95 % CI: 0.5 to 2.2%]) and those with additional diagnostic information on CT (9/672; 1.3% [95 % CI: 0.6 to 2.5%]) (Table 3). Similar incidences of VTE were observed in untreated patients who underwent multi-detector row CT (14/1266; 1.1 % [95% CI: 0.6 to 1.9%]) and single-detector-row CT (4/170; 2.4 % [95% CI: 0.6 to 5.9%]).

Twenty patients returned with symptoms of pulmonary embolism during follow-up. Computed tomography was again used as the diagnostic method in 13 of these 20 patients and was normal in all. No VTE was demonstrated at later follow-up. The overall mortality rate in patients in whom CT excluded pulmonary embolism was 8.6% (129 patients).

Table 3
Venous thromboembolic events during 3-month follow-up in untreated patients

	n	Total VTE n (%; 95% CI)	Fatal PE n (%; 95% CI)
PE unlikely and normal D-dimer	1028	5 (0.5 %; 0.2 to 1.1 %)	0 (0 %; 0.0 to 0.3%)
PE excluded by CT	1436	18 (1.3 %; 0.7 to 2.0%)	7 (0.5 %; 0.2 to 1.0%)
• CT normal	764	9 (1.2%; 0.5 to 2.2%)	3 (0.4 %; 0.1 to 1.1%)
• CT alternative diagnosis	672	9 (1.3 %; 0.6 to 2.5%)	4 (0.6 %; 0.1 to 1.5%)

VTE: Venous Thromboembolic Events

Patients with CT that was inconclusive or not performed

Of the 20 patients with an inconclusive CT, pulmonary embolism was demonstrated by ventilation-perfusion lung scan in 2 patients and they received anticoagulant treatment. During follow-up 1 of the 18 remaining patients had a non-fatal VTE event. Of the 50 patients in whom CT was indicated but not performed, 3 had pulmonary embolism demonstrated by ventilation-perfusion lung scan and 2 patients had DVT demonstrated by CUS; during follow-up one of the remaining 45 patients had a fatal pulmonary embolism, while DVT occurred in 1 patient. The mortality rate for inconclusive CT was 5% (1/20) and for CT not performed 14% (7/50).

Patients with pulmonary embolism confirmed by CT

Of the 674 patients in whom CT had demonstrated pulmonary embolism, 20 patients (3.0%) had a recurrent VTE despite anticoagulant treatment. This included 11 fatal pulmonary embolism, 3 non-fatal pulmonary embolism and 6 DVT. One patient was lost to follow-up. The overall mortality in this group was 7.2% (55 patients).

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Comment

This large cohort study of 3306 consecutive patients with clinically suspected pulmonary embolism demonstrates that the use of a diagnostic algorithm consisting of a dichotomized decision rule, D-dimer testing and CT can guide treatment decisions with a low risk of subsequent pulmonary embolism. No further diagnostic testing was necessary in the third of our patients who had an unlikely clinical probability score in combination with a normal D-dimer test result, with a 3-month incidence of VTE of 0.5%. Computed tomography ruled out pulmonary embolism in all other patients without using other imaging tests (3-month incidence of those with a negative CT of 1.3%). The algorithm was pragmatic in that it could be completed in 98.5% of the eligible patients and allowed a management decision in 97.9%.

Other management studies have documented the safety of a low clinical probability in combination with a normal D-dimer concentration for the exclusion of pulmonary embolism[3-5,17]. In these studies, the rate of VTE during follow-up ranged from 0% to 1.5 %. However, because the sample size was limited, upper confidence limits were as high as 6.0 % [3-5,15]. In contrast to our simple algorithm, a recent study[13] used a more complex flowchart with sequential testing including clinical probability assessment, D-dimer assay, CUS, CT, as well as pulmonary angiography, to exclude pulmonary embolism in patients with a high likelihood and negative workup. As the authors pointed out, their study was not a true outcome study, since CUS was performed in all patients with abnormal D-dimer level, and patients with abnormal CUS and normal CT scan were treated with anticoagulation. That study had a much smaller sample size (674 patients) and a higher rate of exclusion (25 % versus 5.6% in our study).

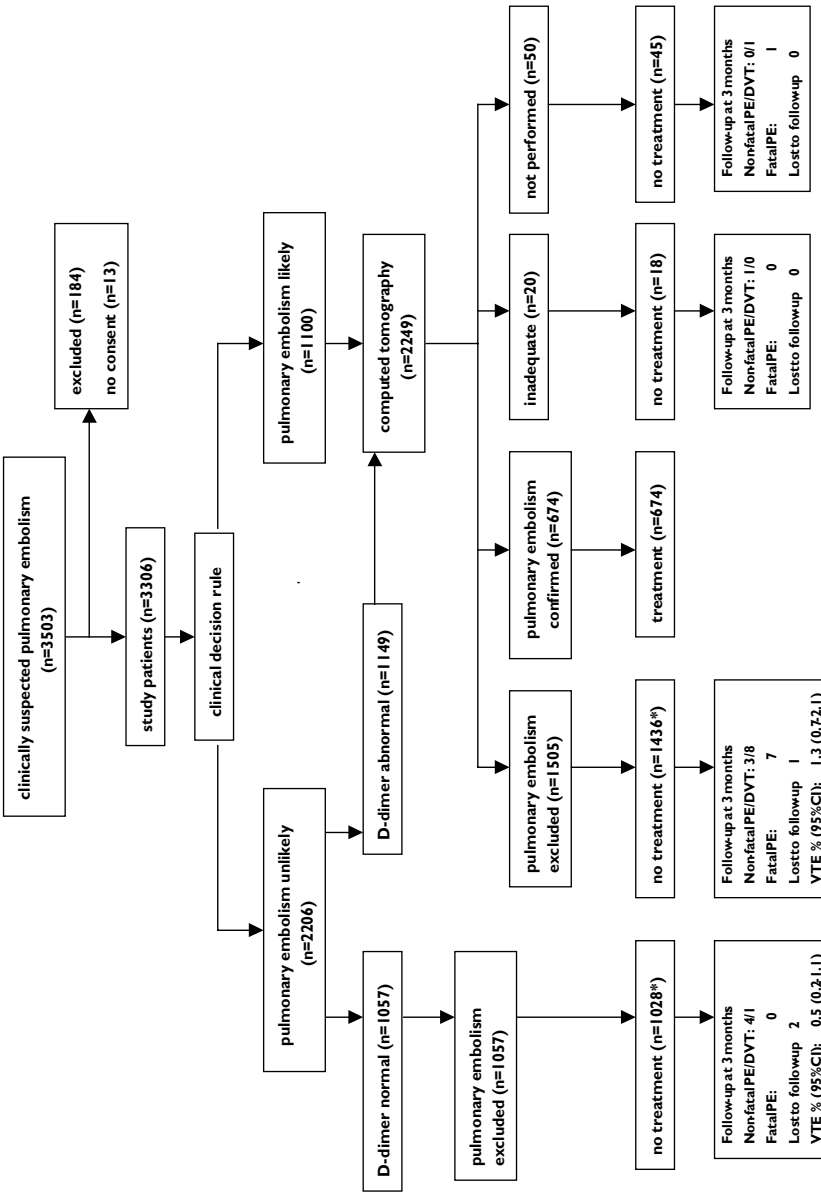
To improve the simplicity and utility of their decision rule, Wells et al. proposed changing their model from the original 3 categories (low, moderate, high) to 2 categories (pulmonary embolism unlikely and pulmonary embolism likely)[3]. Our study is the first to prospectively validate the safety of the dichotomized score in combination with the D-dimer assay. Compared with a combination using 3-category classification, this approach has the potential to increase the number of patients in whom pulmonary embolism can be excluded by approximately 50%[3,17].

Despite concerns that the sensitivity of CT for pulmonary embolism is lower than of pulmonary angiography[18;19], the observed risk of subsequent symptomatic VTE in those patients in whom pulmonary embolism was excluded by CT was comparable to the risk reported after a normal pulmonary angiogram (3-month incidence, 1.3%; 95%CI: 0.7 to 2.0% versus 1.7%; 95%CI: 1.0 to 2.7 %, respectively)[16]. In addition, in our study fatal pulmonary embolism occurred in 0.5 %(95 % CI 0.2-1.0 %) of patients in whom CT had excluded pulmonary embolism, compared with 0.3 % (95% CI 0.02-0.7 %) after normal pulmonary angiography[16]. Computed tomography has the potential advantage of providing additional diagnostic information for the presenting symptoms in patients without pulmonary embolism.

Several potential limitations in our study require comment. First, the absence of pulmonary embolism was not verified by pulmonary angiography. However, the clinical outcome

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Figure 1
Diagnostic flowchart



* without patients receiving anticoagulant therapy for other reasons than venous thrombo-embolism

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after a 3-month follow-up is widely accepted as an appropriate alternative to establish the safety of a diagnostic strategy, given a near-complete follow-up[20].

Second, while our cohort study has the strength of minimal loss to follow-up (3 patients, 0.1 %) and independent blinded adjudication of all outcomes, a randomised controlled study design would have allowed a direct comparison to other validated strategies.

Third, CT was again used to exclude pulmonary embolism in 13 of 20 patients who returned during follow-up with symptoms after CT had excluded pulmonary embolism at baseline. Although these could represent false-negative results, these patients were not treated and further follow-up was uneventful, making this unlikely.

Fourth, the use of multi-detector row CT has the potential for over-diagnosis by imaging very small peripheral subsegmental emboli. Because patients did not undergo confirmatory pulmonary angiography, our study design did not permit assessing the false-positive rate of CT scans. Only 10% of our patients underwent single-detector row CT, so we could not make a meaningful comparison of the impact of each test. However, the overall prevalence of pulmonary embolism in our study (20 %) is comparable to the prevalence in a previous multi-center study performed with single-row detector CT (24%)[9] . This does not support a concern that multi-detector row CT technology will lead to a high number of false positive results.

Finally, a definitive cause of death could not be established for all patients with normal test results who died during follow-up. However, pulmonary embolism was assigned as the cause of death if it could not be confidently excluded, a conservative assumption that strengthens our conclusions about low risk for this strategy.

The generalizibility of our findings should be considered. The baseline clinical characteristics and the incidence of pulmonary embolism for our study population are comparable with those observed in other population-based studies, except for a somewhat younger mean age[5,10,12]. The low proportion of patients excluded and the enrolment of consecutive patients who were referred to both academic and non-academic hospitals, further supports broad applicability of these results, as does the similar rates of VTE during follow-up between inpatients and outpatients.

In conclusion, a diagnostic management strategy using a simple clinical decision rule, D-dimer testing and CT is as effective as other more complex diagnostic strategies in the evaluation and management of patients with clinically suspected pulmonary embolism. Its use is associated with low risk for subsequent fatal and non-fatal VTE.

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Table 4
Deaths related to pulmonary embolism

	Sex	Age	Results of diagnostic tests	Anti-coagulant therapy	Past medical history	Time of death after inclusion (days)	Circumstances of death
1	M	60	CT normal	No	COPD Alcohol abuse	3	Sudden death at home
2	F	65	CT alternative; pulmonary metastases	No	Colon cancer, multiple metastases in liver, spleen, adrenal glands.	18	Dehydration due to chemotherapy induced diarrhoea. Morphine for pain complaints. Sudden death.
3	M	46	CT normal	No	Multiple Myeloma	40	Bedridden due to complaints of pain associated with myeloma. Sudden death at home. Autopsy: PE
4	F	69	CT alternative; interstitial pneumonia	No	Progressive dyspnoea in past half year due to interstitial pneumonia	41	CT at day 34 showed PE. Progressive respiratory insufficiency, tube-dependency, palliative care. Autopsy: PE and bilateral pneumonia
5	F	60	CT alternative; pericarditis carcinomatosa	No	COPD Breast cancer	75	Immobilization in electric wheel chair in nursing home. Gradual worsening, cardiac failure due to pericarditis.
6	F	77	CT alternative; pneumonia. At revision a sub segmental PE had been missed at inclusion.	No	Hypertension	86	Collapse at street with congested face
7	F	31	CT normal	No	2002 PE Diabetes Renal insufficiency Estrogens use	94	Antibiotics for CAPD peritonitis. Sudden death.

CAPD: Continuous Ambulatory Peritoneal Dialysis

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Excluding Pulmonary Embolism without imaging tests; can our diagnostic algorithm be optimized?

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On behalf of the Christopher Study Investigators

Submitted to J Int Med



Palazzo Cavazza, Bologna, Italia

Abstract

Rationale
Excluding pulmonary embolism by a cut-off level of the clinical decision rule of four points to designate patients as "pulmonary embolism unlikely" combined with a D-dimer concentration of 500 ng/ml or less has been demonstrated safe.

Objective
To investigate whether varying the cut-off level of the clinical decision rule as well as the D-dimer test could lead to an increase in clinical utility without jeopardizing safety.

Methods
Data were obtained from a diagnostic outcome study of patients suspected of pulmonary embolism.

Measurement
For each increment of clinical decision rule and D-dimer cut-off point, the number of patients with PE at baseline or during follow-up, the clinical utility and the 3-month thrombo-embolic failure rate were calculated

Results
By increasing the cut-off level of the clinical decision rule from 4 to 5 points, pulmonary embolism could be ruled out in an additional 4% of the study population (from 29.3 to 33.3%) at an expense of an increased three-month thrombo-embolic failure rate of 1.5% (95%CI: 0.6-3.0%). By increasing the D-dimer cut-off level from 500 to 600 ng/ml, PE could be ruled out in an additional 3% of the study population but the three-month thrombo-embolic failure rate increased to 2.2% (95%CI: 1.1-4.0).

Conclusions:
The cut-off level of the clinical decision rule as well as the cut-off level of the D-dimer test should be kept at the original 4 points and 500 ng/ml respectively, in order to prevent exposure of patients to a 3-month thrombo-embolic failure rate exceeding that of normal pulmonary angiography.

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Introduction

Pulmonary embolism (PE) is a potentially fatal disease and one of the leading causes of cardiovascular mortality. Due to the non-specificity of clinical signs and symptoms, only 20-30% of patients with clinically suspected PE do have the disease. Excluding PE by non-invasive tests has been simplified recent years by the introduction of standardized clinical decision rules (CDR) and quantitative D-dimer assays. Several management studies have demonstrated that the combination of a low to moderate clinical probability of PE and a normal D-dimer test safely rules out PE[1-4]. With this approach, it has been demonstrated that additional imaging tests including computed tomography (CT) scan and ventilation-perfusion lung scan can be withheld in approximately 15 to 50% of patients, with a 3-month thrombo-embolic failure rate of less than 1%. Increasing the clinical utility, i.e. the proportion of patients in whom the diagnosis of PE can be safely excluded without additional imaging tests, would be desirable, provided that the safety of excluding PE with this approach is not jeopardized. The original CDR according to Wells categorized patients with clinically suspected PE into three groups, i.e. patients with a low (< 2 points), intermediate (2-6 points) and high clinical probability (>6 points) occurring in 59%, 33% and 8% of the study population respectively[5]. In comparison to patients with a low probability and normal D-dimer results, occurring in 29% of the study population, in a post-hoc analysis it was shown that PE could be confidently ruled out in an additional 20% of patients by using a dichotomized cut-off level of 4 points or less. The safety of using this cut-off level in combination with a normal quantitative D-dimer test (≤ 500 ng/ml) has recently been demonstrated in a large prospective cohort study in patients with clinically suspected PE in which the 3-month thrombo-embolic failure rate was 0.5% (95%CI: 0.2-1.1%)([6]). We retrospectively analyzed the data of this study to evaluate 1) the safety and clinical utility of increasing the cut-off level of the CDR to designate patients as "PE unlikely" while the D-dimer cut-off level remained at 500 ng/ml; and 2) the safety and clinical utility of increasing the cut-off level of the D-dimer test while the CDR cut-off remained at 4 points.

Methods

Patients

Data were obtained from a prospective cohort follow-up study performed between November 2002 and December 2004 in the Netherlands[6]. In this study the safety of excluding pulmonary embolism by a diagnostic algorithm consisting of a CDR, a quantitative D-dimer test and helical CT was evaluated. In- and outpatients with a clinical suspicion of PE were eligible for the study. Exclusion criteria were: age under 18 years, treatment with therapeutic doses of unfractionated or low-molecular weight heparin for more than 24 hours prior to inclusion, a life expectancy of less than three months, pregnancy, allergy to intravenous contrast agents, renal insufficiency (creatinin clearance less than 30 ml/min), logistic reasons, geographic inaccessibility precluding follow up or hemodynamic instability.

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For the present analysis, we used data from 5 of the 12 participating hospitals (1466 of 3306 patients), since these hospitals performed D-dimer test in all included patients, while the other 7 hospitals only performed D-dimer tests in case of a CDR score of 4 or less.

Diagnostic work-up

All patients were followed for a period of three months to document the occurrence of symptomatic venous thromboembolic events. PE was considered unlikely if the CDR was ≤ 4 points, and PE was considered likely in case of a CDR > 4 points[1;5]. Patients with a CDR indicating PE unlikely underwent D-dimer testing and when normal, the diagnosis of PE was considered excluded. In consecutive patients from five hospitals included in this analysis, D-dimer tests were performed for logistic reasons in all patients irrespective of the score on the CDR, but the results were only communicated to the treating physician in case of a CDR indicating "PE unlikely". Patients with a CDR indicating "PE unlikely" and an abnormal D-dimer test and patients with a CDR indicating "PE likely" underwent helical CT to diagnose or exclude PE. All patients in whom the diagnosis of PE was excluded were withheld from anticoagulant treatment and were followed for three months to document the occurrence of symptomatic venous thromboembolism.

The D-dimer concentration was measured using either the Vidas D-Dimer assay (Biomerieux, Marcy L'Etoile, France) or the Tinaquant assay (Roche Diagnostica, Mannheim, Germany). Three hospitals used the Vidas D-dimer and two used the Tinaquant D-dimer. A cut-off level below or equal to 500 ng/ml was defined as normal for both tests in the original study[6].

The Institutional Review Boards (IRB's) of all participating hospitals approved the study protocol and written or oral informed consent was obtained from all participants, depending on the requirements of the local IRB's.

Analysis and statistics

D-dimer increments of 100 and 500 Fibrinogen Equivalent Units (FEU) ng/ml and 1 CDR score-point were used as the varying units of analysis. The reference test for calculation of the test characteristics sensitivity and specificity was the diagnosis of PE at baseline by helical CT or the occurrence of an objectively diagnosed venous thrombo-embolic event during the three months of follow-up. For each increment of CDR and D-dimer cut-off point, the number of patients with PE at baseline or during follow-up and the associated sensitivity, specificity, negative and positive predictive values were calculated. Exact 95% confidence intervals (CI) were calculated around the observed incidences using JavaStat software (http://hometown.aol.com/johnp71/confint.html). The number needed to test (NNT) for the D-dimer to rule out one patient with PE was also calculated. The NNT is the inverse of the proportion of true-negative D-dimer test results, i.e. a normal D-dimer test in patients with a CDR indicating "PE unlikely" and no venous thrombo-embolic events in the three-month follow-up period, divided by the total number of patients that need to be tested. For example, of 100 patients suspected of PE, 50 patients are designated as "PE unlikely" and are tested for D-dimer. Of these, 30 patients have negative D-dimer tests with one patient returning in the follow-up period with a venous thrombosis. The proportion of

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true-negative tests is 29 of 50 (58%) and the NNT is 1.7 (1/0.58). The definition of clinical utility was chosen to be the number of patients that needed imaging tests, divided by the number of patients in which PE could be ruled out by a CDR indicating "PE unlikely" and a negative D-dimer test (CT/D-dimer index). In the aforementioned example, 70 patients needed imaging tests and a CDR indicating "PE unlikely" and a normal D-dimer test ruled out PE without imaging tests in 30 patients, resulting in a CT/DD index of 2.3 (70/30).
Ruling out PE by a combination of a CDR score and a negative D-dimer test was considered safe if the negative predictive value was at least 98% and if the upper confidence limit of the 3-month thrombo-embolic failure rate did not exceed 2.7%, being the upper confidence limit of the 3-month thrombo-embolic rate of a normal pulmonary angiography[7].

Results

Of 1704 eligible patients recruited in 5 hospitals, 90 were excluded because of predefined exclusion criteria or declined informed consent. Data regarding the CDR score were missing in 3 patients, D-dimer results were missing in 99 patients and 46 patients were treated with anticoagulants for reasons other than venous thrombo-embolism (VTE), resulting in a total of 1466 patients (91%) available for analysis (Table 1). The mean age was 54 years, 54% of patients were female and 76% were outpatients. The prevalence of PE was 22% (321 patients diagnosed with PE at baseline and 9 in the follow up period).

Table 1
Baseline characteristics of the study population (n=1466)

Characteristics	n (%)
Age in years	54 (19)[a]
Female sex	822 (54)
Estrogen use*	168 (20)
Immobilisation > 3 days or surgery	303 (20)
History of VTE	209 (14)
COPD	156 (10)
Heart failure	138 (9)
Malignancy	238 (16)
Outpatients	1155 (76)
PE at baseline	321 (21)

[a]mean (SD), *in females only

The prevalence of PE increased with increasing score on the CDR, ranging from 5% in patients with a score of 1 point or less, to 59% in patients with a score of more than 7 points (Figure 1). Similarly, the prevalence of PE increased with increasing concentration of D-dimer, ranging from 1% in patients with D-dimer concentrations below 300 ng/ml to more than 60% with D-dimer concentrations above 5000 ng/ml (Figure 2).

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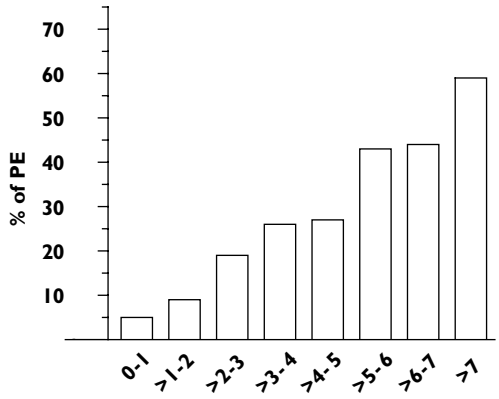


Figure 1 Prevalence of PE according to CDR score

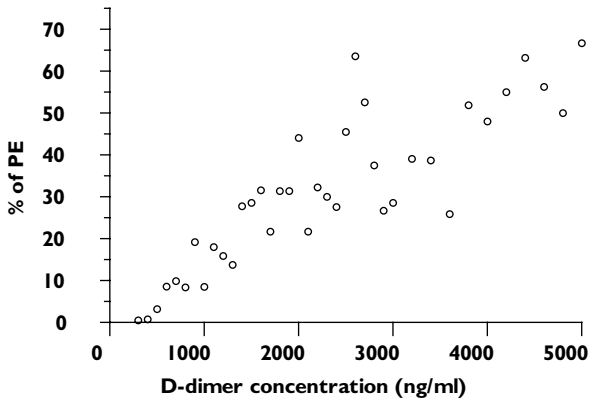


Figure 2 Prevalence of PE according to D-dimer level

Varying the cut-off level of the clinical decision rule

Table 2 demonstrates the effect of varying the cut-off level of the CDR when the D-dimer cut-off level was kept at 500 ng/ml. A total of 960 of the 1466 patients (65.5 %) had a CDR score of four points or less and were tested for D-dimer according to the original study protocol. D-dimer was normal in 430 patients (29.3% of 1466 patients), of whom four had a VTE during three months follow-up (0.9%, 95%CI: 0.3-2.4). The percentage of true-negative D-dimer tests was 44.4% (426/960) and the number of patients needed to test for D-dimer in order to rule out one patient with PE was 2.3 (1/0.444). All other patients who either had a CDR above four points or an abnormal D-dimer test (1036 patients) underwent a CT-scan to rule out PE. The CT/DD index was therefore 2.4 (1036/430). The sensitivity of a normal D-dimer and a CDR cut-off level of four points or less was 98.8% (95%CI: 96.9-99.7), the specificity 37.5% (95%CI: 34.7-40.4) and the negative predictive value was 99.1% (95%CI: 97.6-99.8)(Table 3).

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Table 2
Influence of varying CDR cut-off *

CDR score	Number of DD tests performed n (%)	D-dimer normal n (%)	3-month VTE failure rate n	% (95%CI)	% TN DD	NNT	CT/DD index
≤ 4	960 (65.5)	430 (29.3)	4	0.9 (0.3-2.4)	44.4	2.3	2.4
≤ 5	1213 (82.7)	488 (33.3)	7	1.5 (0.6-3.0)	39.7	2.5	2.0
≤ 6	1384 (94.4)	502 (34.2)	10	2.0 (1.0-3.7)	35.5	2.8	1.9
≤ 7	1416 (96.6)	502 (34.2)	10	2.0 (1.0-3.7)	34.7	2.9	1.9

*D-dimer cut-off remained 500 ng/ml; CDR: Clinical Decision Rule; CT/DD index: Computed Tomography/D-dimer index;
DD: D-dimer; NNT: Number Needed to Test for D-dimer in order to rule out one patient with PE; PE: Pulmonary Embolism;
TN: True-Negative (=normal D-dimer in patients with a CDR unlikely and no VTE in follow-up); VTE: Venous Thrombo-Embolic events

Table 3
Effect of varying CDR cut-off on test characteristics*

CDR score	Sens (95%CI)	Spec (95%CI)	NPV (95%CI)	PPV (95%CI)
≤ 4	98.8 (96.9-99.7)	37.5 (34.7-40.4)	99.1 (97.6-99.8)	31.5 (28.7-34.4)
≤ 5	97.9 (95.7-99.1)	42.3 (39.5-45.3)	98.6 (97.1-99.4)	33.0 (30.1-36.1)
≤ 6	97.0 (94.5-98.5)	43.3 (40.4-46.3)	98.0 (96.4-99.0)	33.2 (30.2-36.3)
≤ 7	97.0 (94.5-98.5)	43.3 (40.4-46.3)	98.0 (96.4-99.0)	33.2 (30.2-36.3)

*D-dimer cut-off level remained 500 ng/ml; CDR: Clinical Decision Rule, NPV: Negative Predicitve Value, PPV: Positive
Predictive Value, Sens: Sensitivity; Spec: Specificity

Increasing the CDR cut-off level from 4 to 5 points or less would have resulted in a total of 1213 patients (82.7%) designated as "PE unlikely" and would have been tested for D-dimer. D-dimer tests would have been normal in 488 patients (33.3% overall). The number of patients in whom the diagnosis of PE would have been ruled out without performing a CT scan increased from 430 at a cut-off level of 4 points or less to 488 patients at a cut-off level of 5 points or less, (58 patients, 4.0 % of the study population) at an expense of 3 additional venous thrombo-embolic events giving a three month VTE failure rate of 1.5% (95%CI: 0.6-3.0%). The proportion of true-negative test results decreased to 39.7% (481/1213) at a CDR cut-off level of 5 and the corresponding number needed to test to rule out one PE by D-dimer test increased to 2.5 (1/0.397). The CT/DD index decreased to 2.0 (978/488). The sensitivity of using a cut-off level of five points while the D-dimer cut-off remained 500 ng/ml was 97.9% (95%CI: 95.7-99.1), the specificity 42.3% (95%CI: 39.5-45.3) and the negative predictive value 98.6% (95%CI: 97.1-99.4)(Table 3).
Further increasing the cut-off level of the CDR to 6 points or less would have resulted in 14 more patients (from 488 to 502, 0.9 % of the total study population) in whom the diagnosis of PE was ruled out without performing a CT scan at an expense of 3 more thrombo-embolic events (from 7 to 10) with a 3-month thrombo-embolic rate of 2.0% (95%CI: 1.0-3.7). The number needed to test for D-dimer increased to 2.8 (1/0.355) while the CT/DD index decreased to 1.9 (964/502).

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Varying the cut-off level of the D-dimer test

Table 4 demonstrates the effect of varying the cut-off level of the D-dimer test when the CDR cut-off level remained at 4 points or less to designate patients as "PE unlikely". By increasing the cut-off level from 500 to 600 ng/ml, the diagnosis of PE could be ruled out without performing a CT scan in an additional 44 patients (from 430 to 474, 3.0% of the total study population) at an expense of 7 more venous thrombo-embolic events (from 4 to 11, 3-month VTE failure rate of 2.2% (95%CI: 1.1-4.0)). The proportion of true-negative test results increased to 48.2% (480/991) and the number needed to test for D-dimer to rule out one patient with PE decreased to 2.1 (1/0.482) while the CT/DD index decreased to 2.1(986/480).

By using the D-dimer cut-off level of 600 ng/ml, the sensitivity decreased to 96.7% (95%CI: 94.1-98.3), the specificity increased to 40.8% (95%CI: 37.9-43.7) and the negative predictive value decreased to 97.7% (95%CI: 95.9-98.8)(Table 5).

Further increasing the cut-off level of the D-dimer concentration to 700 ng/ml to rule out PE resulted in a 3-month thrombo-embolic failure rate of 3.0% (95%CI: 1.8-4.9%).

Table 4

Influence of varying D-dimer cut-off *

D-dimer cut-off	DD tests performed n (%)	D-dimer normal n (%)	3-month VTE failure rate n	% (95%CI)	% TN DD	NNT	CT/DD index
≤ 500	960 (65.5)	430 (29.3)	4	0.9 (0.3-2.4)	44.4	2.3	2.4
≤ 600	960 (65.5)	474 (32.3)	11	2.2 (1.1-4.0)	48.2	2.1	2.1
≤ 700	960 (65.5)	507 (34.6)	16	3.0 (1.8-4.9)	51.1	2.0	1.9
≤ 800	960 (65.5)	545 (37.2)	20	3.5 (2.2-5.4)	54.7	1.8	1.7
≤ 900	960 (65.5)	576 (39.3)	23	3.9 (2.5-5.7)	57.6	1.7	1.5
≤ 1000	960 (65.5)	599 (40.9)	25	4.0 (2.6-5.9)	59.8	1.7	1.4

*Clinical Decision Rule cut-off remained ≤ 4 points; CT/DD index: computed tomography/D-dimer index; DD: D-dimer; NNT: Number
Needed to Test for D-dimer; PE: Pulmonary Embolism; TN: True-Negative; VTE: Venous Thrombo-Embolic events

Table 5

Effect of varying D-dimer cut-off on test characteristics*

D-dimer cut-off	Sens (95%CI)	Spec (95%CI)	NPV (95%CI)	PPV (95%CI)
≤ 500	98.8 (96.9-99.7)	37.5 (34.7-40.4)	99.1 (97.6-99.8)	31.5 (28.7-34.4)
≤ 600	96.7 (94.1-98.3)	40.8 (37.9-43.7)	97.7 (95.9-98.8)	32.2 (29.3-35.2)
≤ 700	95.2 (92.3-97.2)	43.2 (40.3-46.2)	96.8 (94.9-98.2)	32.7 (29.8-35.8)
≤ 800	93.9 (90.8-96.3)	46.2 (43.3-49.2)	96.3 (94.4-97.7)	33.7 (30.6-36.8)
≤ 900	93.0 (89.7-95.5)	48.7 (45.7-51.6)	96.0 (94.1-97.5)	34.5 (31.4-37.7)
≤ 1000	92.4 (89.0-95.0)	50.5 (47.6-53.5)	95.8 (93.9-97.3)	35.2 (32.0-38.5)

*CDR cut-off level remained ≤ 4 points, NPV: Negative Predicitve Value, PPV: Positive Predictive Value, Sens: Sensitivity;
Spec: Specificity

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Discussion

We analysed the safety and clinical utility of varying the cut-off level of the CDR and D-dimer test in a large cohort study of patients suspected of pulmonary embolism. There are two important conclusions to be drawn from our analysis. First, our results show that increasing the cut-off level of the CDR while keeping the D-dimer test cut-of at 500 ng/ml is not safe. The three-month thrombo-embolic failure rate exceeded our predefined upper safety limit of 2.7% even when the CDR cut-off level was only raised from 4 to 5 points. Second, increasing the cut-off level of the D-dimer test had an even more profound effect on safety. By increasing the cut-off level from 500 to 600 ng/ml, the NPV dropped below 98% while the 3-month thrombo-embolic failure rate had an upper confidence limit (4.0%), which clearly exceeded our predefined upper safety limit.
Importantly, the gain of clinical utility, i.e. the proportion of patients in whom PE could be ruled out without the need for additional imaging tests, was modest. By raising the cut-off level of the CDR from 4 to 5 points, the CT/DD-index decreased from 2.4 to 2.0, reflecting only an additional 4.0% of the study population in whom PE could be ruled out. Similarly, by raising the D-dimer cut-off level from 500 to 600 ng/ml, the CT/DD-index decreased from 2.4 to 2.1 meaning that in only an additional 3.0% of the study population PE could be ruled out without imaging tests. In our view this clearly demonstrates that using the CT/DD-index instead of the NNT (number needed to test for D-dimer) is clinically more meaningful because the consequences of changing cut-off levels for the whole population of patients with suspected PE can be directly derived from this index, while the NNT only describes the proportion of negative D-dimer tests in the population tested for D-dimer.

This is the first study that investigated the effect of stepwise variation of both the cut-off level of the CDR as well as the D-dimer test. Two earlier studies have investigated the effect of varying the cut-off level of the D-dimer test in categories of pre-test probability without changing the cut-off levels to designate patients as low, intermediate or high clinical probability[8;9]. In the first study, increasing the D-dimer test cut-off level from 500 to 600 ng/ml in patients with a low pre-test probability led to a marginal gain in diagnostic yield since PE could be ruled out in an additional 2.7% of the total study population. According to our predefined safety limit, the safety was not sacrificed since the 3-month thrombo-embolic failure rate increased only from 0% (95%CI:0-0.8%) to 0.3% (95%CI: 0.01-1.4). This might be explained due to the low prevalence of PE (7%) in this subgroup with a low pre-test probability. Indeed, raising the D-dimer cut-off level from 500 to 600 ng/ml in patients with an intermediate probability (prevalence of PE 35%) in the same study led to an unacceptably high 3-month thrombo-embolic rate of 5.8% (95%CI: 1.9-13.1)[9].
The second study concluded that the use of three pre-test probability-specific D-dimer cut-off points excluded VTE in a larger proportion of patients (49.2%) than using a single cut-off point (36.4%) without sacrificing NPV (98%)[8]. However, the 3-month thrombo-

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embolic failure rate in patients with a low pre-test probability increased from 0% (upper 95% confidence limit 1.5%) to 1.5% (upper 95% confidence limit 4.2%) and the sensitivity decreased dramatically from 100 to 75%. Of note, in this study the highest D-dimer cut-off level was selected on the basis of a negative predictive value of at least 98%. The use of the NPV as a sole criterion of safety may be misleading since it is critically dependent on the prevalence of disease in the population tested. Finally, in the second study a mixed population of patients with clinically suspected PE and DVT was included.

Of note, the safety of a diagnostic approach to rule out a possible fatal PE should be weighed against the clinical utility and costs involved in performing imaging tests. In our study, the increase of the CDR cut-off by one point – from 4 to 5 points- would have led to 0.4 less CT scans that had to be performed for every single D-dimer test that ruled out PE. Extrapolating this figure to the United States, with an estimated incidence of clinically suspected PE of 380.000 cases annually (94.000 PE cases yearly[10], PE prevalence ~ 25%), approximately 120.000 CT scans (32%) are saved by using the original cut-off point of the CDR of 4 points and D-dimer cut-off level of 500 ng/ml, while an additional 15.000 CT-scans (4%) could be saved by using the higher cut-off of the CDR of 5 points[10].

Our study could be criticized for the fact that we used data of 5 of the 12 hospitals participating in a large, prospective management study of a diagnostic algorithm. We do not think this has led to selection bias, since the prevalence of PE as well as the baseline characteristics of the study patients was similar to the overall population of our original cohort[6]. Second, two different D-dimer assays were used. Since there was no statistically significant difference in failure rate between the two tests in the original study, we have taken data from these D-dimer tests together.
Strengths of our study are that we had a relatively large cohort of patients suspected of PE in which the diagnosis was ruled out or diagnosed by a simple algorithm and all outcome events were adjudicated by an independent committee.

In conclusion, our results demonstrate that the cut-off level of the CDR to designate patients as "PE unlikely" and the cut-off level of the D-dimer test to designate a test result as "normal" should be kept at the original CDR cut-off level of 4 points and D-dimer concentration of 500 ng/ml, in order to prevent exposure of patients to a 3-month thrombo-embolic failure rate exceeding that of a normal pulmonary angiography. The challenge for future studies is to provide algorithms, which can safely reduce the percentage of patients undergoing imaging tests for PE.

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5

The Incidence of Subsegmental Pulmonary Emboli in Multi-Detector Row and Single-Detector Row CT

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Abstract

Introduction

The anatomic distribution of pulmonary embolism (PE) in central, segmental and sub-segmental arteries is understudied and an often-debated issue is the possible limitation of computed tomography (CT) to accurately detect peripheral emboli. Multi-detector row CT (MDCT) is thought to increase the detection rate of sub-segmental emboli compared to single-detector row CT (SDCT). We evaluated the prevalence and anatomic distribution of PE in consecutive patients with proven PE diagnosed by MDCT or SDCT.

Methods

Data were obtained from a diagnostic outcome study of patients suspected of PE. An algorithm consisting of sequential application of a clinical decision rule, a quantitative D-dimer test and single- or multi-detector row CT diagnosed PE. The location of PE was classified into three groups (central, segmental and sub-segmental PE) with emphasis on the largest pulmonary arterial branch involved.

Results

A total of 3306 consecutive patients were included in the diagnostic study, of whom 674 (20%) were diagnosed with PE. Data regarding the localisation of PE were missing in 41 patients. Localisation of PE in MDCT was central in 160 patients (29%, 95%CI: 25-33), segmental in 293 patients (53%, 95%CI: 49-57) and sub-segmental in 98 patients (18%, 95%CI: 15-21). In patients diagnosed with SDCT, PE was central in 31 patients (38%, 95%CI: 27-49), segmental in 39 patients (48%, 95%CI: 36-59) and sub-segmental in 12 patients (15%, 95%CI: 8-24). The percentage of detected PE did not differ significantly between MDCT and SDCT (31% vs. 32%, p=0.65), neither the percentage of sub-segmental PE (18% vs. 15%, p=0.48) detected by MDCT or SDCT.

Conclusions

The percentage of detected subsegmental PE did not differ between MDCT and SDCT. There seems to be no danger of over-diagnosis of small subsegmental PE using multi-detector row systems.

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Introduction

Over the past years the role of contrast material-enhanced computed tomography (CT) in the diagnosis of pulmonary emboli (PE) at the level of segmental and central pulmonary arteries is well established; hence this method has become the first line diagnostic test for the evaluation of PE in many institutions[1-3].

The reliability of CT in the detection of smaller emboli in subsegmental arteries has been the subject of debate however[4;5]. Within the past years, multi-detector row CT (MDCT) has been introduced. The most prominent feature of MDCT is its high-speed acquisition, enabling quick coverage of large volumes, and improved spatial resolution. This should theoretically result in the visualisation of more than 90% of subsegmental arteries[6] .

Importantly, the need for diagnosing isolated subsegmental pulmonary embolism, i.e. PE limited to subsegmental arteries, is still uncertain[7]. This is reflected by the discrepancy between the overall sensitivity for PE for single-detector row CT (SDCT) and the outcome studies in which patient management was based on a normal SDCT. Thus, in two large prospective studies the sensitivity of SDCT for detecting all PE has been found to be around 70%[4;8] while the same research groups observed a low 1-2% three months thrombo-embolic risk in patients left untreated based on a single normal SDCT and normal lower limb compression ultrasound[3;9]. It has been argued that diagnosing more subsegmental PE with multi-detector row CT may therefore lead to overtreatment of small pulmonary emboli without apparent clinical need with associated risk of bleeding. Contra wise, there is also expert opinion based consensus that the presence of peripheral emboli may be an important indicator of concurrent deep vein thrombosis and thus potentially heralds more severe embolic events; this would then underscore the need to accurately diagnose subsegmental emboli[10-12]. However, the need for anticoagulant treatment in the presence of an isolated subsegmental pulmonary embolus has never been studied.

In the PIOPED study, the proportion of PE limited to the subsegmental arteries using pulmonary angiography was 6% (95%CI: 4-9%)[13]. In three other studies that used pulmonary angiography, of which one was a retrospective study[10], isolated subsegmental PE was observed in 10-36 % of patients[10;14;15]. Establishing the true prevalence of subsegmental PE is complicated by the 45-66% reported inter-observer variability for detecting emboli at the subsegmental level in pulmonary angiography[16;17]. Using single-detector row CT, the prevalence of subsegmental PE was 22% (29/130)[18] in one study. In two other studies, using multi-detector row CT, the prevalence was 7% (14/187)[2] and 15% (8/54)[19]. These data underline the uncertainty of establishing the prevalence of subsegmental PE and indicate that it is currently not established whether multi-detector row CT is more accurate in diagnosing subsegmental PE than single-detector row CT.

We analysed the distribution of central, segmental and subsegmental PE in a large cohort of consecutive patients diagnosed with PE by multi- or single-detector row CT as part of a large management study in patients presenting with clinically suspected PE[1].

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Materials and Methods

Patients

This study was part of a large management study of diagnosing PE using clinical probability, a quantitative D-dimer test and CT[1]. The study was conducted in twelve Dutch hospitals (five academic and 7 urban hospitals), from November 2002 through September 2004. Approval of the Medical Ethics Committee in all participating institutions was obtained prior to the start of the study. All consecutive in- and outpatients with clinically suspected PE were considered for inclusion. Exclusion criteria were patient age under 18 years, use of low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) more than 24 hours prior to inclusion, pregnancy, allergy to roentgen contrast, life expectancy less than three months, geographic inaccessibility precluding follow-up, renal insufficiency (creatinine clearance < 30 mL/min [0.5 mL/sec]), logistic reasons (unavailability of CT, patient too ill to undergo CT-scanning) and haemodynamic instability.

Study protocol

The study protocol is described in detail elsewhere[1]. In brief, a clinical probability score according to Wells was performed and in patients designated 'PE unlikely' (score ≤ 4 points), a normal quantitative D-dimer test (≤500 ng/ml) excluded PE. In patients designated 'PE likely' (score > 4 points) or with an abnormal D-dimer test, helical CT was performed. If CT demonstrated PE, anticoagulant therapy was initiated. Specifically, patients with PE demonstrated in subsegmental arteries were treated. If CT excluded PE, anticoagulation therapy was withheld.

CT angiography was performed using either single- or multi-detector row systems as described before[1]. The pulmonary arteries were evaluated up to and including the subsegmental vessels from the level of the aortic arch to the lowest hemi-diaphragm. PE was diagnosed if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least two adjacent slices. The decision of the presence or absence of PE was made by a trained attending radiologist. The localisation of the pulmonary embolism was locally assessed and categorised into three classes, according to the largest pulmonary vessel in which PE could be seen: central (main pulmonary stem, right or left main pulmonary artery, lobar artery), segmental or sub-segmental artery.

Statistical analysis

Exact 95% confidence intervals (CI) were calculated around the observed incidences using JavaStat software (http://statpages.org/confint.html). Descriptive parameters were calculated using the SPSS software, version 11 (SPSS, Inc., Chicago, Illinois). The univariate relation between baseline characteristics and outcome was examined by chi-square statistics for categorical variables and t-tests for continuous variables. Fisher's Exact test was used when the expected values were less than five. Non-parametric tests were used for continuous variables that were not normally distributed. A level of significance of 0.05 (two-tailed) was used in all tests.

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Table 1
Characteristics of patients undergoing Multi- versus Single-Detector Row CT

Characteristics	MDCT(%) n=1921	SDCT(%) n=258	p-value
Age – yr*	57 (28)	59 (32)	0.50
Female sex	56	61	0.2
Duration of complaints – days*	2 (6)	3 (6)	0.33
Inpatients	25	19	0.05
Risk factors for venous thromboembolism			
Paralysis, paresis or plaster cast lower limbs‡	4	2	0.1
Immobilisation/bed rest > 3 days‡	27	19	0.004
Immobilisation due to travel by car or air‡	5	4	0.35
Surgery ‡	9	6	0.21
Previous DVT or PE	17	17	0.94
Use of estrogen	11	13	0.47
Heart failure with therapy	9	8	0.65
COPD with therapy	12	13	0.50
Malignancy	19	18	0.73
Clinical findings – %			
Signs of deep vein thrombosis	8	11	0.17
Tachycardia (>100 beats per min)	33	38	0.09
PE more likely than alternative diagnosis	71	74	0.35

*median (IQR), ‡ within previous month. COPD= chronic obstructive pulmonary disease, DVT= deep vein thrombosis, MDCT= multi-detector row computed tomography, PE= pulmonary embolism, SDCT= single-detector row computed tomography

Results

A total of 3503 patients suspected of PE were screened and 184 met one of the exclusion criteria: more than 24 hours of (low molecular weight) heparin (n=50), life expectancy less than 3 months (n=47), pregnancy (n=26), geographic inaccessibility precluding follow up (n=20), and other reasons (n=41). In addition, 13 patients refused consent. A total of 3306 patients were included into the study and a clinical decision rule indicating PE unlikely combined with a normal D-dimer test excluded PE in 1057 patients (32%). The remaining 2249 had to undergo CT scanning, but in 50 patients the protocol was violated and CT was not performed, while in 20 patients CT was inconclusive. A total of 2179 patients underwent CT scanning. Multi-detector row CT was performed in 1921 patients (88%) and single-detector row CT in 258 patients (12%). The baseline characteristics of patients undergoing MDCT and SDCT are shown in Table 1. Patients were comparable in age (median 57 versus 59 years, p=0.5), sex (56% versus 61% female, p=0.2) and duration of complaints (median 2 versus 3 days, p=0.33). The percentage of

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inpatients was higher in MDCT (25%) versus SDCT (19%, p=0.005). The presence of comorbidity, i.e. heart failure, COPD or malignancy was similar in both groups. All other risk factors for thrombosis and clinical findings were equally present in patients undergoing MDCT and SDCT, except for immobilisation due to bed rest, which was significantly more prevalent in patients undergoing MDCT (27%) than in patients undergoing SDCT (19%, p=0.004).

PE was present in 31% of patients who underwent MDCT (591/1921, 95%CI: 29-33) and in 32 of patients (83/258, 95%CI: 27-38, p=0.65) who underwent SDCT. The characteristics of all patients diagnosed with PE are described in Table 2.

Table 2
Baseline characteristics of the 674 patients with PE

Characteristics	PE
Age – yr*	58 (19-100)
< 55 yr, n (%)	296 (44)
≥ 55 – 65 yr, n (%)	117 (17)
> 65 yr, n (%)	261 (39)
Female sex (%)	51
Duration of complaints – days†	2 (0-90)
Localisation of PE (highest branch)ƒ	
Central	191 (30)
Segmental	332 (52)
Subsegmental	110 (17)
Outpatients (%)	78
Risk factors for venous thromboembolism – %	
Paralysis, paresis or plaster cast lower limbs‡	6
Immobilisation/bed rest > 3 days‡	17
Immobilisation due to travel by car or air‡	7
Surgery‡	10
Previous deep vein thrombosis	9
Previous pulmonary embolism	10
Heart failure with therapy	6
COPD with therapy	9
Malignancy	19
Clinical findings – %	
Signs of deep vein thrombosis	15
Tachycardia (>100 beats per min)	37
Haemoptysis	8

*Mean (range), † median (range), ‡ within previous month, PE: Pulmonary Embolism,
ƒ missing data in 41 patients

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Localisation of PE

Data regarding the localisation of PE were missing in 41 patients (6%).

Of the remaining 633 patients, PE was central in 30% of patients (n=191), segmental in 52% of patients (n=332) and subsegmental in 17% of patients (n=110). MDCT had been performed in 551 patients with PE and SDCT in 82 patients. Localisation of PE detected by MDCT was central in 29% (160/551, 95%CI: 25-33), segmental in 53% (293/551, 95%CI: 49-57) and sub-segmental in 18% (98/551, 95%CI: 15-21) (Table 3). Lokalisation of PE detected by SDCT was central in 38% (31/82, 95%CI: 27-49), segmental in 39 patients (48%, 95%CI: 36-59) and sub-segmental in 12 patients (15%, 95%CI: 8-24).

The percentage of detected subsegmental PE did not differ between MDCT and SDCT (18% vs. 15%, p=0.48), neither did the percentage of segmental PE (53% vs 48%, p=0.34). The percentage of central PE was non significantly higher in SDCT compared to MDCT (38% vs. 29%, p=0.11).

Table 3
Multi-detector row CT versus Single-detector row CT

	MDCT		SDCT		p-value
	N	%(95%CI)	N	%(95%CI)	
Percentage of PE	591/1921	31 (29-33)	83/258	32 (27-38)	0.65
Central PE	160/551	29 (25-33)	31/82	38 (27-49)	0.11
Segmental PE	293/551	53 (49-57)	39/82	48 (36-59)	0.34
Subsegmental PE	98/551	18 (15-21)	12/82	15 (8-24)	0.48

Three-month thrombo-embolic risk after a normal CT

In 1505 patients, CT excluded a diagnosis of PE. Of these, 69 patients received treatment with anticoagulants for other reasons than VTE and of the remaining 1436 untreated patients, 18 were diagnosed during follow-up with a thrombo-embolic event (1.3%, 95%CI: 0.7-2.0). In patients in whom the diagnosis of PE was excluded by MDCT, the three-month thrombo-embolic risk of patients was 1.1% (14/1330, 95%CI: 0.6-1.8). The 14 thrombo-embolic events in patients with a normal MDCT consisted of 6 fatal PE's, 3 non-fatal PE's and 5 DVT's.

In patients in whom PE was excluded by SDCT this risk was 2.3% (4/175, 95%CI: 0.6-5.8; p=0.15). These events consisted of 1 fatal PE and 3 DVT's.

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Discussion

Our study shows the anatomical distribution of PE in a large cohort of consecutive in and outpatients with clinically suspected PE. We have shown, using multi row detection systems, 18 % of patients to have pulmonary emboli in their subsegmental arteries as the most proximal location of PE. These findings are well comparable to the range of 6-30% of subsegmental pulmonary emboli reported in the literature (13,18). Using pulmonary angiography, in the largest study isolated PE was observed in 22 of 375 patients with PE (6%). In a study of 487 consecutive patients suspected of PE, using an algorithm with VQ scanning, SDCT and pulmonary angiography, the prevalence of isolated subsegmental PE was 22% (29/130, 95%CI: 16-30)[18] while in two other studies, the prevalence of subsegmental PE detected by MDCT was 15% (8/54, 95%CI: 7-27)[19] and 7% (14/187, 95%CI: 4-12)[2].

Importantly, in spite of the expected superior imaging quality of MDCT, we did not detect a difference in localisation of PE between single row technology and multi-row detector systems. Our findings offer strong support against the argument that the introduction of newer generations of multi row detector CT systems would lead to over-diagnosis of smaller pulmonary emboli in smaller subsegmental arteries and associated over treatment with anticoagulants.

Several limitations in our study require comment. First, the localisation of the highest branch of pulmonary embolism was assessed locally. A central blinded reading of CT's by a team of radiologists might have been more accurate and would have allowed establishing the inter-observer agreement between radiologists. However, our study is a management study and reflects daily practice. Second, the number of patients that underwent single-detector row CT was rather small in comparison to the number of patients undergoing multi-detector row CT. Multi-detector row CT has been introduced rapidly in many hospitals worldwide before any formal evaluation of this technique could have taken place and it is therefore unlikely that a comparison study of single- and multi-detector row CT is going to be performed. Third, a diagnosis of PE was made if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least two adjacent slices. In the ESSEP-study, isolated subsegmental PE was regarded as an inconclusive CT result in patients with a normal lower limb compression ultrasound and further tests were required[9] while in two other studies[2;20] isolated subsegmental PE was diagnosed if defects were multiple. Although the criteria for establishing a diagnosis of PE vary, it is a difficult task to prove the presence of subsegmental PE in a comparative manner. The gold standard, pulmonary angiography, is known to have an inter-observer agreement of only 45-66% for isolated subsegmental PE[16;17] and might therefore perform inadequately in diagnosing subsegmental PE. Moreover, in a porcine model, there appeared to be no difference in accuracy of detecting subsegmental PE between multi-detector row CT and pulmonary angiography[21].

We conclude that using MDCT the incidence of pulmonary emboli at the subsegmental and smaller arteries was not different when using SDCT technology. There seems to be no clear risk of overdiagnosis and associated over treatment using newer multi-row detector system CT technology in patients presenting with clinically suspected PE.

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The Natural Course of Hemodynamically Stable Pulmonary Embolism; Clinical Outcome and Risk Factors in a Large, Prospective Cohort Study

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Abstract

Background

Pulmonary embolism (PE) is a potentially fatal disease with risks of recurrent venous thrombotic events (VTE) and major bleeding from anticoagulant therapy. Identifying risk factors for recurrent VTE, bleeding and mortality may guide clinical decision-making. Objective: To evaluate the incidence of recurrent VTE, hemorrhagic complications and mortality in patients with PE and to identify risk factors and the time course of these events.

Design

We evaluated consecutive patients with PE, derived from a prospective management study, who were followed for three months, treated with anticoagulants and underwent objective diagnostic testing for suspected recurrent VTE or bleeding.

Results

Of 673 patients with complete follow-up, 20 patients (3.0%, 95%CI: 1.8-4.6) had recurrent VTE. Eleven of 14 patients with recurrent PE had a fatal PE (79%, 95%CI: 49-95%), occurring mostly in the first week after diagnosis of initial PE. In 23 patients (3.4%, 95%CI: 2.2-5.1) a hemorrhagic complication occurred, 10 of which were major bleeds (1.5%, 95%CI: 0.7-2.7) and two were fatal (0.3%, 95%CI: 0.04-1.1). During the three-month follow-up, 55 patients died (8.2%, 95%CI: 6.2-10.5). Risk factors for recurrent VTE were immobilisation for more than 3 days; being an inpatient, having COPD or malignancies were risk factors for bleeding. Higher age, immobilisation, malignancy and being an inpatient were risk factors for mortality.

Conclusions

Recurrent VTE occurred in a small percentage of patients treated for an acute PE and the majority of recurrent PE's were fatal. Immobilization, hospitalization, age, COPD and malignancies were risk factors for recurrent VTE, bleeding and mortality. Close monitoring may be indicated in these patients, precluding them from out of hospital start of treatment.

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Introduction

Pulmonary embolism (PE) is a potentially fatal disease with long-term sequelae such as recurrent thrombotic events and major bleeding from anticoagulant therapy. Few studies have investigated the clinical course of PE and varying incidences of recurrent events, bleeding complications and mortality have been reported[1-4]. During the first three months of anticoagulant treatment the reported rate of recurrent venous thrombo-embolism (VTE) in patients with PE has ranged from 2 to 6% [1-4]. The rate of major bleeding during the first three months ranged from 2% to 4%[1-4]. An accurate estimate of both incidences of recurrent VTE and major bleeding is important but moreover, it is desirable to identify risk factors indicating which patients are at increased risk for an adverse clinical outcome of PE. Previous studies[1-4] involved a relatively limited amount of patients diagnosed with PE precluding an accurate estimate of clinical outcomes. Further, in one study, only risk factors for recurrent VTE were assessed while patients diagnosed with PE as well as patients with deep vein thrombosis (DVT) were included, while it is known that patients with DVT may face a more favourable outcome than patients with PE[2;5].

We evaluated the clinical outcome during three months of a large group of consecutive patients with PE. We aimed to assess the incidence of recurrent venous thrombo-embolism, mortality and hemorrhagic complications in patients diagnosed with PE and treated with oral anticoagulants during this follow-up period. Second, we aimed to identify risk factors for recurrence, bleeding and mortality and to determine the time course of these events within 3 months of the start of treatment.

Methods

Study design

Consecutive patients with PE confirmed by helical computed tomography were included. They were derived from a large, prospective management study using a diagnostic algorithm that consisted of a clinical decision rule, a D-dimer test and helical computed tomography (CT)[6]. Out- as well as inpatients were eligible. Exclusion criteria of this management-study were: treatment with therapeutic doses of unfractionated or low-molecular-weight-heparin for more than 24 hours, life expectancy less than 3 months, pregnancy, geographic inaccessibility precluding follow-up, age below 18 years, allergy to intravenous contrast agents or hemodynamic instability (defined as a systolic blood pressure below 90 mmHg or symptoms and signs of shock). The Institutional Review Boards (IRB's) of all participating hospitals approved the study protocol and written or oral informed consent was obtained from all participants, depending on the requirements of the local IRB's.

Before any diagnostic test was performed, demographic data of all patients were recorded. An inpatient was defined as a patient hospitalised for some other health problem than pulmonary embolism that developed symptoms possibly due to PE during hospitalisation. Surgery was defined as major surgery within the past month, heart-failure was defined

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as NYHA class 2-4 for which specific therapy was given and malignancy was defined as active malignancy with ongoing treatment or within the past six months or in the palliative stages. All patients were initially treated with body-weight adjusted therapeutic doses of low-molecular weight heparin for at least five days or bodyweight adjusted unfractionated heparin aiming at an activated partial thromboplastin time between 1.5 and 2 times the baseline value, followed by vitamin K antagonists, aiming at an International Normalized Ratio (INR) of 2.0 to 3.0 for a period of six months.

Follow-up

Follow-up was vigorously pursued and consisted of a fixed hospital visit or telephone interview after three months. In addition, all patients got a detailed instruction on signs and symptoms of recurrent PE and DVT and they were instructed to contact the study centre immediately in case of complaints suggestive of DVT, PE or bleeding. At each visit, information was obtained on complaints suggestive for recurrent venous thrombo-embolism and bleeding. In case of clinically suspected DVT, PE or a hemorrhagic complication, appropriate objective tests were required to confirm or refute the diagnosis.

Outcome

The outcome of the study was the incidence of symptomatic recurrent venous thromboembolism, as well as the incidence of hemorrhagic complications and mortality in patients with confirmed PE during the three-month study period. Symptomatic recurrent venous thrombo-embolism was considered to have occurred if recurrent PE or DVT was documented objectively or if there was a 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 more than 2.5 mm in diameter on pulmonary angiography; a new perfusion defect involving at least 75 percent of a segment, with corresponding normal ventilation (i.e., a high probability lung scan); a new non-diagnostic lung scan accompanied by documentation of deep vein thrombosis by ultrasonography or venography; or confirmation of a new pulmonary embolism at autopsy[7;8]. The objective criterion of a new deep vein thrombosis was a new, non-compressible venous segment or a substantial increase (4mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography[9;10].

Mortality was classified 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. Hemorrhagic complications were the composite of major bleeding and clinically relevant bleeding. A major bleeding was defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of 20 g L^{1} (1.24 mmol L^{1}) or more, or leading to transfusion of two or more units of whole blood

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or red cells[11]. Bleeding was considered clinically relevant when the episode did not qualify as a major bleeding but included one of the following: epistaxis requiring intervention, formation of a large haematoma visible on the skin or spontaneous macroscopic haematuria. All suspected outcome events were reviewed and classified by an independent adjudication committee. Deaths were classified by the committee as caused by pulmonary embolism if autopsy confirmed pulmonary embolism, in case of an objective test demonstrating pulmonary embolism prior to death, or if pulmonary embolism could not be confidently excluded as the cause of death. Other causes of death were classified based on autopsy findings or clinical reports.

Statistical analysis

The univariate relation between baseline characteristics and outcome was examined by chi-square statistics for categorical variables and t-tests for continuous variables. Fisher's Exact test was used when the expected values were less than five. A level of significance of 0.05 (two-tailed) was used in all tests. Multivariate stepwise logistic regression was used to identify independent predictors of recurrent VTE, bleeding and mortality. Variables were included only in the final (multivariate) analysis based on their level of significance ($p<0.10$), except for the variables age and sex that were independent of significance included in the analysis. The odds ratio and corresponding 95% confidence interval was reported for each variable in the model. The analyses were performed using SPSS software, version 11 (SPSS, Inc., Chicago, Illinois).

Results

Study patients

Between November 2002 and September 2004 a total of 3503 patients with clinically suspected PE were screened, of whom 197 (5.6%) were excluded because of predefined exclusion criteria or refused informed consent: more than 24 hours of low molecular weight heparin (n=50), life expectancy less than 3 months (n=47), pregnancy (n=26), geographic inaccessibility precluding follow up (n=20), and other reasons (n=41). In addition, 13 patients refused informed consent[6]. In 674 patients (20%) PE was diagnosed. The baseline characteristics of these patients are described in Table 1. Three-month follow-up was completed in 673 of the 674 patients with PE (99.9%).

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Table 1
Baseline characteristics of the 674 patients with PE

Characteristics	*PE*
Age – yr*	58 (19-100)
< 55 yr, n (%)	296 (44)
≥ 55 – 65 yr, n (%)	117 (17)
> 65 yr, n (%)	261 (39)
Sex - ♀ (%)	51
Duration of complaints – days†	2 (0-90)
Localisation of PE (highest branch)ƒ	
Central	191 (30)
Segmental	332 (52)
Subsegmental	110 (17)
Outpatients (%)	78
Risk factors for venous thromboembolism – %	
Paralysis, paresis or plaster cast lower limbs‡	6
Immobilisation/bed rest > 3 days‡	17
Immobilisation due to travel by car or air‡	7
Surgery‡	10
Previous deep vein thrombosis	9
Previous pulmonary embolism	10
Heart failure with therapy	6
COPD with therapy	9
Malignancy	19
Clinical findings – %	
Signs of deep vein thrombosis	15
Tachycardia (>100 beats per min)	37
Haemoptysis	8

*Mean (range), † median (range), ‡ within previous month, § in females only, PE: Pulmonary Embolism, ƒ missing data in 41 patients
Recurrent symptomatic venous thrombo-embolism

Of the 673 patients with PE and complete follow-up, 20 patients (3.0%, 95%CI: 1.8-4.6) had an objectively confirmed recurrent venous thrombo-embolic event during the 3-months follow-up period. Seventy percent of patients with a recurrent venous thrombo-embolic event (14/20) had a recurrent PE (2.1% overall) and only 30% (6/20) a DVT (0.9% overall). Recurrent PE was fatal in 11 of 14 patients (79%, 95%CI: 49-95%) with recurrent PE (1.6% overall), resulting in a case-fatality rate (number of fatal recurrences divided by total number of recurrences) of 55% (11/20). Recurrent thrombotic events occurred predominantly within the first 3 weeks after the diagnosis (14 of 20 events, Figure 1). Recurrent fatal PE occurred mainly in the first week (6 of 11 events) and significantly earlier (median 5 days, range 58 days) than recurrent non-fatal PE (median 29 days, range 74, p=0.04). All fatal recurrent PE's occurred during hospitalisation, while 1 of 3 non-fatal recurrent PE's and 2 of 6 recurrent DVT's occurred in hospital.

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Figure 1
Timing of recurrent thrombotic events

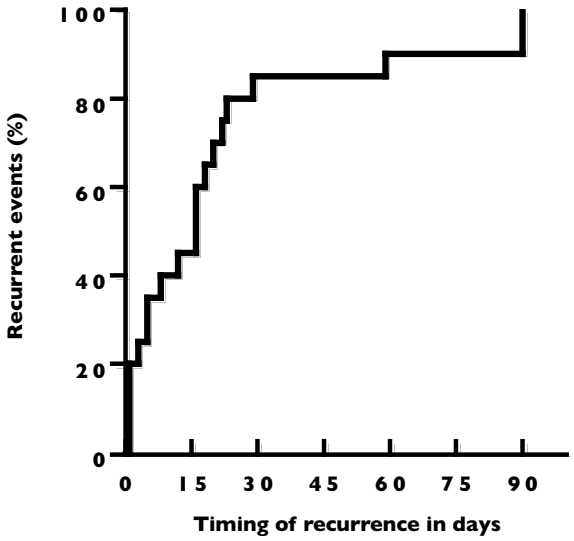


Table 2
Risk factors for recurrent VTE in patients with pulmonary embolism

Risk factors	Patients with PE and recurrence	Patients with PE without recurrence	Univariate analysis	
			p-value	OR (95%CI)
n	20	653		
Age in years*	63 (17)	57 (18)	0.15	1.02 (0.99-1.05)
Sex, female	10 (50%)	331 (51%)	0.96	0.98 (0.40-2.38)
Inpatients	6 (30%)	144 (22%)	0.39	1.52 (0.58-4.04)
Paralysis/paresis	1 (5%)	37 (6%)	1.00	0.87 (0.11-6.67)
Immobilisation > 3 days	8 (40%)	105 (16%)	0.005	3.50 (1.40-8.77)
Travel by air or car	2 (10%)	44 (7%)	0.64	1.55 (0.35-6.88)
Surgery	2 (10%)	66 (10%)	1.00	0.99 (0.23-4.36)
Previous VTE	3 (15%)	126 (19%)	0.78	0.74 (0.21-2.57)
Previous PE	2 (10%)	64 (10%)	1.00	1.02 (0.23-4.52)
Heart failure	0	40 (6%)	0.63	0.94 (0.92-0.96)
COPD	2 (10%)	60 (9%)	0.71	1.09 (0.25-4.83)
Malignancy	4 (20%)	126 (19%)	1.00	1.05 (0.34-3.18)
Signs of DVT	5 (25%)	95 (15%)	0.20	1.96 (0.70-5.51)
Tachycardia	9 (45%)	240 (37%)	0.45	1.41 (0.58-3.46)

* Mean (SD), DVT: Deep Vein Thrombosis, PE: Pulmonary Embolism, VTE: Venous Thrombo-embolic Events

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Predictors of recurrent thrombotic events

Only one single variable, immobilisation for more than 3 days prior to the diagnosis of the initial PE, appeared as a significant predictor of a recurrent thrombotic event in univariate analysis (OR 3.50, 95%CI: 1.40-8.77) and therefore, multivariate analysis was not performed (Table 2). Patients with recurrences were older (a mean of 63 versus 57 years, OR 1.02) but this risk factor did not reach significance. A separate analysis for risk factors of fatal recurrent PE was performed but did not show other results than for the whole group of recurrent events (immobilisation as a risk factor for recurrent fatal PE: OR 2.79, 95%CI: 1.43-5.45, other risk factors and OR's not shown).

Bleeding rate in patients with PE

A hemorrhagic complication of anticoagulant therapy occurred in 23 patients with PE (3.4%, 95%CI: 2.2-5.1). Bleeding was major in 10 patients (1.5%, 95%CI: 0.7-2.7) of which two were fatal (0.3%, 95%CI: 0.04-1.1). Clinically relevant bleeding occurred in the remaining 13 patients (1.9%, 95%CI: 1.0-3.3). The case fatality rate of bleeding was 9% (2/23, 95%CI: 1-28). Both fatal bleeding events occurred out-of-hospital while 7 of the 8 non-fatal major bleedings occurred in-hospital and 7 of 13 clinically relevant bleeding occurred in-hospital.

Table 3
Risk factors for bleeding in patients with pulmonary embolism (clinically relevant and major bleeding)

Risk factors	Patients with PE and bleeding	Patients with PE without bleeding	Univariate analysis		Multivariate analysis	
			p-value	OR (95%CI)	p-value	OR (95%CI)
n	23	650				
Age in years*	56 (17)	58 (18)	0.66	1.00 (0.97-1.02)		
Sex, female	10 (44%)	331 (51%)	0.49	0.74 (0.32-1.72)		
Inpatients	11 (48%)	139 (21%)	0.003	3.39 (1.46-7.85)	0.05	2.63 (1.02-6.77)
Paralysis/paresis	1 (4%)	37 (6%)	1.0	0.75 (0.10-5.70)		
Immobilisation > 3 days	4 (17%)	109 (17%)	1.0	1.05 (0.35-3.14)		
Travel by air or car	0	46 (7%)	0.39	0.93 (0.91-0.95)		
Surgery	6 (26%)	62 (10%)	0.02	3.34 (1.27-8.79)	0.23	1.92 (0.66-5.59)
Previous VTE	4 (17%)	125 (19%)	1.0	0.89 (0.30-2.66)		
Previous PE	3 (13%)	63 (10%)	0.48	1.41 (0.41-4.86)		
Heart failure	1 (4%)	39 (6%)	1.0	0.71 (0.09-5.40)		
COPD	5 (22%)	57 (9%)	0.05	2.88 (1.03-8.05)	0.02	3.89 (1.22-12.4)
Malignancy	9 (39%)	121 (19%)	0.03	2.81 (1.19-6.64)	0.02	3.04 (1.16-7.97)
Hemoptysis	3 (13%)	52 (8%)	0.42	1.73 (0.50-6.01)		

PE: Pulmonary Embolism, VTE: Venous Thrombo-embolic Events, *Mean (SD)

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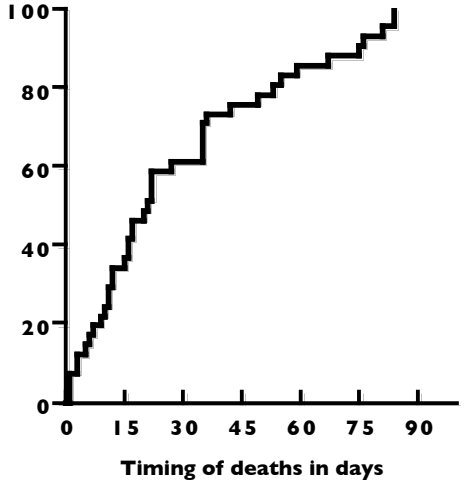
Predictors of bleeding

Table 3 shows the effect of clinical characteristics on the risk of clinically relevant or major bleeding using univariate and multivariate analysis. In multivariate analysis, being an inpatient (OR 2.63, 95%CI: 1.02-6.77), having COPD (OR 3.89, 95%CI: 1.22-12.4) or a malignancy (OR 3.04, 95%CI: 1.16-7.97) remained independent risk factors for bleeding in patients with PE.

Mortality in patients with PE

Of 673 patients diagnosed with PE and with complete follow-up, 55 patients (8.2%, 95%CI: 6.2-10.5) died during the three-month follow-up period. Of these 55 patients, 11 died because of fatal recurrent PE (20%, 95%CI: 10-33). None of these fatal recurrences underwent autopsy to confirm the cause of death. Two patients died because of fatal haemorrhage (4%, 95%CI: 0.4-13). The cause of death in the remaining patients with PE was mainly malignancy (17 patients, 35%) or cardiovascular disease (9 patients, 16%). The time of death in patients with PE ranged from 1 to 90 days with a median of 22 days (Figure 2).

Figure 2
Timing of deaths



Predictors of mortality in patients with PE

In multivariate analysis, 4 clinical characteristics were shown to be independent risk factors for mortality in patients with PE (Table 4); 1) age (OR 1.04, 95%CI: 1.02-1.07); 2) immobilisation for more than 3 days (OR 2.07, 95%CI: 1.06-4.); 3) malignancy (OR 3.02, 95%CI: 1.65-5.52) and 4) being an inpatient (OR 2.11, 95%CI: 1.15-3.88).

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Table 4
Risk factors for mortality in patients with PE

	PE patients who died	PE patients alive after 3 months	Univariate analysis		Multivariate analysis	
			p-value	OR (95%CI)	p-value	OR (95%CI)
n	55	618				
Age in years*	69 (16)	57 (18)	<0.001	1.05 (1.03-1.07)	<0.001	1.04 (1.02-1.07)
Sex, female	25 (46%)	308 (50%)	0.41	0.80 (0.46-1.38)		
Inpatients	25 (46%)	125 (20%)	<0.001	3.31 (1.88-5.83)	0.02	2.11 (1.15-3.88)
Paralysis/paresis	2 (4%)	36 (6%)	0.49	0.60 (0.14-2.57)		
Immobilisation > 3 days	17 (31%)	95 (15%)	0.004	2.41 (1.30-4.44)	0.03	2.07 (1.06-4.05)
Travel by air or car	0	45 (7%)	0.03	0.93 (0.91-0.95)	0.69	0.003 (0-5*10^9)
Surgery	5 (9%)	63 (10%)	0.76	0.86 (0.33-2.24)		
Previous VTE	8 (15%)	116 (19%)	0.40	0.72 (0.33-1.56)		
Previous PE	6 (11%)	60 (10%)	0.77	1.14 (0.47-2.77)		
Heart failure	6 (11%)	32 (5%)	0.12	2.23 (0.89-5.59)		
COPD	10 (18%)	48 (8%)	0.02	2.62 (1.24-5.54)	0.17	1.77 (0.79-3.97)
Malignancy	24 (44%)	104 (17%)	<0.001	3.72 (2.09-6.59)	<0.001	3.02 (1.65-5.52)
Clinical signs of DVT	9 (16%)	91 (15%)	0.74	1.13 (0.54-2.39)		
Tachycardia	25 (46%)	224 (36%)	0.17	1.47 (0.84-2.56)		

*Mean (SD), DVT: Deep Vein Thrombosis, PE= pulmonary embolism, VTE= venous thrombo-embolic events, *Mean (SD)

Table 5
Clinical outcomes during three months in patients with PE

Patients with PE	n (673)	%	95%CI
Overall recurrence	20	3.0	1.8-4.6
Fatal recurrent PE	*11*	*1.6*	*0.8-2.9*
Non-fatal recurrent PE	*3*	*0.5*	*0.09-1.3*
Non-fatal recurrent DVT	*6*	*0.9*	*0.3-1.9*
Hemorrhagic complications	23	3.4	2.2-5.1
Fatal bleeding	*2*	*0.3*	*0.04-1.1*
Major bleeding	*10*	*1.5*	*0.7-2.7*
Clinically relevant bleeding	*13*	*1.9*	*1.0-3.3*
Overall mortality	55	8.2	6.2-10.5

DVT: Deep Vein Thrombosis, PE: Pulmonary Embolis

Discussion

We evaluated the clinical outcome of a large prospective cohort of patients with symptomatic, confirmed PE and aimed to assess an accurate incidence of recurrent venous thrombo-embolism, mortality and hemorrhagic complications during three months of anticoagulant treatment (Table 5). Moreover, we aimed to identify risk factors for these events and to determine the time course within three months of the start of treatment.
There are two important conclusions to be drawn from our analysis. First, a recurrent thrombo-embolic event presenting as a recurrent PE occurred in 2.1 % of patients with

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PE and was fatal in the majority (79%) of these patients, occurring mostly in the first week of follow-up. Second, risk factors for a complicated course of PE, i.e. a recurrent VTE, bleeding or death, were immobilisation for more than three days prior to diagnosis of PE, being an inpatient, higher age and the presence of COPD or a malignancy.

The recurrence rate of 3% that we observed is comparable to three other cohort studies where incidences varied between 2.1% and 3.9%[1;3;4], but lower than the 6% (95%CI: 4.4 – 7.3) recurrence rate in patients with PE in a recently published study[2]. The discrepancy with the last study might be due to a different co-morbidity profile in that study, with a higher prevalence of cardiovascular disease (36% vs. 6%) and older patients (mean 62 years ± 17 SD vs. 58 years ± 18)[2]. Our case fatality rate of recurrent VTE is consistent with the findings of another study, in which a case-fatality rate of 45% was observed[12]. Moreover, the observed clustering of recurrences in the first three weeks has been described previously[2;12] but to our knowledge, the clustering of fatal events in the first week after diagnosis has not been described before.

Surprisingly, the only risk factor predicting a recurrent thrombotic event was immobilisation for more than three days. This finding seems to be in disagreement with an earlier study in which the presence of cancer, chronic cardiovascular disease, chronic respiratory disease and other clinically significant diseases were independent risk factors for recurrent VTE in patients with PE[2]. Immobilization due to these chronic illnesses and subsequent venous stasis might explain the increased risk of recurrence but immobility might as well be a marker for more severe comorbid conditions and these patients are subjected to a higher risk for recurrence[2-4;13].

The mortality rate of 8.2% during three months in patients diagnosed with PE is consistent with the 7.7% found in a study by Perrier et al[13], but lower than the 15% mortality rate in the study by van Strijen and colleagues[4]. In addition, the incidence of fatal PE was lower in our study-population and in that of Perrier and colleagues (1.6% and 2.3%) compared to the 5.6% in the study of van Strijen et al. This latter study however had a relatively high percentage of inpatients (46%) compared to our study (22%) and the study of Perrier and colleagues (0%)[13] which may have led to a high risk population.

There are some limitations of our study that should be addressed. First, the study population was derived from a diagnostic management study and excluded certain patients including those who were treated with therapeutic doses of unfractionated or low-molecular-weight-heparin for more than 24 hours, who had a life expectancy less than 3 months, who were pregnant or hemodynamically instable. Consequently, our findings may not apply to these patients[14]. However, only 5% of our screened population were excluded for abovementioned reasons, therefore, our findings are likely to be generalizable to most patients with PE who are hemodynamically stable. Second, we acknowledge that identifying risk factors for recurrence, bleeding and mortality was not a primary goal of our study and hence, data concerning the adequacy of anticoagulation were not recorded. It is possible that some recurrent VTE episodes were related to inadequate initial anticoagulation, however, only four patients with recurrent VTE had been treated initially with intravenous unfractionated heparin and it is unlikely to have affected our study results relating to risk factors for recurrent

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VTE. Third, our definition of fatal recurrent PE as 'any death in which PE could not be confidently ruled out as a contributing cause' may have led to an overestimation of our fatality rate of recurrence. Fourth, a clear definition of a recurrent venous thrombo-embolic event, occurring during treatment with anticoagulants, is not available and there's no expert opinion on the time limits for calling a venous thrombo-embolic event a complication of a first venous thrombo-embolic event or a recurrent event.

The clinical implications of our study are two-fold. First, recurrent VTE occurs despite anticoagulant therapy and is most frequently encountered in the first three weeks after diagnosis of PE, while fatal recurrences occur predominantly in the first week after diagnosis. Since patients with non-massive PE are increasingly treated with LMWH instead of intravenous unfractionated heparin[15], early discharge or even home treatment is logistically feasible but the safety is unclear since large comparative studies are lacking. Although it has been recommended to extend current organisation for outpatient management of DVT to stable patients with PE[16], outpatient treatment of PE is not widely accepted because no explicit clinical criteria exist to accurately identify patients with PE at high risk of adverse outcomes. Our study was not designed to answer the question regarding the safety of home treatment. It remains to be studied whether the presence of the risk factors for an adverse outcome in patients with PE should guide decisions on hospital or home treatment and preclude early discharge from hospital in patients with these risk factors.
Second, based on our study results, patients in whom recurrent PE occurs, face a substantial risk of mortality. We acknowledge that there is a potential for bias leading to overcall of this observation, since no autopsies were done to substantiate the clinical judgement of the adjudication committee. Whether awareness of this high risk and proper treatment of co-morbidities might decrease this risk should be studied separately.
In summary, in patients diagnosed with PE and treated with anticoagulants, recurrent VTE is more likely to occur in patients who have been immobilized for more than three days while a major or clinically relevant bleeding is more likely to occur when patients are hospitalised or have COPD or a malignancy. Increasing age, immobilisation for more than three days, malignancy and being an inpatient increases the risk of mortality in the first three months after the diagnosis. In patients with these characteristics closer monitoring might be indicated, precluding these patients from early discharge from the hospital. Conformation of these variables as a risk factor for recurrence, death and bleeding needs prospective validation.

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Clinically Suspected Acute Recurrent Pulmonary Embolism: A Diagnostic Challenge

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Abstract

Background

It is unknown whether strategies validated for diagnosing pulmonary embolism (PE) are valid in patients with a history of PE.

Objective

To investigate whether a diagnostic algorithm consisting of sequential application of a clinical decision rule (CDR), a quantitative D-dimer test and computed tomography (CT) safely ruled out a clinical suspicion of acute recurrent PE.

Methods

Data were obtained from a diagnostic outcome study of patients suspected of PE. Acute recurrent PE was ruled out by an unlikely probability of PE (CDR score ≤ 4 points) combined with a normal D-dimer test (≤500 ng/ml) or by a normal CT in all other patients. The primary outcome was the incidence of acute recurrent venous thromboembolism during three months of follow-up in patients with normal tests and not treated with anticoagulants.

Results

Of 3306 patients suspected of acute PE, 259 patients (7.8%) had a history of PE of whom 234 were not treated with anticoagulants. The probability of PE was unlikely in 82 of 234 patients (35%) and 42 had a normal D-dimer test (18%), excluding recurrent PE. None of these patients had a thrombotic event during follow-up (0%, 95%CI: 0-6.9). A CT was indicated in all other patients (192) and ruled out recurrent PE in 127 patients (54%). Only one patient with a negative CT had a fatal recurrent PE during follow-up (0.8%; 95%CI: 0.02-4.3).

Conclusions

This prospective study demonstrates the safety of ruling out a clinical suspicion of acute recurrent PE by a simple diagnostic algorithm in patients with a history of PE.

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Introduction

In recent years many studies have focused on improving the diagnostic management of patients with suspected acute pulmonary embolism (PE) by developing clinical decision rules and implementing computed tomography (CT)[1-3]. However, the management of patients with suspected recurrence is problematic, since it is unclear whether currently used strategies are valid in patients with a prior history of proven PE. In the literature there are no studies that investigated the diagnostic accuracy of objective tests in patients with a history of PE, despite the fact that it is well established that 10-20% of patients with PE will have a recurrence during the first two years after stopping anticoagulant treatment[4;5]. In particular, no study has reported on the safety of withholding anticoagulant therapy on the basis of normal diagnostic tests in patients with a clinical suspicion of recurrent PE. The consequences of misdiagnosis of acute recurrent PE are major. Incorrectly concluding that acute recurrent PE is present exposes the patient to prolonged - and often life-long- anticoagulation[6] with its attendant costs, inconvenience, and bleeding risks. Incorrectly concluding that acute recurrent PE is absent puts the patient at high risk of ongoing PE, which may be fatal. Objective diagnosis of acute recurrent PE in clinically suspected patients is relevant because in parallel it has been shown that patients clinically suspected of recurrent Deep Vein Thrombosis (DVT), only 20-30% have objective recurrent DVT demonstrated by diagnostic methods.

Moreover, the accurate diagnosis of acute recurrent PE is important because it is generally accepted to treat patients with two or more episodes of objectively diagnosed PE indefinitely with anticoagulants[6]. An objective diagnosis is problematic since it may be difficult to distinguish new from old thrombo-emboli. It has been estimated that the percentage of patients with residual pulmonary thrombi is 50% six months after an initial diagnosis of PE[7].

Recently, in a large, prospective cohort study we investigated the safety of a diagnostic algorithm consisting of a clinical decision rule (CDR), quantitative D-dimer test and CT in excluding clinically suspected PE[8]. The aim of the present study is to investigate whether this diagnostic algorithm can also be safely used to exclude the diagnosis of recurrent PE in patients presenting with a clinical suspicion of acute recurrent PE.

Methods

Study design

This study was part of a large, prospective management study in 5 academic and 7 general hospitals in the Netherlands performed between November 2002 and December 2004[8]. This study evaluated the safety of excluding PE by a diagnostic algorithm consisting of a CDR, a quantitative D-dimer test and CT. All patients were followed for a period of three months to document the occurrence of symptomatic venous thrombo-embolic events (VTE).

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Study patients

All consecutive in- and outpatients with a clinical suspicion of recurrent PE, defined as a sudden onset of dyspnea, a deterioration of existing dyspnea or sudden onset of pleuritic chest pain without another apparent cause, were eligible for the study. All patients had a history of confirmed PE, with or without DVT. Previous pulmonary embolism was diagnosed by one of the following; a CT-scan demonstrating PE, a high-probability VQ-scan, an intermediate VQ-scan with CUS demonstrating DVT or pulmonary angiography showing PE. Patients were not systematically screened for the existence of chronic thrombo-embolic pulmonary arterial hypertension.

Exclusion criteria were: age under 18 years, treatment with therapeutic doses of unfractionated or low-molecular weight heparin for more than 24 hours prior to inclusion, a life expectancy of less than three months, pregnancy, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance less than 30 ml/min), logistic reasons, geographic inaccessibility precluding follow up or hemodynamic instability. Patients who were treated with anticoagulants at admission and/or during follow-up were excluded from the present analysis because the safety of withholding anticoagulants could not be established in these patients. The Institutional Review Boards (IRB's) of all participating hospitals approved the study protocol and written or oral informed consent was obtained from all participants, depending on the requirements of the local IRB's.

Diagnostic work-up

The dichotomized clinical decision rule according to Wells was used to determine pre-test probability for PE (Table 1). Patients were designated as PE unlikely if the CDR was ≤ 4 points, and PE likely in case of a CDR > 4 points[3;9]. In patients with a CDR indicating PE unlikely, a D-dimer test was performed. In patients with a normal D-dimer concentration, the diagnosis of recurrent PE was considered excluded. Patients with a CDR indicating PE likely and patients with an abnormal D-dimer test underwent CT[8]. Single-row detector as well as multi-row detector systems were used. In case of a normal CT, recurrent PE was considered excluded. The criterion for the diagnosis of a recurrent PE was the presence of signs of acute PE, i.e. a central filling defect or complete occlusion of a vessel on CT. All patients in whom the diagnosis of recurrent PE was excluded were withheld from anticoagulant treatment and were followed for three months to document the occurrence of symptomatic venous thrombo-embolic events, diagnosed by objective imaging tests.

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Table 1
Clinical decision rule according to Wells et al.

	points
Clinical signs and symptoms of deep vein thrombosis (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/minute	1.5
Immobilisation (> 3 days) or surgery in the previous 4 weeks	1.5
Previous PE or DVT	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the last 6 months or palliative)	1.0

Clinical probability of PE unlikely ≤ 4 points, clinical probability of PE likely > 4 points.

Outcome

The primary outcome of the study was the incidence of symptomatic, recurrent venous thrombo-embolic events during three months follow-up in patients in whom recurrent PE was excluded and who were not treated with anticoagulants. Symptomatic recurrent VTE was considered to have occurred if recurrent PE or DVT was documented objectively or if there was a death in which PE was a contributing cause or could not be ruled out. A diagnosis of PE or DVT was made, based on a priori defined and generally accepted criteria[10]. The criteria for the objective diagnosis of DVT were a non-compressible venous segment during compression ultrasonography or an intraluminal filling defect on venography. The criteria for the objective diagnosis of recurrent PE were signs of acute PE, i.e. a central filling defect or complete occlusion on CT a filling defect or a cut-off of a vessel of more than 2.5 mm on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high-probability lung scan) or PE confirmed by autopsy. An independent adjudication committee, whose members were unaware of the results of the diagnostic algorithm, evaluated all suspected venous thrombo-embolic events and deaths.

Statistical analysis

The incidences of symptomatic recurrent VTE confirmed by objective testing were calculated for a) the group in which recurrent PE was excluded based on a CDR indicating PE unlikely combined with a normal D-dimer test and b) the group of patients in which recurrent PE was excluded based on a normal CT. Exact 95% confidence intervals (CI) were calculated around the observed incidences using JavaStat software (http://statpages.org/confint.html). Descriptive parameters were calculated using the SPSS software, version 11 (SPSS, Inc., Chicago, Illinois). The univariate relation between baseline characteristics and outcome was examined by chi-square statistics for categorical variables and t-tests for continuous variables. Fisher's Exact test was used when the expected values were less than five. A level of significance of 0.05 (two-tailed) was used in all tests. Excluding recurrent PE was considered safe in case of a three-month thrombo-embolic failure rate not exceeding that of the upper confidence level of normal pulmonary angiography (upper 95%CI: 2.7) in patients in whom the diagnosis was excluded and who were not treated with anticoagulants[11].

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Results

Patients

A total of 3503 patients were eligible of which 197 were excluded because of predefined exclusion criteria or no informed consent (Figure 1). Of 3306 patients with a clinical suspicion of PE who were included in the diagnostic management study, 259 patients (7.8%, 95%CI: 6.9-8.8) had a history of PE. Of these, 25 patients were treated with anticoagulants (9.7%) and they were excluded from the present analysis. The baseline characteristics of the 234 remaining patients with previous PE are demonstrated in Table 2. Mean age was 55 years, 61% was female and the median time since the prior PE was 4 years. The 25th percentile of time since previous PE was 1.7 years, the 75th percentile was 7.2 years and the 90th percentile 15.1 years.

Table 2
Baseline demographic and clinical characteristics of 234 patients with a history of PE

Characteristics	n (%)
Age in years, mean (SD^{+})	55 (18)
Female sex	142 (61)
Outpatients	214 (91)
Duration of complaints in days, median (IQR$^{\wedge}$)	3 (1-7)
Time since previous PE in years, median (IQR$^{\wedge}$)	4 (2-7)*
Paralysis	9 (4)
Immobilisation or recent surgery	20 (9)
COPD with treatment	39 (17)
Heart failure with treatment	19 (8)
Malignancy	21 (9)
Oestrogen use[a]	12 (8)
Clinical symptoms of DVT	13 (6)
Heart rate (beats per minute >100)	40 (17)
Hemoptysis	12 (5)
PE at baseline	63 (27)

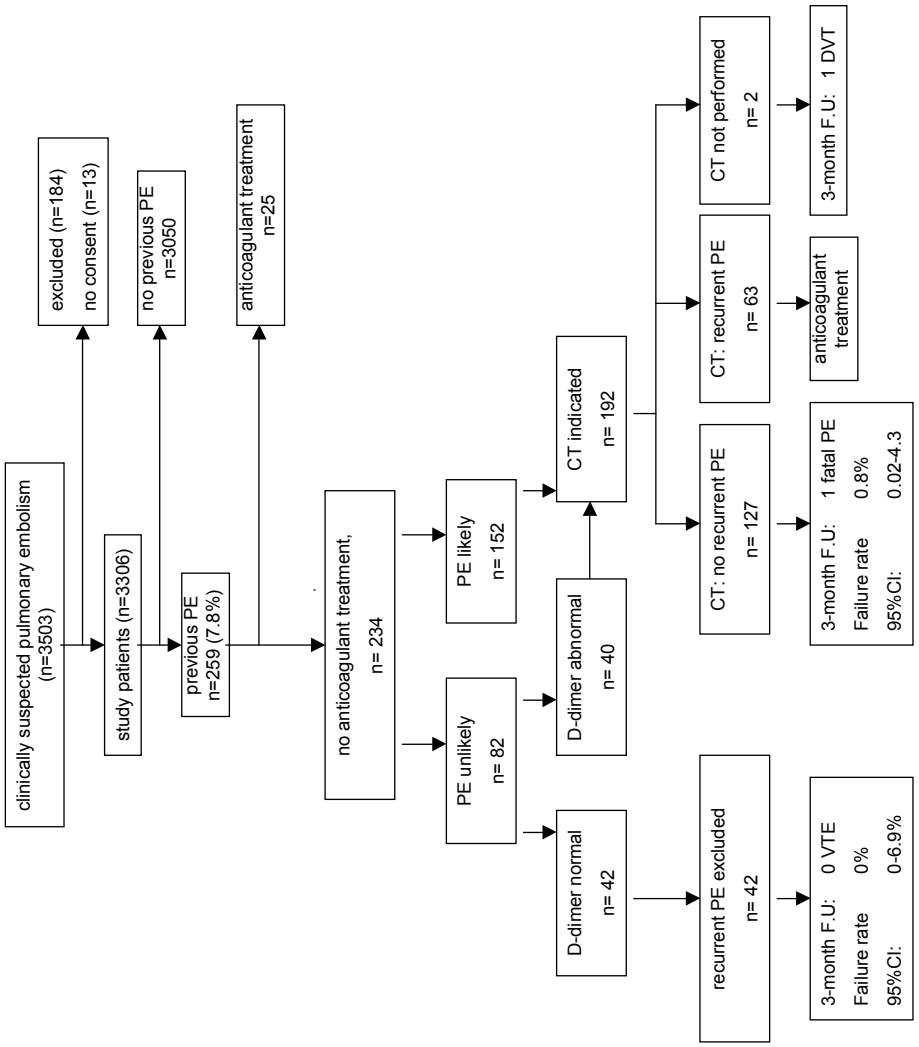
$^{+}$SD= standard deviation, $^{\wedge}$IQR= interquartile range, *missing data in 31 patients, [a] of females only

Results of the diagnostic algorithm

In 63 of 234 patients, recurrent PE was diagnosed (prevalence 26.9%, 95%CI: 21.4-33.1). Compared to patients in whom recurrent PE was excluded, patients with recurrent PE were older (62 versus 52 years, p<0.001), were more often male (56% versus 33%, p=0.002) and had more risk factors for PE, i.e. paralysis (11% versus 1%, p=0.002), immobilization or surgery in last four preceding weeks (17% versus 5%, p=0.003) and malignancy (14% versus 7%, p=0.08).

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Figure 1
Flow-chart



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Excluding recurrent PE by a CDR indicating "recurrent PE unlikely" and a normal D-dimer test

Of 234 patients with clinically suspected recurrent PE, 82 patients (35%) had a CDR indicating PE unlikely and were subsequently tested for D-dimer concentration. D-dimer tests were normal in 42 of 82 patients (51%) with unlikely PE, representing 18% of the total study population. Recurrent PE was excluded in these patients and during the three-months follow-up, completed in all patients, none of the 42 patients returned with a symptomatic recurrent venous thrombo-embolic event (0%, 95%CI: 0-6.9) (Table 3).

Excluding recurrent PE by helical CT

Of the 234 patients with a clinical suspicion of recurrent PE, 152 patients (65%) had a CDR indicating PE likely and 40 patients had a CDR indicating PE unlikely but had an abnormal D-dimer test. Of these 192 patients, 190 underwent CT. In 63 of 190 patients, recurrent PE was diagnosed (prevalence 26.9%, 95%CI: 21.4-33.1). CT was normal in 89 patients and suggested an alternative diagnosis (pneumonia, pleural effusion, malignancy etc.) in 38 patients (127 of 234 patients; 54% overall). During the three-month follow-up period, one of the patients in whom PE was excluded by CT died suddenly and was adjudicated as a possible fatal recurrent pulmonary embolism. Therefore, the 3-month thrombo-embolic failure rate in patients in whom CT had excluded PE was 0.8% (1/127; 95%CI: 0.02-4.3) (Table 3).

In two patients the protocol was violated and a CT was not performed. During follow-up, an arm vein thrombosis was diagnosed in one patient and this patient was treated with anticoagulants. The other patient was not treated with anticoagulants and follow-up was uneventful. If these two patients had been included, the failure rate in patients who were assigned to undergo a CT would have been 1.6% (2/129; 95%CI: 0.2-5.5).

The 3-month thrombo-embolic failure rate of the whole strategy of sequential application of CDR, D-dimer test and CT was 1.2% (2/171; 95%CI: 0.1-4.2)(Table 3).

Table 3
Safety of the diagnostic algorithm in patients with previous PE

	n (%)	3-m VTE failure rate	
		n	% (95%CI)
CDR unlikely and normal D-dimer	42 (18)	0	0 (0-6.9)
PE excluded by CT	127 (54)	1	0.8 (0.02-4.3)
PE excluded by CT + protocol violations	129 (55)	2	1.6 (0.2-5.5)
Whole strategy	171 (73)	2	1.2 (0.1-4.2)

Additional observations

The prevalence of PE in patients with a CDR indicating unlikely PE was 14.6% (12/82; 95%CI: 7.8-24.2) versus 33.6% (51/152; 95%CI: 26.1-41.7) in patients with a CDR

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indicating likely PE. Of 168 multi-row detector CT scans, 54 patients were diagnosed with PE (32%; 95%CI: 25-40%). Of 21 patients with single-row detector systems, 9 patients were diagnosed with PE (43%; 95%CI: 22-66). The diagnostic algorithm could be followed according to the protocol in 232 of 234 patients (99.1%).

Discussion

A simple diagnostic algorithm consisting of sequential application of a CDR, a quantitative D-dimer test and a CT appears to be safe in excluding PE in patients with clinically suspected recurrent PE. A clinical decision rule indicating PE unlikely combined with a normal D-dimer test excluded recurrent PE without the need for additional CT in approximately one-fifth of our total study population suspected of recurrent PE. CT ruled out recurrent PE in all other patients. However, the relatively wide confidence intervals of the 3-month thrombo-embolic risk of the whole strategy (95%CI: 1.2 (0.1-4.2) do not permit to conclude that our approach is as safe as pulmonary angiography.

To our knowledge, this is the first prospective study assessing the value of a standardized diagnostic strategy in patients with clinically suspected acute recurrent pulmonary embolism. In two recent studies evaluating CT in patients with clinically suspected PE a history of venous thrombo-embolism was present in 14% and 19% of the study population respectively, but a separate analysis was not given either with respect to the clinical outcome after a normal CT[1] or accuracy of CT[12] in patients with a prior PE.

We chose to limit the study to patients with a history of PE and did not allow patients with DVT. Patients presenting with DVT have reported scintigraphic evidence of silent PE in 40-50% of cases[13;14]. Including patients with prior DVT in our analysis would have led to a falsely increased feasibility of our algorithm since approximately half of those patients would have been patients with a first suspicion of PE.

Our study warrants additional comment on possible limitations. First, the absence or presence of PE was not verified by pulmonary angiography, the gold standard. However, the clinical outcome after a 3-month follow-up period is widely accepted as an appropriate alternative to establish the safety of excluding PE by a diagnostic strategy, given a near complete follow-up[15]. Although by design, it was not the objective of our study, we cannot exclude the possibility of false-positive CT-scans and overdiagnosis of PE, especially because old thrombi may have mistakenly been judged to be new thrombi and consequently treated as a recurrent PE. Although we used criteria of acute PE to diagnose recurrent PE, the natural evolution of pulmonary clots is currently unknown and it cannot be excluded that signs of acute PE persist longer than is generally presumed. However, the observed 27% prevalence of recurrent PE is fully in line with similar observations in patients with clinically suspected recurrent DVT and does not suggest overdiagnosis in our patients[16;17].

Second, although in our study only patients presenting with an acute sudden onset of dyspnea, a deterioration of existing dyspnea or sudden acute onset of pleuritic chest pain

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without another apparent cause were included, we could not fully exclude the existence of chronic thrombo-embolic pulmonary hypertension as an explanation for the patient's symptoms because we did not systematically screen all patients on CTEPH.

Third, the clinical decision rule consisted of the item "history of VTE" and as a consequence, all patients scored 1.5 points with this item. The discriminative power of the clinical decision rule was expected to be different in patients with prior VTE, and indeed, 35% of our population had a CDR indicating PE unlikely while in our overall cohort in the original study population 67% had a CDR indicating "PE unlikely"[8]. In addition, the combination of a CDR indicating PE unlikely and a normal D-dimer test was present in nearly one-fifth of patients compared to one-third in the original study population. Nevertheless, the prevalence of PE in patients with PE unlikely versus PE likely remained different, i.e. 14.6% versus 33.6%, indicating that the CDR we used is still clinically useful in distinguishing patients with a low and high risk for recurrent PE. Fourth, although our study contains the largest sample of patients with a clinical suspicion of recurrent PE reported, the 95% confidence limits of the three-month thrombo-embolic failure rate were rather wide and, exceeded that of the upper confidence limit of normal pulmonary angiography (2.7%)[11]. Finally it may be criticized that an observation period of three months may be too short to conclude that recurrent PE can be safely excluded. However, three months is a widely used period in diagnostic studies on the safety of excluding PE and any thrombo-embolic event occurring more than three months after a clinical suspicion is raised, is unlikely to be related to the first symptoms.

In conclusion, in patients with a prior history of PE who present with a clinical suspicion of a recurrent PE, either a CDR indicating recurrent PE unlikely combined with a normal quantitative D-dimer test or either a CT in all other patients appears safe in excluding recurrent PE. Larger studies are needed to confirm the safety of excluding recurrent PE by this simple algorithm.

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Resolution of thrombo-emboli in patients with acute pulmonary embolism; a systematic review.

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Chest 2006; 129: 192-197



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Abstract

Study objectives

Much attention has been paid in recent years to optimizing the diagnosis of acute pulmonary embolism (PE). However, little is known about the changes in clot burden that occur at the level of the pulmonary arteries after documented PE. It is often problematic to distinguish between a new or residual defect on lung scintigraphy or helical computed tomography (CT). This may lead to falsely labeling patients with residual PE as having recurrent PE and consequent unnecessary treatment changes.

Design

We performed a systematic analysis of studies of imaging tests (radionuclide and computerized tomography) evaluating resolution rate of PE with independent assessment of predefined methodologic criteria by two investigators.

Results

We identified 29 clinical studies. Of these, 25 were excluded and 4 studies were included in our review. Because studies differed largely in patient selection, duration of anticoagulation, timing of follow up etc., the studies were not pooled but briefly described. The percentage of patients with residual pulmonary thrombi was 87% at eight days after diagnosis, 68% after six weeks, 65% after three months, 57% after six months and 52% after 11 months.

Discussion

This review shows that complete resolution of PE is not routinely achieved between 8 days and 11 months after diagnosis. More than 50% of patients with PE still have defects six months after diagnosis, after which resolution of thrombi appears to reach a plateau phase. Physicians should be aware of the high percentage of incomplete resolution of pulmonary emboli. Routine re-imaging after cessation of anticoagulant therapy in patients with PE to obtain a new baseline could be considered.

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Introduction

Much attention has been paid in recent years to optimizing the diagnosis of acute pulmonary embolism (PE). Helical computed tomography (CT) is increasingly preferred as a first-line test. However, little is known about the subsequent changes in clot burden that occur in pulmonary arteries after objectively documented PE. In patients with symptomatic objectively proven proximal deep vein thrombosis (DVT) of the leg veins, studies[1;2] of sequential ultrasound examinations have demonstrated that persistent residual thrombosis is common after treatment with short-term anticoagulation and, according to one report[3], "normalization" of the image is achieved in 39% at 6 months, 58% after 12 months and 74% at 36 months, while other studies[4;5] suggest other time ranges. Information regarding the rate of resolution of pulmonary thrombi after diagnosis of PE is important because it may facilitate objective diagnosis when patients with PE return with complaints possibly due to recurrent PE. It is often clinically difficult to determine whether defects suggesting pulmonary emboli on lung scintigraphy or helical CT are residual or represent a new event. In a prospective study, it has been shown that 4% of first, symptomatic pulmonary embolism patients develop symptomatic chronic thromboembolic pulmonary hypertension (CTPH) within 2 years[6]. It would be desirable to avoid this outcome if possible and likewise to prevent the cascade of treatment consequent to falsely labeling patients with a recurrent PE. To better understand the natural history of pulmonary artery clot evolution after objectively documented PE, we performed a systematic analysis of published studies addressing this important clinical problem.

Methods

Search strategy

We used electronic search strategies to identify relevant studies. The following electronic databases were searched: PubMed (1966 to November 2004), EMBASE (1980-nov 2004), Cochrane, the Library Issue 1, 2005 and Web of Science using the search terms *residual thrombosis* or *incomplete recovery* or *incomplete resolution* or *(resolving AND (clots OR clot))* or *((Normalization OR Normalisation) AND (pulmonary arteries OR pulmonary artery))* or *(((thrombi AND regression)* or *thrombus regression) AND (pulmonary embolism OR pulmonary embolic OR (pulmonary AND (embolism OR emboli OR embolus)))* or *(Scintigraphic AND control AND pulmonary embolism)*. We augmented our search by reviewing the reference lists of retrieved articles. Studies published in any language were used.

Study selection

We attempted to identify all published clinical studies that evaluated patients with pulmonary embolism and the rate of resolution of pulmonary emboli visualized by follow up objective imaging tests. Of potential articles, abstracts were read to determine eligibility and in case of doubt, full-text articles were retrieved. To be included, a study had to 1) be prospective and involve consecutive patients; 2) objectively diagnose symptomatic

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pulmonary embolism (pulmonary angiography or helical CT, high-probability ventilation/perfusion (VQ) lung scintigraphy or intermediate probability VQ scan with positive compression ultrasonography or venography); 3) use objective imaging tests at follow up; 4) describe the duration and type of treatment of PE with a minimum administration of anticoagulant therapy of 6 weeks and no allowance of vena cava ligation, femoral ligation or pulmonary embolectomy; 5) identify whether there was a prior history of venous thromboembolism; 6) provide a description of the method of follow-up.

Data extraction

Two investigators independently assessed studies for inclusion according to the predefined methodological criteria. Investigator disagreements were resolved by majority opinion of a third investigator. Study authors were contacted as required to retrieve missing information.

Table 1
Excluded studies

Author (Ref)	Year	Diagnosis	N	Reason for exclusion	Time of FU scan	Follow up result
Sautter (16)	1964	PA	2	2,5	25 d, 128 d	100% normalisation
Fred (7)	1966	PA	7	1,2,5	7-19 d	6/7 normalisation
Poe (17)	1967	PA/VQ	20	2,3	7 d- 16 m	40% normalisation
Murphy (18)	1968	PA/VQ	25	2,3,5,6	1-20 w	60% normalization
Dalen (19)	1969	PA	15	2,5	1-34 d	3/15 normalisation
Paraskos (8)	1969	PA	43	1,5	1-7 y	65% normalisation
Mounts (20)	1969	PA	4	2,5	4 w – 3 m	0% normalisation
Sutton (9)	1969	PA/embolect	38	1,5	3-5 y (1-8)	45% normalisation
Tow (21)	1969	clinic/PA	69	2,3,5	4-120 d	48% normalisation
McDonald (22)	1970	PA	9	2	17-48 h	0% normalisation
Walker (10)	1970	VQ	74	1,2,3,5,6	3-277d	32.5% normalisation
Winebright (23)	1970	VQ	70	2,5,6	3m- 1y	27% normalisation
UPET (24)	1973	PA+VQ	105	2,5,6	1-14d, 3,6,12m	77% normalisation
Hall (11)	1977	PA/embolect	88	1,2,5	5 y (1-9 y)	42% normalisation
Fredin (25)	1982	VQ	23	2,4,5	10-14 d	Partial/compl norm. 22/23
Riedel (12)	1982	PA,VQ/+CUS	76	1,2,7	1-15 y	22/49 normalisation
Schwarz (26)	1985	PA	7	2	6 d + 15 m	6/7 normalisation
Palla (30)	1986	VQ	69	3	7,30,180 d	0% normalisation
Prediletto (27)	1990	VQ/PA	33	2	7, 30 d, 6 m	28% normalisation
Pacho (28)	1996	VQ	13	2,7	4 w, 5 m	18% normalisation
Nauffal (13)	1997	VQ/+VA	116	1,2	7,10 d, 6 m	28% normalisation
Otero (29)	1997	VQ, PA, VA	70	2,5,7	6 m	23% normalisation
Menendez (14)	1998	PA,VQ/+VA	96	1	7-10 d, 6 m	68% normalisation
Ribeiro (31)	1999	VQ	67	5	6 w, 1 y	34% normalisation
Gotthardt (15)	2002	VQ	129	1	0-10 y	70% normalisation

PA: pulmonary angiography; VQ: lung scintigraphy; VA: venography of the legs; CT: computed tomography; 1: retrospective study; 2: non-consecutive patients; 3:no objective diagnosis; 4: asymptomatic patients; 5: improper treatment (embolectomy or vena cava or femoral ligation or no treatment); 6: anticoagulant therapy < six weeks; 7: no description of history of VTE; h: hours; d:days, w: weeks; m: months; y: years

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Results

We identified 29 clinical studies. Of these, 25 were excluded because of 1) retrospective design[7-15]; 2) non-consecutive patients[7;10-13;16-29]; 3) lack of objective verification of the diagnosis[10;17;18;21;30]; 4) asymptomatic patients[25]; 5) treatment with inferior vena cava ligation or femoral ligation, embolectomy or no treatment in some patients[7-11;16;18-21;23-25;29;31]; 6) anticoagulant therapy for less than 6 weeks[10;18;23;24]; and 7) no description of history of VTE[12;28;29]. The excluded studies and reason for exclusion are listed in table 1. Four studies remained for inclusion in our review of rate of resolution of thrombi in patients with PE (table 2)[32-35]. Two studies used VQ lung scintigraphy as the follow up test and two studies used helical CT. The included studies differ not only in objective diagnostic tests used at follow up, but also in duration of follow up and duration of treatment. Therefore, we decided not to pool data statistically, but to describe the studies briefly.

Table 2
Included studies

Ref	Test at Diagnosis	Test at FU	n	History VTE	Therapy	FU scan	Follow up result
32	VQ	VQ	30	No	OAT 3 m	6 m	43% normalization
33	VQ	VQ	157	43	OAT 3 m	8 d, 3 m	13% d8, 35% 3 m normalization
34	PA/CT	CT	62	3	OAT ≥6 m/filter/FT	mean 10.5 m	48% normalization
35	PA/VQ	CT	19	No	OAT 6 w	6 w	32% normalization

PA: pulmonary angiography; VQ: ventilation/perfusion lung scintigraphy; CT: computed tomography; VA: venography of the legs; FU: follow up; FT: fibrinolytic therapy; OAT: (oral) anticoagulant therapy; d: days, w: weeks; m: months

Studies using VQ scintigraphy at follow up

Hvid-Jacobsen et al. re-examined 30 consecutive patients 6 months after diagnosis of PE[32]. All had repeat V/Q scans and chest X-rays and all had been treated for 3 months. Six months after diagnosis, 13 patients (43%) had normalized scans, 9 (30%) had minor defects, 6 (20%) had persistent defects and 2 had new defects. None of the patients had developed symptoms of recurrent PE. In this early study, the authors concluded that defects could not be assumed to have resolved 6 months after diagnosis of PE and that re-scanning after treatment should be done to obtain a new baseline. A limitation of this study is the 3-month time interval between cessation of anticoagulant treatment and follow-up scan. The time course of natural resolution of pulmonary thrombi with anticoagulant therapy in this study may be confounded by the asymptomatic recurrence of pulmonary embolism in the 3-month period without treatment.
Wartski et al.[33] included 157 patients from the THESEE study, a multicenter, randomized, comparison of continuous, adjusted-dose intravenous heparin versus once-daily, subcutaneous, low-molecular weight heparin followed by oral anticoagulants for 3 months in 612 patients with acute pulmonary embolism[33;36]. The results of THESEE showed both initial therapies to be equally effective. The 2 treatment groups did not significantly differ in age, sex, weight or percentage of vascular obstruction (PVO) and were therefore pooled. Of 157 patients at study entry, 145 had high-probability lung scans and 12 had intermediate lung scans with deep vein

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thrombosis confirmed by venography or compression ultrasonography. In all patients, routine follow-up perfusion lung scintigraphy was obtained after eight days and after three months. The degree of PVO was calculated for each scan by assigning a weight to each lobe, based on regional blood flow distribution, and subsequently estimating a quantitative score from 0 (no perfusion) to 1 (normal perfusion) on the basis of gamma count defects seen in each lobe. Lobar perfusion score was calculated by multiplying the assigned weight of each lobe by the perfusion score. The overall score is the sum of the six separate lobar scores (the lingula is counted as a separate lobe) and PVO (%) is calculated as follows: (1- total perfusion score) × 100%. Three months after diagnosis, fifty-three patients (34%) had normalized perfusion lung scans; 21 of these (13% of the total) had already normalized perfusion by day 8. Of the 157-patient cohort, 16 (10%) had no resolution of perfusion defects whatsoever after 3 months. An additional 28 (18%) of the total cohort had some improvement by day 8 but no further resolution by 3 months. These authors also concluded that follow-up scintigraphy serves as a new baseline for the diagnosis of recurrent PE[33]. Furthermore, they suggest that a follow-up scan may help to identify patients who are likely to progress to chronic thromboembolic pulmonary hypertension on the basis of extensive residual defects.

Studies using helical CT at follow up

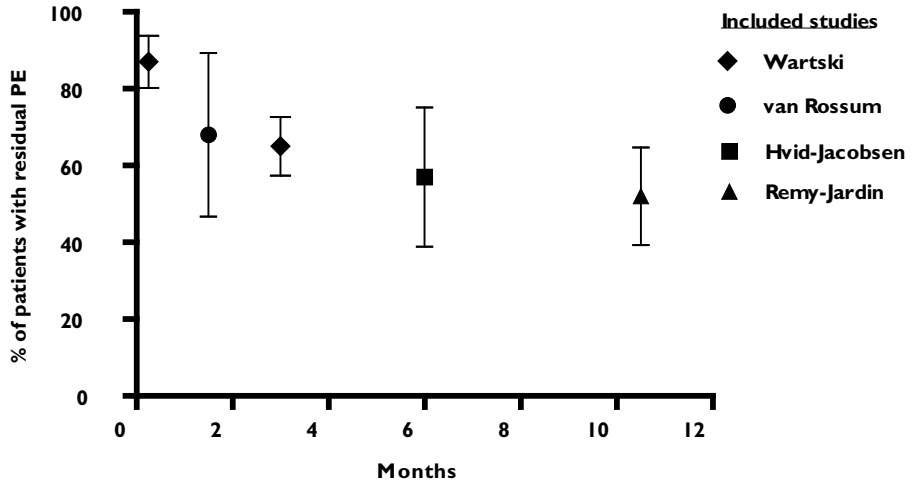
Remy-Jardin et al. were among the first to use helical CT as a follow-up test to evaluate the resolution of acute pulmonary embolism[34]. In 62 consecutive patients who had been referred to an intensive care unit with massive acute PE, a follow up CT scan was performed a mean of 11 months after onset to analyze the outcome of endoluminal clots after at least 6 months of anticoagulation therapy. The diagnosis of acute PE was made with pulmonary angiography (n=43) or helical CT (n=19). For 59 of the 62 patients, the massive acute PE was their first episode of thromboembolism; three of 62 had a history of chronic thrombo-embolic disease. Complete resolution of thrombi at a mean of 11 months (range, 1-53 months) was shown in 48% of patients and endovascular abnormalities were present in 52%[34]. Within this follow-up period there were no clinical episodes of recurrent PE. Follow-up scans were categorized as showing resolution of thrombi (group 1) or endovascular abnormalities (group 2). Group 1 patients showed no cardiopulmonary symptoms or echocardiographic abnormalities, while 6 of 32 (9,7% overall) group 2 patients had dyspnea on exertion and 5 group 2 patients (8,1% overall) had echocardiographic findings of pulmonary hypertension. Furthermore, group 2 patients were categorized into a) patients with partial resolution of initial thrombi (n=24) and b) patients with CT features of chronic PE, defined as severe arterial narrowing of more than 50% of the arterial diameter developing between the time of the initial diagnosis and the post-therapeutic follow-up. A striking finding was that 8 patients (13%) had CT signs of chronic PE over a median follow-up of 8.5 months (range 2-30 months) despite an anticoagulant course of at least six months and no symptomatic recurrences. The authors conclude that helical CT might help in understanding changes within central pulmonary arteries after massive acute PE, enabling not only the in vivo surveillance of organized and recanalized clots, but also of arterial narrowing (a sign of chronic PE) in asymptomatic patients.

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Van Rossum et al. described the helical CT appearance of clots 6 weeks after acute PE[35]. Clots on the initial and follow-up scan were divided into five categories; (1) central filling defect or complete occlusion (the established CT criteria for acute PE); (2) eccentric clot contiguous with the vessel wall at the site of acute PE on the initial scan; (3) filling defect with central contrast material indicating recanalization; (4) severe arterial luminal narrowing or vessel occlusion of a stenosed artery (the established criteria for chronic PE); and (5) normally enhancing vessels at follow-up indicating complete resolution of clots. At the initial CT scan, all patients (n=19) had type (1) clots, signs of acute PE. Normalization of pulmonary arteries at 6-week follow-up was seen in 6 patients (32%). Of the 13 (68%) patients with residual abnormalities, two patients still had solely type (1) clots. In the 11 remaining patients, most emboli had disappeared but some residual emboli were present as eccentric emboli contiguous with the vessel wall (22% of initial 153 clots) or filling defects with central contrast material (3% of initial 153 clots) representing recanalization (i.e., type 2 and 3 clots). In one of these patients, signs of chronic PE at the initial scan remained unchanged at follow-up. The authors of this study wondered whether existing CT criteria for chronic PE are as specific as assumed since this study showed that eccentric emboli contiguous with the vessel wall and evidence of recanalization are already present at six weeks follow-up in 22% and 3% of clots, respectively. No vascular narrowing or stenosis with occlusion was found, which may be more specific criteria for chronic PE.

Figure 1 summarizes our findings regarding the percentage of patients with residual thrombi in patients who presented with acute PE in the four studies described.

Figure 1
Residual thrombi in patients with PE



95% Confidence Intervals of the percentage of residual PE are depicted by the y error bars

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Discussion

This review shows that complete resolution of pulmonary thrombo-embolism is not routinely achieved between 8 days and 11 months after acute PE. Overall, more than 50% of patients with PE have persistent defects at their follow up scan six months after diagnosis (figure 1). Afterward, resolution of thrombi seems to reach a plateau phase since complete resolution is found in 43% of patients after six months and in nearly the same percentage of patients (48%) after eleven months. Of interest is the wide variation in resolution of thrombi in individual patients. Complete resolution of pulmonary thrombi was already present in 13% of patients 8 days after diagnosis of PE while in 10% of patients no change in thrombotic occlusion was seen after three months. The pathophysiological mechanisms of resolution of thrombi and the risk factors and clinical consequences of partial resolution remain largely unknown.

There are several methodological issues within the included studies in our review. First, the timing of follow-up was not standardized between the studies, varying from 8 days to 6 months. In the study of Remy-Jardin there was no pre-specified timing of follow-up and hence follow-up ranged from 1 to 53 months[34]. Similarly, the duration of anticoagulation therapy differed in length and in timing related to the follow up scan, varying from 6 weeks to more than 6 months. Also, there is no current standard technique for imaging resolution of PE. Two studies used VQ scintigraphy and two used CT as a follow up diagnostic method, but it is apparent that these two techniques are not interchangeable. Perfusion scintigraphy is a functional test but is reported to underestimate the presence of thromboembolic disease and also the severity of angiographic and hemodynamic compromise in CTPH[37;38]. Helical CT depicts the morphology of the pulmonary arteries but contains no information regarding pulmonary functional status. Moreover, no uniform criteria are used in defining chronic imaging defects, even when similar l imaging methods were used. Last, a confounding but unavoidable fact in prior or future studies is that for patients diagnosed with a first PE, it cannot be confidently ruled out that imaging defects were already present before the diagnosis since the majority of patients have no scan before their first thromboembolic event. With radionuclide scans, physicians cannot be certain, even with the aid of concomitant chest CT scans, that persistent defects represent residual thrombi rather than other defects responsible for decreased perfusion.

What are the implications of our findings for the future management of PE? First, physicians should be aware that complete resolution of pulmonary thrombi is not achieved in more than 50% of patients six months after diagnosis of PE and that this fact may complicate the objective and accurate diagnosis of recurrent pulmonary embolism. Second, an attempt should be made to generate an international consensus among physicians caring for PE patients, including radiologists and nuclear medicine physicians, regarding the optimal way of imaging, interpreting and reporting of resolution of pulmonary emboli and diagnosing chronic PE. Third, routine re-imaging after cessation of anticoagulant

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treatment in patients with PE to obtain a new baseline could be considered[39]. Finally, in patients with persisting thrombo-embolic obstruction or with persisting cardiopulmonary complaints, one should be alert for chronic PE and the development of chronic thromboembolic pulmonary hypertension[6].

In conclusion, resolution of pulmonary thrombi is not routinely achieved after an acute PE. The pathophysiologic mechanisms, risk factors and clinical implications of incomplete resolution are not well established. There is a clear need for prospective well-designed follow-up studies to more accurately define the resolution rate after documented PE and related prognostic factors.

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Diagnosing pulmonary embolism in pregnancy: Rationalising fetal radiation exposure in radiological procedures

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In pregnancy, the diagnosis of pulmonary embolism (PE) is problematic. There is doubt as to whether objective diagnostic tests are needed and confusion as to what objective test is the safest with respect to fetal radiation exposure. A recent study has reported a very low (1·8%) prevalence of high-probability ventilation-perfusion (VQ) lung scans in pregnant women suspected of PE.[1] From this study it is apparent that the clinical diagnosis of PE is inaccurate and therefore objective diagnostic tests are mandatory, in order to avoid treatment of women that do not have PE.

Currently, helical computerised tomography (CT) and VQ scintigraphy are the most common diagnostic tests used in non-pregnant patients with suspected PE. Physicians are reluctant to perform helical CT in pregnant women because of potential adverse effects of radiation exposure to the fetus. VQ scintigraphy has been assumed to be associated with less radiation exposure than helical CT. To compare the relative amounts of radiation exposure to the fetus, we calculated fetal radiation exposure when single- and multi-detector row helical CT and VQ scintigraphy were performed using our local hospital protocols. Further, we compared our data with data of the literature.

Since there are no established methods for calculating fetal radiation exposure in diagnostic radiological procedures, we used a pragmatic approach. The amount of radiation absorbed by the fetus was assumed to be equal to that absorbed by the uterus of a non-pregnant woman. Assessment of the uterus dose was achieved by measurement of the computed tomography dose index and the application of organ dose conversion factors.[2] The following CT protocols were used for fetal dose assessment: 120kV, 250 mAs, slice thickness 3 mm and pitch factor 1·7 for single-detector row helical CT (Philips AVE) and 120 kV, 85 mAs, slice thickness 16 × 0·5 mm and pitch factor 1·4 for multi-detector row helical CT (Toshiba Aquilion 16). The scanned range extends from the dorsal lung sinus to the top of the lung. Since fetal radiation exposure was calculated, physical measures (eg. abdominal shielding with lead) to reduce radiation exposure were not taken into account.

For the perfusion scintigraphy protocol we used 40 MBq of Technetium-labelled albumin aggregates. In our institution, ventilation scintigraphy is performed with Krypton-81m, which is inhaled for two minutes per image. The Rubidium-Krypton generator generates 450-750 MBq per minute.

Our calculated data of CT radiation exposure were compared with doses in nuclear medicine and doses calculated by the International Commission on Radiological Protection (ICRP) and the National Radiological Protection Board (NRPB) of the UK.[3,4]

The calculated dose of radiation absorbed by the fetus for a single-detector row helical CT was 0·026 mSv. An even lower dose (0·013 mSv) was calculated for the multi-detector row helical CT. In comparison, the calculated dose of fetal radiation with perfusion scintigraphy was 0·11-0·20 mSv. In comparison with doses given by the ICRP and NRPB (table 1), our calculated doses of helical CT were low.

Our study suggests that performing a helical CT according to our local protocol, whether single- or multi-detector row, exposes the fetus to less radiation than perfusion

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scintigraphy. Our findings are clearly contradictive to the general idea that helical CT is more hazardous to the fetus than perfusion scintigraphy.

Table 1
Radiation dose to the fetus by radiological examination

	LUMC(mSv)	ICRP(mSv)	NRPB(mSv)
Single-detector row helical CT	0·026	0·06	0·06
Multi-detector row helical CT	0·013	n.d.	n.d.
Perfusion scintigraphy(99mTc MAA, 200 MBq)	n.a.	0·4-0·6	0·2-0·4
Perfusion scintigraphy (99mTc MAA, 40 MBq)	0·11-0·20	n.d.	n.d.
Ventilation scintigraphy (99mTc aerosol)	n.a.	0·1-0·3	0·3-1·2
Ventilation scintigraphy (81mKr, 600MBq)	0·0001	n.d.	n.d.

n.a.= not applicable, n.d.= not determined
LUMC= University Medical Centre Leiden
ICRP= International Commission on Radiological Protection
NRPB= National Radiological Protection Board

Regarding the generalizability of our data, it is apparent that our calculated fetal radiation dose for CT is well within the range of that found by others. It has been documented that radiation exposure to the patient for a given radiological procedure can vary considerably between different institutions and even within the same institution. There are several factors that affect radiation dose from CT, e.g. (beam energy, tube-current time product, pitch, collimation, patient size and dose reduction options). Each institution should therefore carefully scrutinize its protocol for performing helical CT and define the optimal balance between minimal patient radiation exposure and maximal diagnostic CT image quality.
Calculating patient radiation exposure with a computerized model beholds accepting certain assumptions, which possibly differ from an exact measurement. An exact measurement is however, impossible to perform, both in helical CT as well as in scintigraphy. Due to lack of more appropriate measurements it is commonly assumed that radiation dose to the uterus is a good approximation of the radiation dose to the fetus in early pregnancy. This period of early pregnancy is the most important period, since the fetus is considered to be most vulnerable to radiation effects in the period of organogenesis (in the 3rd until the 15th week). The main issue following in-utero exposure at typical diagnostic levels is induction of malignancies. The number of excess malignancy cases up to age 15 years following irradiation in utero is considered to be 1 in 16000 per mSv.[5]

We conclude that when a clinical suspicion of pulmonary embolism is raised in a pregnant patient, only objective diagnostic testing can rule out the disease. Our calculation of fetal radiation dose in helical CT justifies performing this objective diagnostic method as a first line test in pregnancy. It is hoped that increased awareness of the risks and benefits of imaging in pregnant patients suspected of pulmonary embolism will result in a more rational management to this patient group.

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Diagnosis of deep vein thrombosis and pulmonary embolism in pregnancy; a systematic review

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J Thromb & Haemost 2006; 4: 496-500



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Abstract

Introduction

Diagnosing deep vein thrombosis (DVT) and pulmonary embolism (PE) in pregnancy is challenging. Many of the common diagnostic tests, including compression ultrasonography (CUS), ventilation-perfusion scintigraphy (VQ scan) and helical computed tomography (hCT) that have been extensively investigated in non-pregnant patients, have not been appropriately validated in pregnancy. Extrapolating results of diagnostic studies of DVT and PE in non-pregnant patients to those who are pregnant may not be correct because during pregnancy, physiologic and anatomic changes may affect diagnostic test results, presentation and natural history of VTE.

Methods

We performed a systematic analysis of published studies addressing accurate diagnostic testing for DVT and PE in pregnancy to determine the accuracy of these tests in pregnancy.

Results

Our initial search yielded 530 articles of which four remained for inclusion, three studies investigating diagnostic testing in patients with a clinical suspicion of DVT and one study in patients with a clinical suspicion of PE.

Conclusions

From our systematic analysis of published studies investigating diagnostic testing for a clinical suspicion of DVT or PE in pregnancy we conclude that; 1) two studies support withholding anticoagulant therapy in pregnant women with a clinical suspicion of DVT and normal results on serial IPG (impedance plethysmography), however, IPG is no longer used; 2) one study demonstrated that a normal CUS at presentation combined with a normal D-dimer test or an abnormal D-dimer test combined with normal serial CUS appears promising for safely excluding DVT in pregnant patients, but too few patients were included in this pilot-study to draw firm conclusions; and 3) one study investigated pregnant patients with a clinical suspicion of PE and this study concluded that in patients with normal or non-diagnostic VQ scans, withholding anticoagulant therapy might be safe, but this needs confirmation in larger studies. Recommendations on diagnostic testing of pregnant patients with a clinically suspected DVT or PE are provided.

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Introduction

Diagnosing deep vein thrombosis (DVT) or pulmonary embolism (PE) in pregnancy presents challenges to clinicians. Non-thrombotic leg or respiratory symptoms are commonly experienced in pregnancy and are often clinically indistinguishable from those found in patients with DVT and PE. Hence, the clinical diagnosis is inaccurate and accurate diagnostic testing is essential to exclude or diagnose venous thromboembolism (VTE). However, many of the common diagnostic tests including compression ultrasonography (CUS), ventilation-perfusion scintigraphy (VQ scan) and helical computed tomography (hCT), that have been extensively investigated in non-pregnant patients, have not been appropriately validated in pregnancy. Extrapolating results of diagnostic studies of DVT and PE in non-pregnant patients to those who are pregnant may not be correct because of physiologic changes during pregnancy and the possibility of differences in pathophysiology and presentation of VTE in pregnancy. Also, studies of non-pregnant patients invariably report on subjects who are, on average, older and are more likely to have co-morbid cardio-respiratory conditions that can result in an abnormal VQ scans.
The purpose of this review is to establish the evidence concerning the accuracy of diagnostic tests performed for a clinical suspicion of PE and DVT during pregnancy. Therefore, we undertook a systematic analysis of published studies addressing diagnostic testing for DVT and PE in pregnancy. Further, recommendations for diagnostic testing are made for clinicians when they evaluate pregnant patients with clinically suspected DVT or PE.

Methods

Search strategy

We used electronic search strategies to identify relevant studies. The following electronic databases were searched: PubMed (1966 to November 2004), EMBASE (1980-nov 2004), Cochrane, the Library Issue 1, 2005 and Web of Science using the search terms *pregnancy, gestational period, pulmonary embolism, venous thrombosis, deep vein thrombosis, radiological tests, diagnosis, pulmonary angiography, helical or spiral computed tomography, ventilation-perfusion lung scintigraphy, magnetic resonance imaging, compression ultrasound, impedance plethysmography* and *venography*. We augmented our search by reviewing the reference lists of retrieved articles. Studies published in any language were used.

Study selection

We attempted to identify all published clinical studies that evaluated pregnant patients with a clinical suspicion of deep vein thrombosis or pulmonary embolism. Of potentially eligible articles, abstracts were read to determine eligibility and in case of doubt, full-text articles were retrieved. To be included, a study had to 1) involve consecutive pregnant patients with a clinical suspicion of DVT or PE; 2) use validated diagnostic tests to diagnose DVT (CUS or impedance plethysmography (IPG) or venography for a suspicion of DVT or magnetic

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resonance imaging for a suspicion of iliac vein thrombosis) and PE (pulmonary angiography or hCT, or VQ lung scanning); 3) use validated diagnostic testing in patients with suspected VTE in follow up; 4) describe a pre-specified duration of follow-up of patients with negative tests; and 5) withhold anticoagulant treatment in patients with negative tests.

Data extraction

Two investigators independently assessed studies for inclusion according to the predefined methodological criteria. Investigator disagreements were resolved by majority opinion of a third investigator.

Results

Our initial search identified 530 articles, of which 14 were potentially eligible for analysis[1-14]. According to the predefined inclusion criteria, 10 of the 14 studies were excluded (Table 1). Reasons for exclusion were: consecutive patients were not evaluated[5;6;10], only patients with confirmed instead of suspected DVT were included [1;2;7;8], objective testing was not performed in all patients[2;10] and no pre-specified duration of follow-up of patients with negative tests was stated [2-6;9;10]. Therefore, four studies were included in the primary analysis, three studies investigating diagnostic testing in patients with a clinical suspicion of DVT and one study investigating diagnostic testing in patients with a clinical suspicion of PE[11-14]. As there were so few studies, each study is briefly discussed.

Table 1
Excluded studies

Ref	Test(s) used	Patients	Nr of patients	no DVT/PE	Duration of follow-up and nr. of events in patients with normal tests
(1)	Venography, plethysmography, thermography	Confirmed DVT	17	0	not applicable
(2)	Clinical diagnosis	Suspicion of DVT	13	?	not described
	Venography, plethysmography	Confirmed DVT	30	0	not applicable
(3)	Venography	Suspicion of DVT	29	17	not described
(4)	CUS	Suspicion of DVT	28	21	not described
(5)	Doppler US	Suspicion of VTE	58	4	not described
(6)	Venography + color Doppler ultrasound	Suspicion of VTE	59	9	not described
(7)	Duplex, Venography or autopsy	Confirmed DVT or PE	32	0	not described
(8)	Doppler, IPG, venography, CT/MRI, VQ, PA	Confirmed DVT or PE	165	0	not described
(9)	MRI	Suspicion of Iliac thrombosis	10	7	not described, no VTE
(10)	VQ scintigraphy	Suspicion of PE	82	64	median 25 months (range 3-60 months), 2 events with IP VQ scan

CUS: Compression UltraSound, DVT: Deep Vein Thrombosis, IP: intermediate probability, IPG: Impedance Plethysmography, MRI: Magnetic Resonance Imaging, PE: Pulmonary Embolism, US: UltraSound, VQ: (ventilation) perfusion lung scintigraphy, VTE: Venous Thrombo-Embolism

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Studies investigating diagnostic testing for a clinical suspicion of DVT in pregnancy

Two studies evaluated the clinical validity of negative results by serial IPG in pregnant patients with a clinical suspicion of DVT[11;12]. In the study of Hull et al, patients had serial testing on the day of presentation and days 3, 5 or 7, 10 and 14 when IPG remained normal[12]. Of 152 patients, 139 had normal results on serial IPG and none had VTE during follow-up (3 months postpartum, 0%; 95% confidence interval (CI), 0-2.6%). In the second study, of 77 obstetric patients (47 pregnant, 30 postpartum) with suspected DVT, 45 had normal serial IPG and none had VTE during a 6-month follow-up period (0%; 95%CI, 0-6%)[11].

One pilot study evaluated CUS in the diagnosis of DVT in pregnancy[13]. Two hypotheses were tested: 1) a normal CUS on the day of presentation combined with a normal SimpliRed D-dimer (SRDD) test and 2) an abnormal SRDD at presentation but with normal serial CUS would both reliably exclude DVT in symptomatic pregnant women. Based on the initial CUS and SRDD result, women were categorized into one of four groups and managed accordingly; 1) CUS normal, SRDD normal; clinical follow up until 6 weeks postpartum; 2) CUS normal, SRDD abnormal; CUS was repeated 3 and 7 days later and those with normal serial CUS were followed until 6 weeks postpartum; 3) CUS equivocal; venography was performed; 4) CUS positive; DVT was diagnosed. Of 53 included patients, 7 were diagnosed with DVT (13%, 95%CI: 5.5-25.3%). Group 1 comprised 31 patients and none of them developed objectively diagnosed VTE during follow-up (0%, 95%CI: 0-9.2%). Four of the 18 women in group 2 were diagnosed with DVT on serial CUS and of the remaining 14 patients, none developed VTE during follow-up (0%, 95%CI: 0.7-26.8%). The authors conclude that a normal CUS at presentation combined with a normal SRDD or an abnormal SRDD combined with normal serial CUS appears to safely exclude DVT in pregnant patients, but larger confirmatory studies are needed.

Based upon the results of our systematic review of published studies investigating diagnostic testing for a clinical suspicion of DVT, there is clearly a huge need for large prospective studies evaluating currently available and new tests for the diagnosis of DVT in pregnant women. Unfortunately, 2 of 3 studies involved evaluation of IPG, a test that is no longer performed. The use of CUS with or without D-dimer testing merits further evaluation.

Studies investigating diagnostic testing for a clinical suspicion of PE in pregnancy

Chan et al. retrospectively studied the distribution of lung scan results and safety of withholding anticoagulation therapy following a normal or non-diagnostic scan in pregnant women[14]. Eight of 121 cases (6.6%) were already receiving treatment for venous thromboembolism prior to VQ scanning. In the remaining 113, 83 (73.5%) scans were interpreted as normal, 28 (24.8%) as non-diagnostic and 2 (1.8%) as high probability. In the 104 women who did not receive anticoagulation therapy following lung scanning (80

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normal and 24 non-diagnostic), no venous thromboembolic events were reported during a mean follow-up period of over 20 months (0%, 95%CI: 0.0-1.0%). The authors conclude that the prevalence of high-probability VQ scans in pregnant women with suspected PE is very low. Withholding anticoagulation in pregnant women with normal perfusion scans is safe. Unfortunately, the small number of patients with non-diagnostic VQ scans and the fact that in non-pregnant patients, as many as 25% of patients with such scans have PE, do not allow us to conclude that PE can be excluded in a pregnant women with a non-diagnostic scan. Large prospective studies are needed to evaluate diagnostic strategies for pregnant women with suspected PE.

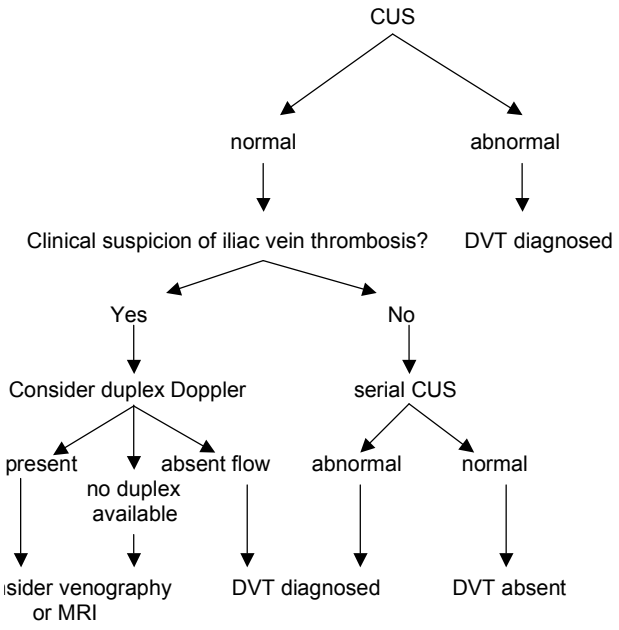
Based on the results of our systematic analysis of studies investigating diagnostic tests for a clinical suspicion of DVT or PE in pregnancy, there is dire need for properly designed studies of pregnant women with suspected DVT or PE. Consequently, the following recommendations for clinical practice regarding the diagnostic approach of a pregnant patient with a clinical suspicion of DVT or PE are partly driven by the personal opinion of the authors.

Recommended diagnostic testing of a clinical suspicion of deep vein thrombosis in a pregnant patient

Although there are no large, prospective studies evaluating CUS in pregnant patients for a clinical suspicion of DVT, there is no biologic reason why a clearly abnormal CUS wouldn't make a firm diagnosis of DVT. Therefore, compression ultrasonography should be performed as a first test in a pregnant patient with a clinical suspicion of DVT (Figure 1). Patients with an abnormal CUS, defined as a non-compressible segment of the popliteal or a more proximal vein can be diagnosed with DVT and should be treated appropriately with unfractionated or low molecular weight heparin. However, a normal CUS might not be as safe reassuring in non-pregnant patients since isolated iliac DVT is thought to be more common in pregnant than in non-pregnant patients and such thrombi are difficult to detect by CUS. Patients with a normal CUS should undergo serial CUS testing after day 6-8, or sooner – days 2 to 3 - when clinical suspicion is strong, to detect proximal extension of distal thrombi. If CUS becomes abnormal, DVT can be diagnosed. If doubt about the presence of DVT persists, limited venography with abdominal shielding should be considered. The amount of fetal radiation exposure with venography and abdominal shielding is less than 0.5 mSv (Table 2)[15]. This amount is much lower than the threshold dose for induction of malignancies (100 mSv) and justifies the use of diagnostic testing involving radiation in pregnancy for the exclusion of potentially fatal VTE[16;17]. If iliac or pelvic vein thrombosis is suspected, duplex Doppler ultrasound or full venography can be performed. In centres with availability of, and experience with MRI, MR venography is a reasonable alternative test to venography in demonstrating iliac or pelvic vein thrombosis. However, the safety of excluding DVT when MR venography is normal has not been demonstrated. The roles of pre-test probability assessment and D-dimer testing in the diagnosis of suspected DVT in pregnancy have yet to be defined.

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Figure 1
Algorithm for a clinical suspicion of DVT in pregnancy



DVT: Deep Vein Thrombosis, CUS: Compression UltraSonography, MRI: Magnetic Resonance Imaging

Table 2
Radiation dose to the fetus by radiological examination

Diagnostic test	Radiation (mSv)
Unilateral venography without shielding	3.14
Unilateral venography with shielding	< 0.5
Pulmonary angiography via femoral route	2.21-3.74
Pulmonary angiography via brachial route	< 0.5
Perfusion scintigraphy(99mTc MAA, 200 MBq)	0.2-0.6
Perfusion scintigraphy (99mTc MAA, 40 MBq)	0·11-0·20
Ventilation scintigraphy (99mTc aerosol)	0.1-0.3
Ventilation scintigraphy (81mKr, 600MBq)	0·0001
Single-detector row helical CT	0·026
Multi-detector row helical CT	0·013

Estimates of radiation exposure are derived from McMaster University and University Medical Centre Leiden(15,17)
To convert mSv to rads: 1 mSv ~ 0,1 rad.

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Recommended diagnostic testing of a clinical suspicion of pulmonary embolism in a pregnant patient

High quality evidence from prospective studies of the safety of ruling out PE by VQ scintigraphy or CT scan is lacking. Although there are no strong reasons to believe that VQ scintigraphy and CT scan results should be interpreted differently in pregnant compared to non-pregnant patients, there is a theoretical possibility of compression of the lung bases by the uterus in late pregnancy that may result in an abnormal VQ scan, the evidence of which however is lacking. Therefore, when confronted with a clinical suspicion of PE in a pregnant patient, one should start with VQ scan, a helical CT, or bilateral CUS, depending on local availability and expertise (Figure 2). Helical CT has the advantage of low fetal radiation exposure (Table 2), a low number of non-diagnostic results and the ability to make an alternative diagnosis that can explain the patient's complaints. The visualisation of an arterial filling defect is diagnostic for PE. The safety of using helical CT as a stand-alone test has been argued[18]. Two studies have shown DVT on CUS in 6 to 8% of (non-pregnant) patients with a suspicion of PE despite a negative helical CT[19;20]. These results contrast with another study in which CUS revealed DVT in only 2 of 378 (0.5%) patients with no PE on helical CT[21]. This discrepancy might be explained by the timing of CUS; in the first two studies CUS was performed before or concomitant with helical CT while in the latter study, CUS was performed after helical CT revealed no PE.

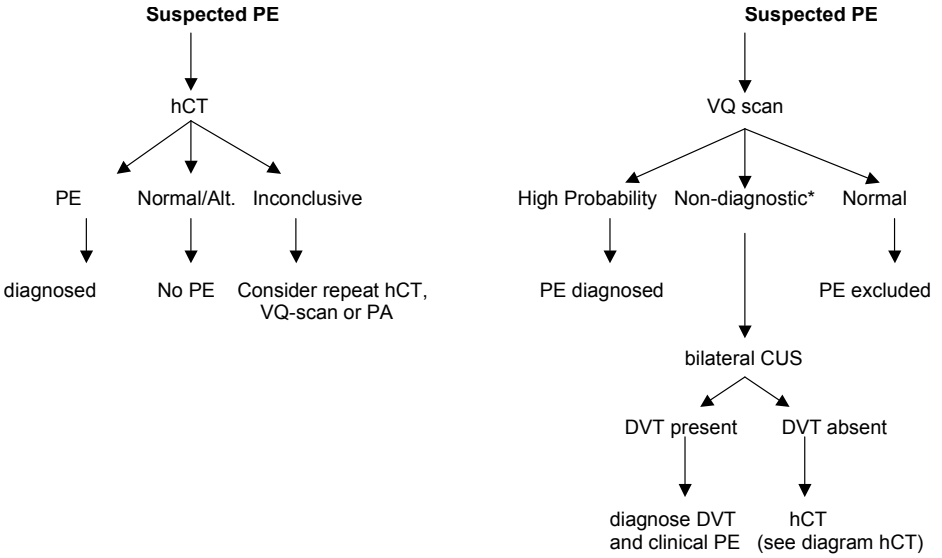
Ventilation-perfusion scintigraphy is to be considered a first line diagnostic test and rules out the diagnosis of PE when the result of the perfusion scan is normal. When a high probability scan is obtained, the diagnosis of PE can be considered confirmed. All other abnormal VQ-scan results are non-diagnostic and the diagnosis of PE needs to be confirmed or excluded by additional testing with a hCT scan or alternatively shielded pulmonary angiography. Ultrasonography can be used as a first line test to demonstrate DVT or as an additional test when VQ scanning is non-diagnostic. When CUS demonstrates DVT, further testing is not necessary and the patient can be considered to have a VTE. A normal CUS is always to be followed by additional tests to rule out PE. The roles of pre-test probability assessment and D-dimer testing in the diagnosis of suspected PE in pregnancy have yet to be defined.

Future perspectives

Although guidelines can be given for objective DVT and PE diagnosis in pregnant patients, there is a clear need for prospective studies. Two large prospective management studies in the diagnosis of pulmonary embolism in pregnancy have been started recently. In the first study in Canada a decision tree with clinical risk factors, CUS and VQ-scanning is being evaluated. In another study in the Netherlands helical CT as a first line and sole test for the diagnosis of PE is evaluated by studying the safety of withholding anticoagulants in pregnant women with clinically suspected PE and a normal CT-scan.

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Figure 2
Algorithms for a clinical suspicion of PE in pregnancy



PE: Pulmonary Embolism, hCT: helical Computed Tomography, VQ scan: VentilationPerfusion scan, PA: Pulmonary Angiography, CUS: Compression UltraSonography, DVT: Deep Vein Thrombosis, *Non-diagnostic= no high-probability and no normal result on VQ scan.

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11

Summary and Conclusions



Overview of Bologna, Italy

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Pulmonary embolism is a potentially fatal disease in which early recognition and institution of anticoagulant treatment can prevent mortality. The diagnostic tools available to establish whether a patient has a pulmonary embolism were limited to pulmonary angiography and ventilation-perfusion scintigraphy. Both tests have considerable limitations. Helical CT evolved as a new technique in diagnosing PE and gained widespread interest but has been implemented rapidly, without appropriate assessment in clinical practice. Two accuracy studies, comparing helical CT to the golden standard pulmonary angiography, showed a disappointing sensitivity of only 70%, but management studies showed a 3-month thrombo-embolic failure rate (the risk of developing DVT or PE despite negative tests) of less than 2% after a negative helical CT combined with other techniques. These diagnostic algorithms were usually complicated and therefore not easily implemented in clinical practice.

The Christopher-study was performed to investigate whether a dichotomization of the Wells clinical decision rule, classifying patients into 'PE unlikely' and 'PE likely' in combination with a D-dimer test is safe to rule out pulmonary embolism in patients with a clinical suspicion. Furthermore, the study was designed to investigate whether helical CT is safe to rule out PE without performing any additional diagnostic tests.
In **Chapter 3**, the results of this prospective management-study are described in 3306 consecutive patients suspected of PE. The Wells clinical decision rule classified patients as 'PE unlikely' in 2206 (66.7%) of patients. These patients underwent D-dimer testing and 1057 (32.0%) had a negative D-dimer result (≤500 ng/ml). PE was considered excluded in these patients. All other patients, i.e. those classified as 'PE likely' or those classified as 'PE unlikely' but with an abnormal D-dimer test, underwent helical CT. PE was diagnosed in 674 (20.4%) patients and these were consequently treated with anticoagulants. In 1505 patients (45.5%), CT excluded PE. In 50 patients (1.5%) the protocol was violated and CT was not performed and in 20 (0.9%) patients the CT was inconclusive. Hence, the diagnostic algorithm could be completed according to the protocol in 3256 (98.5%) patients and allowed a management decision in 3236 patients (97.9%). In patients in whom PE was excluded by a clinical decision rule indicating 'PE unlikely' combined with a negative D-dimer and were not treated with anticoagulants, during three months of follow-up venous thrombo-embolism was diagnosed in 5 out of 1028 untreated patients (0.5%, 95%CI: 0.2-1.1). In patients in whom CT had ruled out PE and were not treated with anticoagulants during three months follow-up 18 of 1446 untreated patients experienced a venous thrombo-embolic event (1.3%, 95%CI: 0.7-2.0). In conclusion, the Christopher-study demonstrates that a simple diagnostic algorithm consisting of a dichotomised clinical decision rule, D-dimer and helical CT can guide treatment decisions with a low risk of subsequent venous thrombo-embolism.

Chapter 4 discusses whether varying the cut-off level of the clinical decision rule as well as the cut-off level of the D-dimer test could lead to an increase in clinical utility (i.e. the proportion of patients in whom the diagnosis of PE can be safely excluded without additional imaging tests) without jeopardizing safety. For each increment of clinical decision rule and D-dimer

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cut-off point, the number of patients with PE at baseline or during follow-up, the clinical utility and the 3-month thrombo-embolic failure rate were recalculated. By increasing the cut-off level of the clinical decision rule from 4 to 5 points, pulmonary embolism could be ruled out in an additional 4% of the study population (from 29.3 to 33.3%) at an expense of an increased three-month thrombo-embolic failure rate of 1.5% (95%CI: 0.6-3.0%) in comparison to 0.9% (95%CI: 0.3-2.4) for patients who had a clinical decision rule cut off at 4 points. By increasing the D-dimer cut-off level from 500 to 600 ng/ml, PE could be ruled out in an additional 3% (from 29.3% to 32.3%) of the study population but the three-month thrombo-embolic failure rate increased 0.9 (95%CI: 0.3-2.4) to 2.2% (95%CI: 1.1-4.0). This sub-study concluded that at the prevalence of 29.3%, the cut-off level of the clinical decision rule as well as the cut-off level of the D-dimer test should be kept at the original 4 points and 500 ng/ml respectively, in order to prevent exposure of patients to a 3-month thrombo-embolic failure rate exceeding that of a normal pulmonary angiography.

The anatomic distribution of pulmonary embolism in central, segmental and sub-segmental arteries is understudied and an often-debated issue is the possible limitation of computed tomography to accurately detect peripheral emboli. Multi-detector row CT is thought to increase the detection rate of sub-segmental emboli compared to single-detector row CT. In **Chapter 5**, we evaluate the prevalence and anatomic distribution of PE in consecutive patients with proven PE diagnosed by MDCT or SDCT. The location of PE was classified into three groups (central, segmental and sub-segmental PE) with emphasis on the largest pulmonary arterial branch involved. A total of 3306 consecutive patients were included in the diagnostic study, of whom 674 (20%) were diagnosed with PE. Data regarding the localisation of PE were missing in 41 patients. Localisation of PE in MDCT was central in 160 patients (29%, 95%CI: 25-33), segmental in 293 patients (53%, 95%CI: 49-57) and sub-segmental in 98 patients (18%, 95%CI: 15-21). In patients diagnosed with SDCT, PE was central in 31 patients (38%, 95%CI: 27-49), segmental in 39 patients (48%, 95%CI: 36-59) and sub-segmental in 12 patients (15%, 95%CI: 8-24). The percentage of detected PE did not differ significantly between MDCT and SDCT (31% vs. 32%, p=0.65), neither the percentage of sub-segmental PE (18% vs. 15%, p=0.48) detected by MDCT or SDCT. In conclusion, based on these data there seems to be no danger of over-diagnosis of small subsegmental PE using multi-detector row systems.

In **Chapter 6**, the natural course of patients diagnosed with PE is described in terms of incidence of recurrent venous thrombo-embolism, bleeding and mortality. Moreover, risk factors for these events were identified as well as the time course of these events. Of 673 patients with complete follow-up, 20 patients (3.0%, 95%CI: 1.8-4.6) had recurrent VTE. Eleven of 14 patients with recurrent PE had a fatal PE (79%, 95%CI: 49-95%), occurring mostly in the first week after diagnosis of initial PE. In 23 patients (3.4%, 95%CI: 2.2-5.1) a hemorrhagic complication occurred of whom 10 were major bleeds (1.5%, 95%CI: 0.7-2.7) and two were fatal (0.3%, 95%CI: 0.04-1.1). During the three-month follow-up, 55 patients died (8.2%, 95%CI: 6.2-10.5). Risk factors for recurrent VTE were immobilisation for more

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than 3 days, while being an inpatient, having COPD or malignancies were risk factors for bleeding. Age, immobilisation, malignancy and being an inpatient were risk factors for mortality. In conclusion, recurrent VTE occurred despite anticoagulant therapy in 3 % of patients with PE and the majority of recurrent PE's (79%) were fatal. Also, patients with PE have a high mortality rate, 8.2% during three months of follow-up. Immobilization, hospitalization, age, COPD and malignancies were risk factors for complications of PE. Close monitoring may be indicated in these patients, precluding them from out of hospital start of treatment.

It is unknown whether strategies validated for diagnosing pulmonary embolism are valid in patients with a history of PE. **Chapter 7** describes whether the Christopher-algorithm, consisting of sequential application of a clinical decision rule (CDR), a quantitative D-dimer test and helical computed tomography, could safely rule out a clinical suspicion of recurrent PE. All patients of the Christopher-study who had a history of PE were included in this sub-study. Recurrent PE was ruled out by an unlikely probability of PE (CDR score ≤ 4 points) combined with a normal D-dimer test (≤500 ng/ml) or by a normal CT in all other patients. The primary outcome was the incidence of recurrent venous thrombo-embolism during three months of follow-up in patients with normal tests and not treated with anticoagulants. Of 3306 patients suspected of PE, 259 patients (7.8%) had a history of PE. Of these, 25 (9.7%) were treated with anticoagulants and excluded. The probability of PE was unlikely in 82 of 234 patients (35%) and 42 had a normal D-dimer test (18%), excluding recurrent PE. None of these patients had a venous thrombotic event during follow-up (0%, 95%CI: 0-6.9). A CT was indicated in all other patients (n=192) and ruled out recurrent PE in 127 patients (54%). One patient had a fatal recurrent PE during follow-up (0.8%; 95%CI: 0.02-4.3). This is the first prospective study that demonstrated the safety of ruling out a clinical suspicion of recurrent PE by a simple diagnostic algorithm in patients with a history of PE.

Much attention has been paid in recent years to optimizing the diagnosis of acute pulmonary embolism. However, little is known about the changes in clot burden that occur at the level of the pulmonary arteries after documented PE. It is often problematic to distinguish between a new or residual defect on lung scintigraphy or helical computed tomography. This may lead to falsely labeling patients with residual PE as having recurrent PE and consequent unnecessary treatment changes.
In **Chapter 8** a systematic analysis is shown of studies of imaging tests (radionuclide and computerized tomography) evaluating resolution rate of PE with independent assessment of predefined methodological criteria by two investigators. We identified 29 clinical studies. Of these, 25 were excluded and 4 studies were included in our review.. The percentage of patients with residual pulmonary thrombi was 87% at eight days after diagnosis, 68% after six weeks, 65% after three months, 57% after six months and 52% after 11 months. No definite conclusions can be made on the resolution of PE beyond 11 months after diagnosis.

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This review shows that complete resolution of PE is not routinely achieved between 8 days and 11 months after diagnosis. More than 50% of patients with PE still have defects six months after diagnosis, after which resolution of thrombi appears to reach a plateau phase.

In pregnancy, the diagnosis of pulmonary embolism is problematic. There is doubt as to whether objective diagnostic tests are needed and confusion as to what objective test is the safest with respect to fetal radiation exposure. However, pulmonary embolism is still one of the leading causes of maternal mortality and it is critically important to objectively diagnose pulmonary embolism since a clinical diagnosis is notoriously inaccurate. However, physicians are reluctant to perform helical CT in pregnant women because it is assumed that helical CT exposes the fetus to a higher radiation dose than VQ scintigraphy. In **Chapter 9** we describe the results of a calculation of fetal radiation dose by helical CT and compare these to VQ scintigraphy. Our calculation of fetal radiation dose in helical CT was based on the assumption that radiation dose to the uterus is a good approximation of the radiation dose to the fetus in early pregnancy. This early period is the most important period since the fetus is considered to be most vulnerable to radiation exposure. The calculated dose of radiation absorbed by the fetus for a single-detector row helical CT was 0·026 mSv. An even lower dose (0·013 mSv) was calculated for the multi-detector row helical CT. In comparison, the calculated dose of fetal radiation with perfusion scintigraphy was 0·11-0·20 mSv.

Diagnosing deep vein thrombosis and pulmonary embolism in pregnancy is challenging. Many of the common diagnostic tests, including compression ultrasonography (CUS), ventilation-perfusion scintigraphy and helical computed tomography that have been extensively investigated in non-pregnant patients, have not been appropriately validated in pregnancy. Extrapolating results of diagnostic studies of DVT and PE in non-pregnant patients to those who are pregnant may not be correct because of differences in pathophysiology and presentation of DVT and PE in pregnancy. In **Chapter 10** a systematic analysis is shown of published studies addressing diagnostic testing for DVT and PE in pregnancy to determine the accuracy of these tests in pregnancy. According to our predefined inclusion criteria, only four studies remained for inclusion, three studies investigating diagnostic testing in patients with a clinical suspicion of DVT and one study in patients with a clinical suspicion of PE. From our systematic analysis of published studies investigating diagnostic testing for a clinical suspicion of DVT or PE in pregnancy we conclude that; 1) two studies support withholding anticoagulant therapy in pregnant women with a clinical suspicion of DVT and normal results on serial IPG (impedance plethysmography), however, IPG is no longer used; 2) only one study demonstrated that a normal CUS at presentation combined with a normal D-dimer test or an abnormal D-dimer test combined with normal serial CUS appears promising for safely excluding DVT in pregnant patients, but too few patients were included in this pilot-study to draw firm conclusions; 3) only one study investigated pregnant patients with a clinical suspicion of PE and this study concluded that in case of normal or non-diagnostic VQ scans, withholding anticoagulant therapy might be safe, but this needs confirmation in larger studies.

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Conclusions

The Christopher-study demonstrates that a simple diagnostic algorithm consisting of a dichotomised clinical decision rule according to Wells, D-dimer test and helical CT is safe in excluding pulmonary embolism with a low risk of subsequent venous thrombo-embolism. In one-third of the study population, PE could be ruled out without using imaging tests. In all other patients, a helical CT demonstrating no PE turned out to be safe in excluding PE without performing additional tests. Furthermore, the algorithm of the Christopher-study is easily implemented in daily clinical practice since 98% of the patients could be managed according to our protocol. In order to prevent exposure of patients to a 3-month thrombo-embolic failure rate exceeding that of a normal pulmonary angiography, the cut-off level of the clinical decision rule as well as the cut-off level of the D-dimer test should be strictly adhered to at the original 4 points and 500 ng/ml respectively. As regards to the type of CT-scanner, i.e. multi- or single-detector row CT, we did not find a significant difference in the percentage of detected PE between MDCT and SDCT, neither in the percentage of sub-segmental PE. Based on these data, there seems to be no danger of over-diagnosis of small subsegmental PE using multi-detector row systems.

In patients diagnosed with PE and treated with anticoagulants, recurrent VTE occurred despite anticoagulant therapy in a small percentage of patients and the majority of recurrent PE's were fatal, occurring mostly in the first week after diagnosis of PE. Also, patients with PE have a high mortality rate during three months of follow-up. Immobilization, hospitalization, age, COPD and malignancies were risk factors for complications of PE, i.e. recurrent venous thrombo-embolic events, bleeding or mortality. Close monitoring may be indicated in these patients, precluding them from out of hospital start of treatment.

In patients with a clinical suspicion of recurrent PE, the Christopher-design appeared to rule out recurrent PE safely, although confidence limits of the three-month thrombo-embolic risk were rather wide and do not permit to conclude that our approach is as safe as pulmonary angiography. The proportion of patients with a clinical suspicion of recurrent PE that could be ruled out without using imaging tests was one-fifth compared to one-third in patients without a history of PE. The less discriminative power of the clinical decision rule in patients with a history of PE is due to the item "history of VTE" on which all patients score 1.5 points.

A complicating factor in diagnosing recurrent PE, is that it is currently unknown whether pulmonary emboli resolve completely. There seems to be a wide variation in resolution of thrombi in individual patients and the pathophysiologic mechanisms and clinical consequences remain largely unknown. Physicians should be aware that complete resolution of pulmonary thrombi may not be achieved and it may complicate the objective and accurate diagnosis of recurrent PE.

Another group of patients that need major concern in diagnosing pulmonary embolism are pregnant patients. Despite the fact that pulmonary embolism is still one of the leading causes of maternal mortality, there's a major lack of evidence concerning the accuracy

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of diagnostic tests in pregnant women. One complicating factor is fear of radiation exposure. Based on our calculation with a computerized model, taking into account certain assumptions, we conclude that helical CT exposes the fetus to less radiation than perfusion scintigraphy. The main issue following in-utero exposure at typical diagnostic levels of radiation is induction of malignancies with a number of excess malignancies cases up to age 15 years following in-utero exposure is considered to be 1 in 16.000 per mSv. Fear of radiation exposure is therefore not an argument to withhold objective tests in pregnant patients with a clinical suspicion of PE and to expose them to a potential fatal disease.

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Samenvatting

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Een longembolie is een potentieel fatale aandoening waarbij vroege herkenning en het starten van behandeling met anticoagulantia mortaliteit kan doen voorkomen. De diagnostische testen die beschikbaar zijn om aan te tonen dat een patiënt een longembolie heeft waren tot voor kort beperkt tot pulmonalis angiografie en ventilatie-perfusie scintigrafie. Beide testen hebben aanzienlijke beperkingen. Spiraal CT is opgekomen als een nieuwe techniek in het diagnosticeren van longembolieën en heeft een brede belangstelling verkregen maar is echter snel in de praktijk geïmplementeerd zonder een adequate evaluatie. Twee studies hebben de accuraatheid van spiraal CT vergeleken met die van de gouden standaard, de pulmonalis angiografie. Zij lieten een teleurstellende sensitiviteit van slechts 70% zien. Echter, management studies toonden dat de kans op het alsnog krijgen van een DVT of longembolie ondanks negatieve testen, minder dan 2% is gedurende drie maanden follow-up na een normale spiraal CT gecombineerd met andere technieken. Deze diagnostische algoritmes zijn veelal gecompliceerd en daardoor moeilijk te implementeren in de dagelijkse klinische praktijk. Dit heeft geleid tot het ontstaan van de Christopher-studie.
De Christopher-studie is uitgevoerd om te onderzoeken of een dichotomisatie van de klinische beslisregel volgens Wells, die patiënten classificeert in 'longembolie onwaarschijnlijk' en 'longembolie waarschijnlijk', in combinatie met een D-dimeer test, veilig is in het uitsluiten van de diagnose longembolie bij patiënten met een klinische verdenking. Daarnaast is de studie ontworpen om te onderzoeken of spiraal CT veilig is in het uitsluiten van de diagnose longembolie zonder het verrichten van additionele diagnostische testen.

In **Hoofdstuk 3** zijn de resultaten van deze prospectieve management studie beschreven bij 3306 opeenvolgende patiënten. De klinische beslisregel volgens Wells classificeerde patiënten als 'longembolie onwaarschijnlijk' in 2206 (66.7%) van de patiënten. Deze patiënten ondergingen een D-dimeer test en 1057 (32.0%) patiënten hadden een negatief resultaat (≤500 ng/ml). De diagnose longembolie werd uitgesloten geacht bij deze patiënten. Alle andere patiënten, die geclassificeerd waren als 'longembolie waarschijnlijk' of die geclassificeerd waren als 'longembolie onwaarschijnlijk' maar met een abnormale D-dimeer test, ondergingen spiraal CT. De diagnose longembolie werd gesteld bij 674 (20.4%) patiënten en zij werden vervolgens behandeld met anticoagulantia. In 1505 patiënten (45.5%) sloot CT de diagnose longembolie uit. In 50 patiënten (1.5%) was er sprake van een protocol violation en CT werd niet verricht. In 20 (0.9%) patiënten bleek de CT inconclusief en kon de diagnose longembolie niet worden gesteld of verworpen. Het diagnostisch algoritme kon volgens protocol worden gevolgd in 3256 (98.5%) patiënten en leidde tot een management beslissing bij 3236 patiënten (97.9%).
Van alle 1028 patiënten waarbij een longembolie was uitgesloten middels een klinische beslisregel 'longembolie onwaarschijnlijk' gecombineerd met een normale D-dimeer test en die niet werden behandeld met anticoagulantia, werden 5 patiënten alsnog gediagnosticeerd met een veneuze trombose gedurende de follow-up van drie maanden (0.5%, 95%CI: 0.2-1.1). Van alle patiënten waarbij een CT scan de diagnose longembolie had uitgesloten en die niet werden behandeld met anticoagulantia, kregen 18 patiënten van de 1446 alsnog

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een veneuze trombose gedurende de drie maanden follow-up (1.3%, 95%CI: 0.7-2.0). Concluderend, de Christopher-studie toont aan dat een simpel diagnostisch algoritme bestaand uit een gedichotomiseerde klinische beslisregel, D-dimeer test en spiraal CT, veilig en efficiënt is in het uitsluiten van de diagnose longembolie met een lage kans op het alsnog ontstaan van een veneuze trombose in de drie volgende maanden.

Bij de huidige afkappunten van de klinische beslisregel (kleiner of gelijk aan 4) en de D-dimeer test (≤500 ng/ml) kan bij 32% van alle patiënten de diagnose longembolie worden uitgesloten zonder het verrichten van beeldvormende diagnostiek. In **hoofdstuk 4** wordt beschreven of door het variëren van de afkappunten van de klinische beslisregel en de D-dimeer test, er meer patiënten beeldvormende diagnostiek kan worden onthouden zonder daarbij de veiligheid op het spel te zetten. Indien het afkappunt van de klinische beslisregel van 4 naar 5 punten werd opgehoogd, kon de diagnose longembolie bij een additionele 4% van alle patiënten worden uitgesloten, echter ten koste van een verminderde veiligheid (1.5% kans op veneuze trombose tegenover 0.9% bij een afkappunt van 4). Door het ophogen van het afkappunt van de D-dimeer test van 500 naar 600 ng/ml, kon in een additionele 3% van alle patiënten de diagnose longembolie worden uitgesloten tegenover een verhoogde kans op het krijgen van alsnog een veneuze trombose gedurende de volgende drie maanden (2.2% ipv 0.9%). Als veiligheidsgrens wordt aangehouden de bovenste limiet van het 95% betrouwbaarheidsinterval van een normale pulmonalis angiografie (=2.7%). Om patiënten niet bloot te stellen aan een groter veiligheidsrisico dan bij een normale pulmonalis angiografie, dienen de afkappunten van zowel de klinische beslisregel als de D-dimeer test te worden gehandhaafd op respectievelijk 4 punten en 500 ng/ml.

Een vaak terugkerend debat is de mogelijke beperking van CT om accuraat perifere, kleine embolieën te detecteren. Multi-detector row CT zou beter subsegmentele longembolieën kunnen detecteren in vergelijking met single-detector row CT. Echter, of deze kleine embolieën klinisch relevant zijn, en dus behandeld moeten worden is vooralsnog onbekend. **Hoofdstuk 5** beschrijft de prevalentie en anatomische distributie van longembolieën bij patiënten die MDCT of SDCT hebben ondergaan. De lokalisatie van de longembolie bij patiënten die MDCT ondergingen was centraal in 29%, segmentaal in 53% en subsegmentaal in 18%. Bij patiënten die SDCT ondergingen was de longembolie lokalisatie centraal in 38%, segmentaal in 48% en subsegmentaal in 15%. Het percentage gedetecteerde longembolieën (31% vs. 32%, p=0.65), en het percentage subsegmentele longembolieen (18% vs. 15%, p=0.48) was niet significant verschillend tussen MDCT en SDCT. Hiermee lijkt er geen gevaar te bestaan dat MDCT kleine subsegmentele longembolieën overdiagnosticeert.

In **Hoofdstuk 6** wordt het natuurlijk beloop gedurende drie maanden van patiënten waarbij de diagnose longembolie is gesteld, beschreven. Van 673 patiënten ontwikkelden 20 patiënten (3.0%, 95%CI: 1.8-4.6) een recidief trombose tijdens behandeling met anticoagulantia (14 longembolie, 6 DVT). Van de 14 patiënten met een recidief

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longembolie, bleken 11 fataal (79%, 95%CI: 49-95%), meestal optredend in de eerste week na de initiële diagnose longembolie. In 23 patiënten (3.4%, 95%CI: 2.2-5.1) trad een bloedings-complicatie op waarvan 10 werden geclassificeerd als belangrijk (1.5%, 95%CI: 0.7-2.7) en twee fatale bloedingen (0.3%, 95%CI: 0.04-1.1). De all-cause mortaliteit gedurende drie maanden follow-up was 8.2%. Risicofactoren voor een complicatie (recidief trombose, bloeding of mortaliteit) waren immobilisatie langer dan drie dagen, hogere leeftijd, hospitalisatie, COPD en maligniteiten. Het nauwgezet monitoren van deze patiënten is mogelijk geïndiceerd, waarbij deze patiënten niet in aanmerkingen komen voor thuisbehandeling.

Het is onbekend of strategieën die gevalideerd zijn voor het uitsluiten van longembolieën ook veilig zijn bij patiënten met een voorgeschiedenis van longembolieën. **Hoofdstuk 7** beschrijft de resultaten van de Christopher-studie bij patiënten met een eerdere longembolie. Een recidief longembolie was uitgesloten geacht bij patiënten met een klinische beslisregel 'longembolie onwaarschijnlijk'in combinatie met een normale D-dimeer test, of, in alle andere gevallen, door een normale spiraal CT. Van alle 3306 patienten geincludeerd in de Christopher-studie, hadden 259 patiënten (7.8%) al eerder een longembolie gehad. Hiervan werden 25 (9.7%) behandeld met anticoagulantia en daarom geëxcludeerd. Een longembolie was onwaarschijnlijk volgens de klinische beslisregel in 82 van de 234 patiënten (35%) en hiervan hadden 42 een normale D-dimeer test (18%), waardoor de diagnose recidief longembolie kon worden uitgesloten. Geen van deze patiënten ontwikkelde een veneuze trombose in de drie maanden follow-up (0%, 95%CI: 0-6.9). Alle andere 192 patiënten ondergingen een spiraal CT, die een recidief longembolie uitsloot in 127 patiënten (54%). Eén patiënt uit deze groep had een fataal recidief longembolie tijdens de follow-up (0.8%; 95%CI: 0.02-4.3). Dit is de eerste prospectieve studie die aantoont dat ook bij patiënten met een eerdere longembolie, het diagnostisch algoritme waarschijnlijk veilig kan worden gebruikt in het uitsluiten van een recidief longembolie.

Er is veel aandacht in de laatste jaren geweest voor het optimaliseren van de diagnostiek naar een acute longembolie. Echter, er is weinig bekend over de veranderingen die optreden in de stolsels in het pulmonale vaatbed als de diagnose longembolie eenmaal is gesteld. Het is vaak ook problematisch om het onderscheid tussen een oude en een nieuwe trombus te maken. Dit zou kunnen leiden tot het misdiagnosticeren van een recidief longembolie terwijl er sprake is van residuale longembolie, met vervolgens onnodige behandeling met anticoagulantia. In **Hoofdstuk 8** wordt een systematische analyse gepresenteerd van studies naar beelvormende diagnostiek die het aanwezig zijn van residuale stolsels na een diagnose longembolie hebben geëvalueerd. Van 29 gevonden studies zijn 25 volgens vantevoren vastgestelde criteria geëxcludeerd. Het percentage patiënten met residuale pulmonale trombi was 87% acht dagen na diagnose, 68% na zes weken, 65% na drie maanden, 57% na zes maanden en 52% na 11 maanden. Dit review toont aan dat het compleet oplossen van pulmonale stolsels na de diagnose longembolie niet altijd wordt bereikt in een tijdsbestek van 8 dagen tot 11 maanden na de diagnose longembolie.

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Een longembolie is een van de meest frequente doodsoorzaken in de zwangerschap. Echter, diagnostiek naar een longembolie in de zwangerschap is problematisch. Er is twijfel over het belang van verrichten van objectieve diagnostische testen en verwarring ten aanzien van welke test het meest veilig is wat betreft foetale stralingsbelasting. Aangezien een klinische diagnose aspecifiek is, het missen van een longembolie potentieel fataal is en behandeling significante risico's met zich mee brengt, is objectieve diagnostiek noodzakelijk. Artsen zijn vaak weerhoudend in het verrichten van een spiral CT in de zwangerschap omdat het wordt aangenomen dat een CT meer stralenbelasting oplevert dan een perfusiescan. In **Hoofdstuk 9** beschrijven we de resultaten van een mathematisch model waarin de foetale stralingsbelasting wordt berekend voor zowel CT als perfusiescan. Hierin is gebruik gemaakt van de aanname dat stralingsbelasting op de uterus een goede benadering is van de stralingsbelasting van de foetus in d vroege zwangerschap. Juist deze vroege periode in de zwangerschap is het meest belangrijk aangezien de foetus het meest kwetsbaar is voor stralenbelasting. De berekende stralingsdosis voor een single-detector row CT is 0·026 mSv en een zelfs lagere dosis voor de multi-detector row CT (0·013 mSv). Ter vergelijking, de foetale stralingsdosis voor een perfusiescan is 0.11-0·20 mSv. Concluderend, in de vroege en meest kwetsbare periode van de zwangerschap is de foetale stralenbelasting minder met een spiraal CT dan met een perfusiescan.
Vele van de diagnostische testen, zoals compressie echografie, ventilatie-perfusie scintigrafie en spiraal CT, die uitgebreid zijn gevalideerd bij niet-zwangere patiënten met een verdenking longembolie of DVT, zijn niet onderzocht bij zwangere patiënten. Het extrapoleren van de data van diagnostische studies bij niet-zwangeren naar zwangere vrouwen, zou niet correct kunnen zijn vanwege verschillen in pathofysiologie en presentatie van een trombosebeen of longembolie in de zwangerschap. Om de diagnostische accuraatheid van verschillende testen gebruikt ter uitsluiting van een longembolie danwel DVT in de zwangerschap aan te tonen, hebben we een systematische analyse verricht naar gepubliceerde studies over dit onderwerp (**Hoofdstuk 10).** Volgens vantevoren opgestelde inclusie criteria, kwamen slechts 4 studies in aanmerking voor inclusie. Hieruit kan worden geconcludeerd dat; 1) twee studies ondersteunen het niet starten van behandeling met anticoagulantia bij zwangere vrouwen met een klinische verdenking op een trombosebeen indien er normale resultaten zijn van seriële impedantie plethysmografie, echter deze techniek wordt hedendaags niet meer gebruikt; 2) slechts 1 studie toonde aan dat een normale compressie echografie gecombineerd met een normale D-dimeer test of een abnormale D-dimeer test gecombineerd met een normale seriële echo, veilig lijkt in het uitsluiten van een DVT bij zwangere vrouwen, echter er waren te weinig patiënten in de studie geïncludeerd om harde conclusies te trekken; 3) slechts 1 studie betrof zwangere vrouwen met een klinische verdenking longembolie en concludeerde dat bij een normale of niet-diagnostische ventilatie-perfusiescan het onthouden van anticoagulantia waarschijnlijk veilig is, maar dat dit bevestiging vereist in grotere, prospectieve studies.

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Curriculum Vitae

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De auteur van dit proefschrift werd geboren op 9 februari 1977, in Groningen. In 1995 behaalde zij haar eindexamen VWO aan het Werkman College in Groningen. Hierna volgde van 1995 tot 2001 de studie Geneeskunde aan de Rijksuniversiteit van Groningen. Van 1997 tot 1998 was zij betrokken bij het grootschalige Gronings bevolkingsonderzoek genaamd 'PREVEND', waar onder leiding van Prof. P.E. de Jong de prevalentie van micro-albuminurie en risico's op hart-en vaatziekten in de populatie werd bestudeerd. In 1999 vloog zij voor haar wetenschappelijke stage naar Zuid-Afrika, om daar onder leiding van Prof. Rheeder een half jaar te werken aan de kwaliteit van screening en behandeling van diabetische nefropathie, in het Pretoria Academisch Ziekenhuis te Pretoria. Na het behalen van het arts-examen in december 2001, werd zij in 2002 aangenomen als AGNIO Interne Geneeskunde/Longziekten in het Martini-ziekenhuis te Groningen. Een jaar later, in 2003, is zij begonnen met haar promotie-onderzoek op de afdeling Interne Geneeskunde van het Leids Universitair Medisch Centrum (Dr. M.V.Huisman, Prof. A.E. Meinders). Van 10 januari tot 10 april 2006 is zij op uitnodiging van Prof. G. Palareti, op de afdeling 'Angiologia" in het Santa Orsola - Malpighi University Hospital te Bologna, Italië, een studie gaan opzetten naar residuale longembolieën. Op 1 mei 2006 startte zij met de opleiding tot intenist in de regio Leiden, waarvan zij momenteel werkzaam is in het Rijnland ziekenhuis te Leiderdorp (Dr. Cluitmans).

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List of Publications

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Nijkeuter M, Geleijns J, de Roos A, Meinders AE, Huisman MV. Diagnosing pulmonary embolism in pregnancy: Rationalising fetal radiation exposure in radiological procedures. J.Thromb Haemost 2004, Oct; 2(10): 1857

Nijkeuter M, Huisman MV. More on: Diagnosing pulmonary embolism with helical computed tomography during pregnancy: What about exposure to iodinated contrast agents? J Thromb Haemost 2005 Apr; 3(4): 814.

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The Christopher Study Group. Effectiveness of Managing Suspected Pulmonary Embolism using an Algorithm combining Clinical Probability, D-dimer Testing and Computed Tomography. *JAMA 2006; 295, 2: 172–179*

Nijkeuter M, Ginsberg JS, Huisman MV. Diagnostic management of deep vein thrombosis and pulmonary embolism in pregnancy; a systematic review. *J Thromb & Haemost 2006*; 4: 496-500.

Nijkeuter M, Hovens MMC, Davidson BL, Huisman MV. The rate of resolution of pulmonary thrombo-embolism in patients with pulmonary embolism; a systematic review. *Chest 2006;* 129: 192-197

Sohne M, Kruip MJ, Nijkeuter M, Tick LW, Kwakkel H, Halkes SJ, Huisman MV, Buller HR; The Christopher Study Group. Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD, or heart failure and in older patients with suspected pulmonary embolism. *J Thromb Haemost 2006; May 4(5):1042-6.*

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Nijkeuter M, Sohne M, Tick LW, Kamphuisen PW, Kramer MMH, Laterveer L, van Houten AA, Kruip MJHA, Leebeek FWG, Büller HR, Huisman MV. The Natural course of Pulmonary Embolism; Clinical Outcome and Risk Factors in a Large, Prospective Cohort Study. *Chest 2007 Feb;131(2):517-23.*

Klok FA, Karami Djurabi R, Nijkeuter M, Huisman MV. Alternative diagnosis other than pulmonary embolism as a subjective variable in the Wells clinical decision rule: not so bad after all. J Thromb Heamost 2007 May; 5(5); 1079

Nijkeuter M, Kwakkel- van Erp HM, Sohne M, Tick LW, Kruip MJHA, Ullmann EF, Kramer MHH, Büller HR, Prins MH, Leebeek FWG, Huisman MV. Clinically Suspected Recurrent PE: A Diagnostic Challenge. *Accepted for publication in Thromb & Haemos*

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List of Co-authors

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List of Abbreviations

CDR	:	Clinical Decision Rule
CI	:	Confidence Interval
COPD	:	Chronic Obstructive Pulmonary Disease
CT	:	Computed Tomography
CUS	:	Compression UltraSonography
DVT	:	Deep Vein Thrombosis
IPG	:	Impedance Plethysmography
MDCT	:	Multi-row Detector Computed Tomography
mSv	:	milliSievert
PE	:	Pulmonary Embolism
SDCT	:	Single-row Detector Computed Tomography
VTE	:	Venous Thrombo-embolic Events
VQ	:	Ventilation Perfusion

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