Adjustments in the diagnostic work-up, treatment and prognosis of pulmonary embolism

Josien van Es

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Ach zie de lammeren nou toch lurken, aan hun vers geschoren moeders
En hoe de jonge zwanen, donzen in de zachte sloot
En hoe de zwoele wind de wolken waait, tot pas gewassen luchten

Kan iets mooier dan het mooi is, kan iets groter zijn dan groot

En voel de hosta nou toch lonken, haar knoppen staan op barsten
Het nieuwe riet drinkt gulzig water, uit de smalle vaart

Kan iets frisser dan het fris is, wulpser dan het wulpste

Ach ik ben Goddank, dus nog een keer
Een jonge lente waard

En zie de irissen nou toch pronken, met hun stampers als koralen
Een varen rolt haar blaren, als een leguanentong
En zie de veulens nou toch wankelen, en de vogels naar hun nesten

Kan iets verser dan het vers is, kan iets jonger zijn dan jong

Zie hoe de zon een scherpe schaduw trekt, onder de wijde wilgen
De puppies rennen rondjes, bijtend naar hun eigen staart

Kan iets leuker dan het leuk is, jeugdiger dan jeugdig

Ach ik ben Goddank, dus nog een keer
Een jonge lente waard

Dit is zo mooi
Het is om te janken zo mooi
Mooi, om te janken zo mooi

En nu de wingerd zich wellustig, en het onkruid onbezonnen
En ik mezelf aftel, van volwassen naar bejaard

Wordt het groener dan het groen was
Nu ik grijzer dan ik grijs ben

Ach ik ben Goddank, dus nog een keer
Een jonge lente waard

Mooi
Het is om te janken zo mooi
Mooi, om te janken zo mooi

En als vannacht de open hemel, de sterren strak laat stralen
En ik buiten op mijn rug lig, starend naar het firmament

Kan het stiller dan het stil is, eeuwiger dan eeuwig

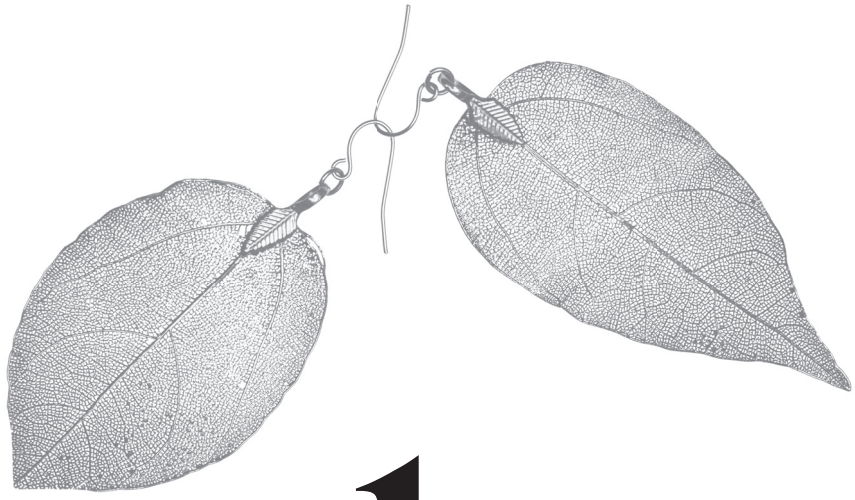
Dan ben ik Goddank, dus nog een keer
Gevangen in het moment

Dit is zo mooi
Om te janken zo mooi

Maarten van Roozendaal

voor mijn opa en oma

TABLE OF CONTENTS



CHAPTER 1

Introduction and outline of the thesis

J. van Es
S. Middeldorp
P.W. Kamphuisen

General introduction

Pulmonary embolism (PE) is a potentially fatal condition, in which an embolism, usually a thrombus originating from one of the deep veins of the legs, blocks one or more pulmonary arteries, causing impaired blood flow and increased pressure of the right cardiac ventricle. PE and deep vein thrombosis (DVT) are considered two entities of the same disease: venous thromboembolism. The clinical presentation of patients with suspected acute PE is nonspecific and varies widely, from only limited symptoms, to severe shortness of breath, pain on exertion, syncope, cardiogenic shock and death. As PE is a frequently occurring disease, with an incidence of 1-2 per 1000 to nearly 8 per 1000 in older-aged patients per year, it is the third most common cardiovascular disorder in Western society (1;2).

The first step in the diagnostic work-up of suspected PE consists of clinical history taking and physical examination, in order to determine the clinical probability of PE. Information regarding clinical signs and symptoms can be used to classify patients in probability categories, by either using implicit judgement or validated clinical decision rules. Although four clinical decision rules have been proven to perform equally (3), the most commonly used clinical decision rule is the Wells score (4). This score consists of items obtained from clinical history such as risk factors for PE, physical examination such as increased heart rate and signs of DVT, and a subjective item, where the physician judges whether an alternative diagnosis is more likely than PE (5). When the low clinical probability (Wells score ≤ 4 points) is combined with a normal D-dimer test result, PE is safely excluded in 20 to 40% of the patients with suspected PE, without the need for imaging techniques (6). Fibrin D-dimer is the final product of the plasmin-mediated degradation of cross-linked fibrin and D-dimer levels are typically elevated in patients with acute venous thromboembolism. The sensitivity of the D-dimer, using a cut-off value of 500 μg/L, is nearly 100% (7). In contrast, since D-dimer levels can be elevated in other clinical conditions, e.g. malignancy, increased age, infection, postoperative states and pregnancy, the specificity for acute venous thromboembolism is only between 30% and 40% (7-9), and further decreases with advancing age. As aging increases the risk of PE, it is likely that a higher D-dimer cut-off results in higher specificity without a relevant fall in sensitivity in older patients (10;11). Indeed, in a retrospective analysis the use of an age-adjusted cut-off of the D-dimer (patient's age x 10 μg/L) in combination with an unlikely clinical decision rule greatly increased the number of patients above 50 years in whom PE could safely be excluded (12). These results need to be confirmed in a

prospective study where patients are managed according to their age-adjusted D-dimer level.

If the clinical probability of PE is likely or the D-dimer test is abnormal, further imaging is necessary to confirm or exclude the diagnosis. Next to the clinical decision rule-D-Dimer strategy, computed tomography (CT-) scan has increasingly become the most preferred imaging test to either confirm or exclude PE (13). With the introduction of multi-detector row CT-scan, the sensitivity of the CT-scan has greatly improved, ranging from 83% to 100% with specificity ranging from 96% to 100% (14;15), and even small subsegmental emboli can now be visualized (16). Besides, compared to the previous reference standard, i.e. ventilation perfusion scintigraphy (if necessary followed by pulmonary angiography), advantages of CT-scan are that the CT-scan is easily accessible, quickly performed and non-invasive. Another potential advantage of the CT-scan is the capability of detecting other findings supporting an explanation for the patient's complaints or symptoms when PE is excluded (17). On the other hand, the newer generation of CT-scans increases the rate of subsegmental filling defects and the clinical relevance of these subsegmental emboli is a topic of debate (18).

Besides, despite the improvement of diagnostic yield with the clinical decision rule-D-dimer strategy, of the patients with an indication for CT-scan only 20% to 30% indeed has a diagnosis of PE (19). This proportion is even lower in the United States, where it is approximately 10% (20). Additionally, CT-scan can also cause adverse effects, such as an increased lifetime risk of (breast) cancer from radiation exposure, especially in young women, and the risk of contrast nephropathy (21;22). These concerns force physicians to use a diagnostic strategy, which results in fewer CT-scans and the lowest possible false negative rates.

Regarding the treatment and prognosis of PE, important questions have surfaced. Although most hemodynamically stable patients with PE benefit from standard anticoagulant treatment, the rates of residual thrombosis at the end of anticoagulant therapy and the short-term clot resolution with anticoagulant treatment is not well known. Nowadays, although without solid evidence for clinical relevance, physicians often perform repeat CT-scans after six months of anticoagulant treatment, as the presence of residual thrombotic obstruction appears to have two important implications. First, repeat scans after discontinuation of anticoagulant therapy may aid in the differentiation between residual and recurrent thrombi in the diagnostic work-up of patients with suspected recurrent PE. This is of importance given the therapeutic consequences of prolonged or even lifelong anticoagulant treatment after a recurrence

(23). Second, patients with residual thrombotic occlusion may be at increased risk of recurrent PE or chronic thromboembolic pulmonary hypertension (24). Finally, little attention has been paid to the quality of life in patients after PE.

Outline of the thesis

This thesis consists of two parts. The first part focuses on the diagnosis of PE. In ***chapter 2,*** an age-adjusted cut-off point (patient's age x 10 μg/L) of D-dimer levels was validated in four recently introduced and widely used clinical decision rules, which all four showed to perform equally well. In ***chapter 3,*** the performance of these four clinical decision rules was investigated in patients with cancer and suspected PE.

An alternative diagnostic strategy, in which women younger than 50 years of age with a high risk of PE are investigated with the combination of a chest X-ray and perfusion scintigraphy, in order to avoid CT-scanning and thereby radiation exposure to the breasts, is prospectively evaluated in ***chapter 4***. In ***chapter 5,*** the accuracy of the D-dimer test is tested in patients with zero, one or two items of the Wells score, and additionally, in ***chapter 6*** we designed a new clinical decision rule that includes the D-dimer as a first step, with the aim to further lower the number of unnecessary CT-scans.

Next, in ***chapter 7*** we studied whether alternative diagnoses observed on CT-scans, ordered for PE, have diagnostic or therapeutic consequences. In ***chapter 8,*** we investigated whether the level of prothrombin fragments in serum and urine in patients with venous thromboembolism and myocardial infarction is elevated compared to healthy volunteers.

Part II of this thesis focuses on the treatment and the prognosis of PE. An overview of the current treatment and the potential of the new oral anticoagulants in PE patients is presented, as well as the treatment in 'special' populations, such as patients with obesity or severe renal failure, in ***chapters 9 and 10.***

Chapter 11 focuses on the resolution of the pulmonary clots in patients with acute PE, diagnosed with either a CT-scan or a perfusion-scan, and followed up by a similar scan after three weeks of anti-coagulant treatment. Furthermore, in ***chapter 12***, residual pulmonary thrombi are investigated with a CT-scan after six months of anticoagulant treatment, by two independent radiologists. ***Chapter 13*** investigated the clinical outcome of patients with subsegmental PE versus more proximal PE (segmental

and central PE). The influence of the duration of complaints before CT-scanning on the D-dimer level and the prognosis of patients is described in ***chapter 14.*** The quality of life in patients with a history of PE is described and compared to patients with other (cardio-) pulmonary diseases in ***chapter 15.***

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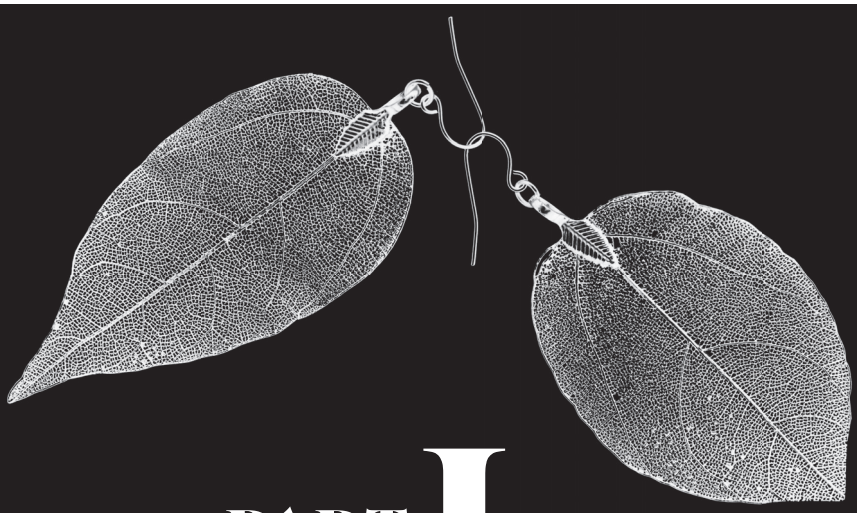
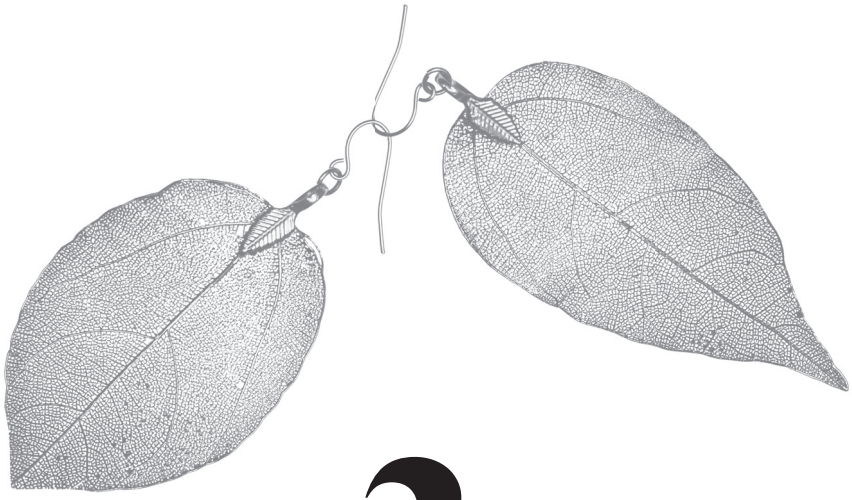


PART I

The diagnostic work-up of pulmonary embolism



CHAPTER 2

Age-adjusted D-dimer safely and efficiently increases the proportion of patients in whom acute pulmonary embolism can be excluded, regardless the clinical decision rules used

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Abstract

Background: Four clinical decision rules (CDRs) (Wells score, Revised Geneva Score (RGS), simplified Wells score and simplified RGS) safely exclude pulmonary embolism (PE), when combined with a normal D-dimer test. Recently, an age-adjusted cut-off of the D-dimer (patient's age x 10 μg/L) safely increased the number of patients above 50 years in whom PE could safely be excluded. We validated the age-adjusted D-dimer test and assessed its performance in combination with the four CDRs in patients with suspected PE.

Methods: 414 consecutive patients with suspected PE older than 50 years were included. The proportion of patients in whom PE could be excluded with an 'unlikely' clinical probability combined with a normal age-adjusted D-dimer test was calculated and compared with the proportion using the conventional D-dimer cut-off. We assessed VTE failure rates during 3-months follow-up.

Results: In patients above 50 years, a normal age-adjusted D-dimer level in combination with an 'unlikely' CDR substantially increased the number of patients in whom PE could be safely excluded: from 13-14% to 19-22% in all CDRs similarly. In patients over 70 years, the number of exclusions was nearly fourfold higher, and the original Wells score excluded most patients, with an increase from 6% to 21% combined with the conventional and age-adjusted D-dimer cut-off, respectively. The number of VTE failures was also comparable in all CDRs.

Conclusion: Irrespective of which CDR is used, the age-adjusted D-dimer substantially increases the number of patients above 50 years in whom PE can be safely excluded.

Introduction

The clinical presentation of patients with suspected acute pulmonary embolism (PE) is nonspecific and varies widely, from only limited symptoms, to severe dyspnea, pain on exertion, syncope, or even cardiogenic shock. Moreover, although the incidence of PE increases with age from 1 per 1000 to nearly 8 per 1000 in older-aged patients (1-4), the prevalence of objectively proven PE in patients with suspected PE is relatively low, 20-30% (5;6).

For the determination of probability in the diagnostic work-up of PE standardised clinical decision rules (CDRs) combined with a D-dimer test are commonly used (7): an 'unlikely' CDR combined with a D-dimer test result safely excludes PE in 20-40% of the patients with suspected PE (6;8). However, the specificity of the D-dimer test is 30-40% and even decreases with age, whereas aging, on the other hand, increases the risk of PE (9-12). This lower specificity makes the D-dimer less useful to exclude PE in older patients (6;13-16). In addition, avoiding imaging tests such as CT scans would have several advantages for (older) patients, in which the risk of contrast nephropathy and unnecessary radiation may be considerable. It has recently been shown that an age-adjusted cut-off of the D-dimer (patient's age x 10 µg/L) in combination with an unlikely CDR greatly increased the number of patients above 50 years in whom PE could safely be excluded (17). This adjusted D-dimer cut-off has however not yet been validated in another prospective cohort of patients with suspected PE.

Several CDRs in patients with suspected PE have been derived and validated (18-21). The most commonly used CDR is the Wells score, consisting of items obtained from history, such as risk factors for PE, physical examination, including heart rate and signs of DVT, and a subjective item where the physician can judge whether an alternative diagnosis is more likely than PE (22) (Table 1). More recently, the Revised Geneva Score (RGS) was introduced. The RGS is comparable with the Wells score, but consists of more variables, such as age > 65 years (20;23) (Table 1).

Table 1. Four different Clinical Decision Rules; Wells, Simplified Wells, Revised Geneva Score and Simplified Revised Geneva Score.

Wells rule			**Revised Geneva Score**		
Items	**Original**	**Simplified**	**Items**	**Original**	**Simplified**
Clinically suspected DVT	3	1	Age ≥ 65 years	1	1
alternative diagnosis less likely than PE	3	1	Previous DVT or PE	3	1
Heart rate ≥ 100 beats per minute	1.5	1	Surgery or fracture within 1 month	2	1
Immobilization/ surgery in past 4 weeks	1.5	1	Active malignant condition	2	1
Haemoptysis	1	1	Unilateral lower limb pain	3	1
Active malignant condition	1	1	Haemoptysis	2	1
			Heart rate 75-94 beats per minute	3	1
			Heart rate ≥ 95 beats per minute	5	1*
			Pain on deep palpation of lower limb and unilateral oedema	4	1
PE unlikely	**≤ 4**	**≤ 1**	**PE unlikely**	**≤ 5**	**≤ 2**
PE likely	**> 4**	**> 1**	**PE likely**	**> 5**	**> 2**

Heart rates of 75 to 94 beats per minute receive 1 point, while heart rates higher than 94 beats per minute receive a further point (i.e. 2 points in total)
DVT, deep venous thrombosis; PE pulmonary embolism

In order to simplify the calculation of the scores, both Wells and RGS scores have been simplified: all items are assigned with one point (Table 1) (18;19;21). These four different CDRs (Wells score, RGS, simplified Wells score and simplified RGS) have recently been validated prospectively and all showed a similar safety and clinical utility in patients with suspected PE (24). Because the (simplified) RGS includes the item 'age > 65 years', this CDR may be less specific in older patients. Since the Wells rule has no age-specific item, it may rule out PE in a higher percentage of patients above 50

years of age, especially in combination with the age-adjusted cut-off of the D-dimer. We performed a study to evaluate the four different CDRs' performance and safety in combination with the age-adjusted D-dimer cut-off value in patients above 50 years with suspected PE.

Methods

We analyzed the data from a recently published prospective cohort study, which included 807 consecutive in-and outpatients with clinically suspected acute PE [24]. Patients were included in 7 participating academic and non-academic medical centers in the Netherlands between July 2008 and November 2009. For the present analysis, only patients older than 50 years were included.

Patients were excluded if they were under the age of 18 years, had a life expectancy of less than 3 months, were treated with therapeutic-dose low molecular weight heparin or unfractionated heparin that was initiated 24 hours or more prior to eligibility assessment, received treatment with vitamin K antagonists, had a contraindication to helical CT scan because of allergy to intravenous iodinated contrast or renal insufficiency (creatinine clearance of < 30 ml/min, using the Cockroft-Gault formula), were pregnant or unable to return for follow-up. Patients were followed up for 3 months.

Ethical review boards of all participating hospitals approved the study protocol and informed consent was obtained from all included patients.

Data analysis

In the original study cohort, the Wells, simplified Wells, RGS and simplified RGS clinical prediction rule were calculated in all patients. PE was considered 'unlikely' in case of a Wells score of 4 points or less, a simplified Wells score of 1 point or less, an RGS score of 5 points or less and a simplified RGS score of 2 points or less. A score above the respective cut-offs of all CDRs, was indicated as PE 'likely'.

Demographic data and additional relevant information (e.g. recent trauma or surgery, cancer, use of anticoagulants, duration of time since symptom onset and D-dimer test result) were collected on a Case Report Form (CRF), available in paper and digital format. A high-sensitivity quantitative D-dimer test was performed, depending on the local practice, either VIDAS D-dimer assay, BioMerieux, Marcy L'Etoile, Tinaquant assay, Roche diagnostica, STA-liatest D-di, Diagnostica Stago or Innovance D-dimer, Siemens. The computerized design forced the physician to start the diagnostic process

with clinical evaluation of the patient and to enter all variables necessary to calculate the four CDRs and the D-dimer test result into the computer. The computer program calculated the four individual CDR scores. If at least one of the four CDRs was classified as 'likely' or in case of an elevated D-dimer result a CT scan was ordered. The physician initiated the next recommended step in the diagnostic process according to a predefined study flow: either exclusion of PE based on an unlikely CDR and a negative D-dimer level or performing a CT scan.

We investigated the efficiency, defined as the percentage of patients above 50 years in whom PE could be excluded by an 'unlikely' CDR in combination with a normal D-dimer, according the conventional cut-off value (500 μg/L) as well as the new age-adjusted cut-off value (age x 10 μg/L) for all CDRs. Besides, in order to investigate whether the efficiency increases with age, we also looked at patients above 70 years. Furthermore, the failure rate was calculated for each CDR in combination with the D-dimer, defined as the number of patients in whom VTE was diagnosed during the diagnostic evaluation or during follow-up, despite an unlikely CDR and normal age-adjusted D-Dimer. Student's t-test was applied for continuous variables and categorical data were analyzed using the chi-square test. Exact 95% confidence intervals (CI) around the observed incidences were calculated. All analyses were performed using SPSS version 16.0 (SPSS, Chicago il, USA).

Results

A total of 807 consecutive patients with suspected PE were included, of whom 456 were above 50 years (57%). In 42 of these 456 patients, no D-dimer test was performed, all patients with a high clinical probability. In 110 of the remaining 414 patients older than fifty years (27%), PE was confirmed by CT. Table 2 shows the clinical characteristics of the cohort.

The conventional D-dimer test was normal in 68/414 patients (16.4%, 95% CI 13-20), of whom one patient had PE during follow up (failure rate: 1.5%, 95% CI 0-7.9). With the age-adjusted cut-off value, the D-dimer test was normal in 105/414 patients (25.4%, 95% CI 21-30), two of whom turned out to have PE during follow-up (failure rate: 1.9%, 95% CI 0.2-6.7) (Table 2). The absolute increase in patients with an unlikely CDR and a normal D-dimer test according to the age-adjusted cut-off ranged from 6% (13.3% to 19.3% using the simplified Wells rule) to 7.7% (14.5% to 22.2% in

the original Wells score). The increase was 5.3% for the D-dimer in combination with both the simplified and the original RGS (Table3).

Table 2. Baseline characteristics of the patients with clinically suspected pulmonary embolism older than 50 years.

Characteristics	Value
Age in years, mean (SD)	65 (10)
Female, n (%)	225 (54)
History of VTE, n (%)	26 (6.3)
Active malignancy, n (%)	73 (18)
Recent surgery or immobilisation, n (%)	96 (23)
Hemoptysis, n (%)	20 (4.8)
Heart rate > 100 beats per minute, n (%)	107 (26)
Clinical signs of DVT, n (%)	44 (11)
Inpatient, n (%)	163 (20)
Negative D-dimer:	
– Conventional cut-off (< 500 µg/L), n (%)	68 (16)
– Age-adjusted cut-off (< age x 10 µg/L), n (%)	105 (25)

DVT, deep venous thrombosis; SD standard deviation, VTE venous thromboembolism

Although not significant, the diagnostic yield for excluding PE with the conventional cut-off appeared to be highest in combination with the original Wells rule (14.5%), compared to 13.5% with the simplified Wells and 13.8% with both original and simplified RGS. Similarly, the age-adjusted D-dimer cut-off in combination with the Wells score resulted in the largest number of patients in whom PE could be excluded (22.2%) compared with the simplified Wells (19.3%, p=0.12) and with the RGS and simplified RGS (19.1%, p=0.09) (Table 3). The failure rates were similar for all CDRs. For the conventional cut-off this was one patient (Wells: 1.7%, 95% CI 0-8.9), simplified Wells: 1.8%, 95% CI 0.-9.7, (simplified) RGS: 1.8%, 95% CI 0-9.3) compared with two patients for the age-adjusted cut-off (Wells: 2.2%, 95% CI 0-7.6, simplified Wells: 2.5%, 95% CI 0-8.7%, (simplified) RGS: 2.5%, 95% CI 0-8.9) (Table 3).

In patients aged > 70 years, the number of patients in whom PE could be ruled out increased three- to fourfold with all four CDRs (Table 3). However, when comparing the diagnostic yield of the four CDRs in patients above 70 years, PE could be excluded in more patients using the original Wells rule: 21% compared to 17.4% with the simplified

Wells score (p=0.44) and to 12% with both simplified and original RGS (p < 0.05) (Table 3).

Table 3. Proportion of patients with an unlikely CDR (Wells, simplified Wells, Revised Geneva Score, and simplified Revised Geneva Score) in whom pulmonary embolism can be excluded based on a negative D-dimer test using the age dependent cut-off.

	Wells		**Simplified Wells**		**RGS**		**Simplified RGS**	
	>50 years n=414	>70 years n=132	>50 years n=414	>70 years n=132	>50 years n=414	>70 years n=132	>50 years n=414	>70 years n=132
CDR unlikely and **conventional D-dimer** negative, n % (95% CI)	60 **14.5%** (11-18)	8 **6.0%** (2.6-12)	55 **13.3%** (10-17)	7 **5.3%** (2.2-11)	57 **13.8%** (11-17)	4 **3.0%** (0.8-7.5)	57 **13.8%** (11-17)	4 **3.0%** (0.8-6.5)
Failure rate n % (95% CI)	1 1.7% (0-8.9)	1 12.5% (0-53)	1 11.8% (0-9.7)	1 14.3% (0-58)	1 1.8% (0-9.3)	1 25% (0.6-81)	1 1.8% (0-9.3)	1 25% (0.6-81)
CDR unlikely and **age adjusted D-dimer** negative n % (95% CI)	92 **22.2%** (18-26)	28 **21.0%** (14-29)	80 **19.3%** (16-23)	23 **17.4%** (11-25)	79 **19.1%** (15-23)	16 **12.0%** (7.0-19)	79 **19.1%** (15-23)	16 **12.0%** (7-19)
Failure rate n % (95% CI)	2 2.2% (0-7.6)	1 3.6% (0-18)	2 2.5% (0-8.7)	1 4.3% (0.1-22)	2 2.5% (0-8.9)	1 6.3% (0-30)	2 2.5% (0-8.9)	1 6.3% (0-30)

CDR Clinical Decision Rule, CI Confidence Interval, n number, RGS Revised Geneva Score

The failure rate in the patients above 70 years was similar (one patient) for both cut-off values and all CDRs. Because the proportion of older patients in whom PE was excluded was larger using the age-adjusted cut-off, the failure rate in the age-adjusted D-dimer cut-off group was relatively lower compared with the conventional cut-off (p=0.04 for all CDRs; conventional D-dimer vs age-adjusted D-dimer: Wells 12.5% vs 3.6%, (95% CI 0-53 vs 0-18), simplified Wells 14.3% vs 4.3% (95% CI 0-58 vs 0.1-22), (simplified) RGS: 25% vs 6.3% (95% CI 0.6-81 vs 0-30) (Table 3).

Discussion

This study confirms that four different CDRs combined with the new cut-off performed equally. The original Wells rule, however, excluded PE in significantly more patients than if combined with the (simplified) RGS in patients above 70 years, which may be due to the fact that the RGS includes the factor age already. For the simplified Wells and the (simplified) RGS, this difference was not-significant. Previously, Douma et al investigated the age-adjusted D-dimer in three prospective cohorts with a total of 5132 consecutive patients with suspected PE (24). In one cohort, using the original Wells score in patients above 50 years, the proportion of patients in whom PE could be ruled out with the age-adjusted D-dimer cut-off value increased by 10% (95% CI 7% to 12%), compared to the conventional D-dimer cut-off. In patients older than 70 years this increase was 14% (95% CI 11% to 25%). These findings are in agreement with the present results, as we found an absolute increase in the proportion of patients in whom the diagnosis could be excluded using the Wells score of up to 15% in older patients when the age-adjusted D-dimer cut-off was used. Furthermore, the age-adjusted D-dimer cut-off level, combined with an unlikely clinical probability score, increases the proportion of patients older than 50 years in whom PE can safely be excluded, in comparison to the conventional cut-off value of 500 μg/L. These results extend those found in the previous studies, since we now also show that not only the Wells and revised Geneva scores, but also the simplified Wells and simplified RGS have the same ability, with a slight advantage for the original Wells score in older patients (17;24). The number of excluded PE of this new cut-off point increased significantly with age, with a nearly fourfold increase in the number of patients older than 70 years. However, it should be noticed that the number of patients > 70 years were rather small. In addition, the age-adjusted cut-off value did not come at the expense of decreased safety, since no differences in the false negative rates between the conventional and the age-adjusted cut-off value was observed. Although there were very few patients with recurrent VTE during three months follow-up, the diagnostic failure rate even showed a relative decrease in the older-aged patients above 70 years.

Clinical relevance of the age-adjusted D-dimer

The age-adjusted cut-off reduced the number of patients in whom CT scan or other radiological imaging test is necessary to exclude PE. Theoretically, this will reduce the risk of contrast nephropathy, radiation exposure and the length of hospital stay, hence potentially reducing total costs. Furthermore, the number of patients in whom PE could

be excluded using the age-adjusted D-dimer cut-off differed per CDR. The simplified rules are easier to compute compared to the original scores, since all items count for just one point. However, combined with either the conventional or the new D-dimer cut-off value, the original Wells score excluded more patients compared to the other CDRs in patients older than 70 years. This difference might be due to the item 'age above 65 years' in the (simplified) RGS, so older patients with suspected PE will get a higher CDR result when using both simplified and original RGS, thus increasing the rate of additional imaging tests.

Although our study involved a cohort of consecutive patients with suspected PE, and the D-dimer levels and all items of the different CDRs were collected prospectively, the performance of the four different clinical CDRs combined with the adjusted D-dimer was analysed retrospectively. In addition, the number of patients was rather small and therefore the 95% confidence intervals of the false negative rate are wide. There was, however, no significant difference between the failure rates of the four clinical CDRs or with the failure rates, obtained with the conventional and the age-adjusted D-dimer cut-off.

In this analysis we dichotomized the CDRs, since this stratification is easier to apply in clinical practice. Furthermore, the Wells rule has extensively been studied with these two categories. Nevertheless, the original scheme of low-, intermediate- and high category may lead to a higher number of excluded PE. Moreover, the failure rate in these older patients seemed to be lower with the age-adjusted D-dimer, because of the increased number of exclusions of PE with the age-adjusted D-dimer cut-off. However, there is still a need for confirmation of our results in larger cohorts of patients. Finally, different D-dimer assays were used in the participating centres. Although there was no significant difference between these assays and the new D-dimer cut-off, the study was not sufficiently powered to detect small differences.

To conclude, irrespective of which CDR is used in patients above 50 years, the age-adjusted cut-off D-dimer greatly increases the number of older patients in whom PE can be excluded, without the expense of safety. The original Wells score combined with the age-adjusted D-dimer cut-off might exclude PE in more patients above 70 years compared with the simplified Wells score and significantly more compared with both the original and the simplified RGS. However, prospective validation with more patients is needed to validate this.

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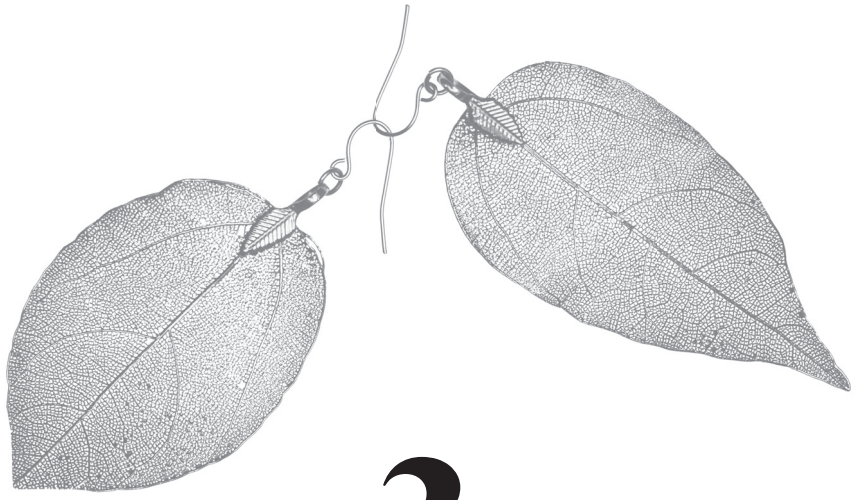

CHAPTER 3

Performance of four clinical decision rules in patients with malignancy and suspected pulmonary embolism

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Abstract

Background: Pulmonary embolism (PE) frequently occurs in patients with malignancy, whereas the diagnostic yield of the clinical decision rule (CDR) and D-dimer test in the exclusion of PE is lower than in non-malignant patients. Four different CDRs, Wells score, Revised Geneva (RGS), Simplified Wells, and simplified RGS are used to exclude PE. In this study, we assessed which of these CDRs is associated with the highest exclusion rate in patients with a malignancy and suspected PE.

Methods: 807 consecutive patients with suspected PE were included in the study of whom 114 had a malignancy. The proportion of patients who had an unlikely CDR and a negative D-dimer was calculated for all CDRs. VTE failure rate was assessed during 3-month follow-up.

Results: In patients with malignancy 58% had an unlikely Wells score, which was higher compared to the other CDRs, without an increase in the failure rate. However, the addition of a normal D-dimer test greatly reduced the proportion of patients where PE could be excluded to a similar proportion as the other CDRs.

Conclusion: In cancer patients with suspected PE, the convential Wells score gave the highest proportion of an "unlikely" score. The number of patients where PE could be excluded was not different compared to the other CDRs because of the very low number of normal D-dimer tests.

Introduction

A substantial proportion (4-10%) of patients with suspected pulmonary embolism (PE) has a malignancy (1). Conversely, patients with malignancy have a 4 to 7-fold increased risk of developing PE and particularly in patients with metastatic disease, in whom the incidence vary from 4% to 20% (2). PE worsens the prognosis in these vulnerable patients, because of the increased morbidity and mortality (3). In the diagnostic strategy of PE, standardised clinical decision rules (CDRs) are commonly used to assess the probability of PE, with variables quantifying the likelihood of the diagnosis. Several CDRs have been derived and validated (4-7). The most common CDR is the Wells score, consisting of items obtained from history, physical examination and a subjective item: a physician should judge if an alternative diagnosis is more likely than PE (8). The Revised Geneva Score (RGS) is comparable, but lacks the subjective item and assigns different weight to the different variables (9). In order to simplify the calculation of the scores, the Wells score and RGS have both been simplified: all items are now assigned with one point instead of the different weight per item in the original scores (4;5). These four CDRs (Wells score, RGS, simplified Wells and simplified RGS) have recently been validated prospectively in patients with suspected PE and all showed a similar safety and clinical utility in excluding PE in combination with a negative D-dimer (10). Interestingly, the subjective item: "alternative diagnosis less likely than PE" seemed predictive for PE in patients with malignancy (11). Since the original and simplified Wells scores contain this item, these CDRs might exclude PE more often in patients with malignancy compared to the (simplified) RGS. However, because the item "active malignancy" is present in all CDRs, and D-dimer levels are often above the cut-off level in patients with malignancy, this diagnostic strategy is less specific for this high-risk category (11;12). We assessed the performance of the four CDRs in excluding PE combined with a negative D-dimer test in patients with suspected PE and a malignancy.

Methods

We analyzed the data from a prospective multicentre cohort study, which included 834 consecutive in-and outpatients with suspected PE.

Study patients

We analyzed the data from a recently published prospective multicentre cohort study, which included 834 consecutive in-and outpatients with clinically suspected acute PE [24]. Patients were included in 7 participating academic and non-academic medical centers in the Netherlands between July 2008 and November 2009. For the current analysis, only patients older than 50 years were included.

Patients were excluded if they were under the age of 18 years, had a life expectancy of less then 3 months, were treated with therapeutic-dose low molecular weight heparin or unfractionated heparin that was initiated 24 hours or more prior to eligibility assessment, received treatment with vitamin K antagonists, had a contraindication to helical CT scan because of allergy to intravenous iodinated contrast or renal insufficiency (creatinine clearance of < 30 ml/min, using the Cockroft-Gault formula), were pregnant or unable to return for follow-up. Patients were followed up for 3 months. Only patients older than 50 years were included in the current analysis for this paper. Institutional ethical review boards of all participating hospitals approved the study protocol and informed consent was obtained from all included patients.

Data analysis

In the original study cohort, the Wells, simplified Wells, RGS and simplified RGS clinical prediction rule were calculated in all patients. PE was considered 'unlikely' in case of a Wells score of 4 points or less, a simplified wells score of 1 point or less, an RGS score of 5 points or less and a simplified RGS score of 2 points or less. A score above the respective cut-offs of all CDRs, was indicated as PE 'likely'. Demographic data and additional relevant information (e.g. recent trauma or surgery, cancer, use of anticoagulants, duration of time since symptom onset and D-dimer test result) were collected on a Case Record Form (CRF). A high-sensitivity quantitative D-dimer test was performed, depending on the local practice, either VIDAS D-dimer assay, Biomereux, Marcy L'etoile, Tinaquant assay, Roche diagnostica, STA-liatest D-di, Diagnostica Stago or Innovance D-dimer, Siemens. The computerized design forced the physician to start the diagnostic process with clinical evaluation of the patient and to enter all variables necessary to calculate the four CDRs and the D-dimer test result into the computer. The

computer program calculated the four individual CDR scores. If at least one of the four CDRs was classified as 'unlikely' or in case of an elevated D-dimer result a CT scan was performed. The physician initiated the next recommended step in the diagnostic process according to a predefined study flow: either exclusion of PE based on an unlikely CDR and a negative D-dimer level or performing a CT scan.

We investigated the efficiency, defined as the percentage of patients with – and without a malignancy and a suspicion of PE, in whom PE could be excluded by an 'unlikely' CDR in combination with a normal D-dimer, according the cut-off value of 500 µg/L. When patients were cured from a malignancy and did not receive any kind of treatment anymore for the last six months, we considered the patients as having no malignancy. We calculated the percentage of patients in whom PE could be excluded in all CDRs, by the number of 'unlikely' PEs in combination with a negative D-dimer, according the cut-off point of 500µg/L. Furthermore, the failure rate was evaluated for each CDR in combination with the D-dimer, defined as the number of patients in whom VTE was diagnosed during the diagnostic evaluation or during follow-up, despite an unlikely CDR and normal age-adjusted D-Dimer. 95% Confidence intervals (CI) were calculated around the observed incidences. All analyses were performed using SPSS version 16.0 (SPSS, Chicago il, USA).

Results

Of 807 consecutive patients with suspected PE, 114 (14%) had a malignancy, of whom 34 patients (30%) were diagnosed with PE. The mean age was 60 years and 58% were females (table 1). First, we looked at the results of the CDRs without taking the D-dimer test results into account. In patients with a malignancy, significantly more patients had an unlikely CDR using the original Wells score (58%, 95% CI 49-67) compared to the simplified Wells score (19%, 95% CI 13-28) and both the original and simplified RGS (32%, 95% CI 21-37). Nonetheless, the prevalence of PE in patients with an 'unlikely' score was did not differ significantly between the four CDRs; Wells 18% (95% CI 11-29), Simplified Wells 9% (95% CI 2-28), RGS 24% (95% CI 13-40), Simplified RGS 22% (95% CI 12-38).

The sensitivity of the simplified Wells score (94%, 95% CI 81-98) was higher compared to the other three CDRs (Wells score 65% (95% CI 48-95%), RGS 74% (95% CI 57-84%), simplified RGS 76% (95% CI 60-88%), respectively) ($p < 0.05$). The specificity of the simplified Wells (25%, 95% CI 17-36) was lower compared to the other CDRs 68% (95% CI 57-77%) for the Wells score, and 35% (95% CI 25-46%) for both RGS,

respectively ($p < 0.05$). Moreover, the negative predictive value (NPV) of the simplified Wells score (91%, 95% CI 72-97) was markedly higher compared to the Wells score (82%, 95% CI 71-89), RGS (76%, 95% CI 60-87%) and the simplified RGS (78%, 95% CI 62-88%).

Table 1. Baseline characteristics of patients with clinically suspected Pulmonary Embolism (PE) plus malignancy and the sensitivity, specificity and negative predictive value (NPV) of four different clinical decision rules (CDRs) to evaluate the difference in value of in this category of patients.

Characteristics	**patients with suspected PE and malignancy, n=114**
Age in years, mean (SD)	60 (15.5)
Female, n (%)	66 (58)
History of VTE, n (%)	4 (3.5)
Recent surgery or immobilisation, n (%)	50 (44)
Haemoptysis, n (%)	5 (4.4)
Heart rate > 100 beats per minute, n (%)	35 (31)
Clinical signs of DVT, n (%)	5 (4.4)
Use of hormonal therapy, n (%)	6 (5.3)
CDR unlikely and negative D-dimer	
Wells, n, (%, 95% CI)	7 (6.0, 3-12)
Simplified Wells, n, (%, 95% CI)	2 (1.8, 0.5-6)
RGS, n, (%, 95% CI)	4 (3.5, 1-8.7)
Simplified RGS, n, (%, 95% CI)	4 (3.5, 1-8.7)
Sensitivity, n (%, 95% CI)	
Wells	22/34 (65, 48-79)
Simplified Wells	32/34 (94, 81-98)
RGS	25/34 (74, 57-85)
Simplified RGS	26/34 (76, 60-88)
Specificity, n,(%, 95% CI)	
Wells	54/80 (68, 57-77)
Simplified Wells	20/80 (25, 17-36)
RGS	28/80 (35, 25-46)
Simplified RGS	28/80 (35, 25-46)
NPV, n (%, 95% CI)	
Wells	54/66 (82, 71-89)
Simplified Wells	20/22 (91, 72-97)
RGS	28/37 (76, 60-87)
Simplified RGS	28/36 (78, 62-88)

CI Confidence Interval, CDR Clinical Decision Rule, DVT, deep venous thrombosis; n number, RGS Revised Geneva Score, SD standard deviation, VTE venous thromboembolism

As expected, in the group with malignancy only few patients had a negative D-dimer test (9.4%). Consequently, the number of patients in whom PE could be excluded, based on the CDR combined with a negative D-dimer test result, was low and no significant differences were found between the Wells score, which excluded 7 patients (6%, 95% CI 3-12), the simplified Wells score, which excluded 2 patients (1.8%, 95% CI 0.5-6%) and both RGS scores 4 patients (3.5%, 95% CI 1-9%) respectively.

No patient with an unlikely CDR and a negative D-dimer developed PE during follow-up. Due to the relative small number of patients with a malignancy, the upper 95% CI of the false negative rates ranged from 30%-70% in the Wells score and simplified Wells score respectively.

Discussion

This analysis confirms that the clinical utility of a CDR combined is significantly lower among patients with compared to those without active malignancy. Fewer patients with a malignancy were categorised as PE "unlikely" with the Wells rule and less had a normal D-dimer test. Consequently, the proportion of patients in whom PE can be excluded based on CDR and D-dimer test is lower in patients with malignancy (6% versus 26.4% using the Wells score).

Moreover, this analysis showed that in patients with malignancy 58% had an unlikely original Wells score versus 19%, with an unlikely simplified Wells score ($p < 0.001$). However, the D-dimer test performed less well in patients with malignancy compared to patients without. For this reason, fewer patients had a normal D-dimer test, 7% using the Wells score and 2% using the simplified Wells score, compared to 26% in both scores in the malignancy group ($p < 0.001$).

Previously, Carrier et al. investigated the strategy of CDR-D-dimer test combination in patients with a malignancy and suspected DVT (13). In only 6% of the patients DVT was excluded, based on a negative D-dimer test result combined with an unlikely Wells score. The findings of the current study are in line with the literature (14). Furthermore, in patients with a malignancy and suspected PE, an unlikely Wells score combined with a negative D-dimer test excluded PE in 10% of the patients, with a failure rate of 2% (95% CI 0.05-10.9) during 3-month follow-up (12). These findings were not significantly different from our present findings. Moreover, it seems safe to exclude PE in patients with a malignancy in case of an unlikely CDR and a normal D-dimer result. Because of the low specificity of 21%, however, the D-dimer has a lower clinical utility in these

high-risk patients (11;12;15). Di Nisio et al. concluded that when testing 100 patients with suspected PE and a malignancy, a normal D-dimer concentration safely excludes PE in only 15 patients with and in 43 patients without a malignancy (15).

In the present study we assessed the performance of four commonly used CDRs in patients with malignancy and suspected PE. The simplified Wells score had the highest sensitivity and NPV (Table 1) and therefore seemed most attractive in the work up of patients with a malignancy and suspected PE. However, after combining the CDRs with a negative D-dimer test the number of patients in whom PE could be excluded was modest, only 2-6%. This is in clear contrast to the 20-30% of patients without a malignancy. Whether elevating the D-dimer cut-off in patients with malignancy could increase the clinical utility of the CDR – D-dimer combination has been reported by Douma et al; raising the cut-off to < 700 μg/l for these patients resulted in a modest absolute increase in the proportion of patients in whom PE could be excluded of 5%, whereas the false-negative rate increased from 0.0% (95% CI: 0.0- 8.8) to 1.6% (95% CI: 0.3- 8.7) (11). Consequently, there is clear need for a CDR specifically designed for patients with a malignancy, ideally combined with a sensitive biomarker, which is less influenced by presence of malignancy.

Unfortunately, we had no information about tumour type, stage or treatment. These factors could have influenced the D-dimer result (16). Furthermore, although this was a cohort of consecutive patients with suspected PE, and the D-dimer levels and all items of the CDRs were collected prospectively, the performance of the different CDRs in the malignancy group was analysed retrospectively. Also, the number of patients with a malignancy and a negative D-dimer was rather small; therefore the 95% CIs of the failure rates were wide. Finally, different D-dimer assays were used in the participating centres. Although there was no significant difference between these assays, this study might not have been sufficiently powered to detect a difference.

In conclusion, direct comparison of four different CDRs in patients with malignancy and suspected PE suggests that the simplified Wells score might have a higher sensitivity and NPV compared to the other CDRs. This did not translate in a higher number of patients in whom PE could be excluded without the need of imaging, probably due to the low number of patients with a normal D-dimer result.

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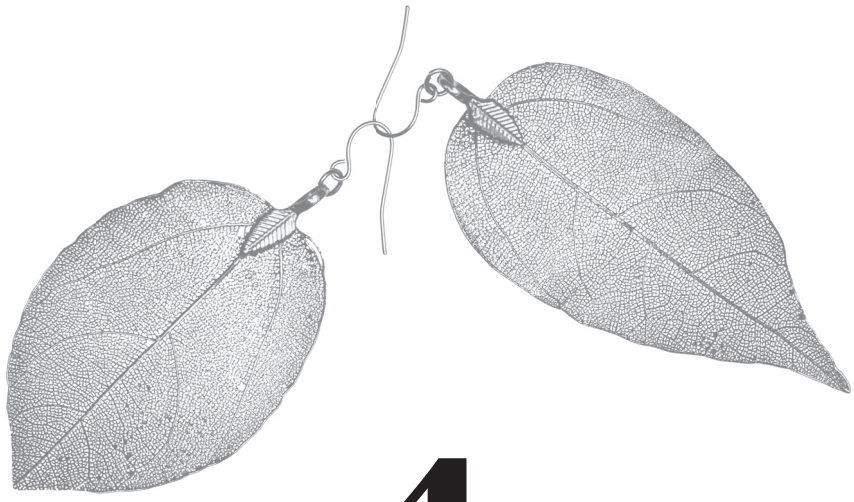

CHAPTER 4

The accuracy of chest X-ray in combination with perfusion scanning as an alternative for CTPA in young patients with a high risk of pulmonary embolism

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Abstract

Background: Computed tomography pulmonary angiogram (CTPA) has become the standard test in the diagnostic workup of patients with suspected pulmonary embolism (PE). However, especially young patients have an increased risk of cancer due to radiation exposure with CTPA and may benefit from an alternative diagnostic modality. Perfusion scanning combined with chest X-ray result (X/Q) by using the PISAPED criteria seems an adequate alternative, but has never been prospectively validated. We therefore directly compared this strategy with CTPA in patients aged < 50 years with suspected PE.

Methods: Consecutive patients with a likely clinical probability or an abnormal D-dimer level were included, in whom both CTPA and X/Q were performed. X/Q-scans were independently analyzed by two trained nuclear physicians. The accuracy of X/Q according to the PISAPED criteria in terms of sensitivity, specificity positive predictive value (PPV) and negative predictive value (NPV) was calculated.

Results: A total of 76 patients were included. The prevalence of PE was 33%. The interobserver agreement for X/Q-scan reading was high (κ=0.89). After consensus reading, 21 patients (28%, 95% confidence interval (CI) 19-38%) were categorized as 'PE present', 54 (71%, 95% CI 60-80%) as 'PE absent', and two (2.6%, 95% CI 0.8-9.0%) as 'non-diagnostic'. In 17 cases (22%, 95% CI 14-32%) was a discrepancy between CPTA and the X/Q result. The PPV and NPV were 71% (95% CI 50-86%) and 83% (95% CI 71-91%), respectively.

Conclusion: Although the X/Q-strategy seems promising in literature to reduce CTPA in young patients, its diagnostic accuracy was limited in our cohort.

Introduction

A diagnostic algorithm based on clinical probability, D-dimer, and computed tomography pulmonary angiogram (CTPA) has been shown to be a safe and efficient strategy in the management of patients with suspected pulmonary embolism (PE) (1). However, concerns have been raised regarding the risk of cancer following radiation exposure with CTPA, especially among young women (2;3). In this group of patients, the lifetime risk of cancer incidence is considerable, particularly the risk of breast cancer (2;3). Compared to CTPA, breast irradiation with ventilation/perfusion scintigraphy is approximately 50-100 times lower (4-6).

Although ventilation/perfusion scintigraphy (V/Q-scan) is an established diagnostic test, ventilation scintigraphy is expensive and not available in many hospitals. Also, the proportion of non-diagnostic scan results is around 50%, which limits its use in clinical practice. Previously, several studies have evaluated whether ventilation lung scanning could be replaced by the chest X-ray in defining a segmental perfusion defect to be matched or mismatched in patients with suspected PE (X/Q-scan) (7-9). Although the positive predictive value (PPV) of a high probability X/Q-scan was high (86%), the proportions of non-diagnostic test results were still considerable (ranging from 21% to 49%).The use of only perfusion scanning instead of the V/Q-scan is also supported by a prospective study by the PISAPED group (Prospective Study of Acute Pulmonary Diagnosis) (10). A retrospective validation (9), showed a sensitivity and specificity of 80% and 97%, respectively, compared to CTPA (9). However, because of the retrospective design, the Q-scans were performed without following the PISAPED protocol. These studies assessed patients without stratification according to pre-test clinical probability combined with the D-dimer test. Moreover, young patients have less co-morbidity than elderly patients. Consequently, this may improve the diagnostic yield of an X/Q scan in this subgroup of patients (11;12).

The aim of this study was to prospectively investigate the sensitivity, specificity, PPV and the negative predictive value (NPV) of the X/Q-scan according to the PISAPED criteria in comparison to CTPA in patients aged < 50 years, and with a likely clinical probability of PE or an abnormal D-dimer result. Furthermore, we assessed the proportion of perfusion scans classified as 'non-diagnostic' according to the PISAPED criteria, requiring CT-scanning.

METHODS

Patients

The study was a prospective, multi-center cohort study of consecutive in- and outpatients younger than 50 years old with suspected PE, who had either a likely clinical probability (according to Wells and/or Revised Geneva Score) (13;14) or an abnormal D-dimer test result (1). The D-dimer test was considered normal when below 500 μg L^{-1}. Next to the CTPA, a chest X-ray and Q-scan were performed within 24 hours in all participants.

Patients were included in seven academic and non-academic medical centers in the Netherlands and Belgium between October 2008 and June 2011. Participants were managed according to the outcome of the CTPA, and according to local hospital practice. Exclusion criteria were age below 18 years or above 50 years, pregnancy, use of therapeutic dose LMWH or unfractionated heparin for longer than 48 hours prior to eligibility assessment and inability to perform a perfusion scan within 24 hrs after CTPA. Demographic data and additional relevant information were collected on a Case Record Form. Institutional ethical review board of all participating centers approved the study protocol and informed consent was obtained from all included patients.

Although three months follow-up was not performed, we retrospectively evaluated whether PE occurred in patients with a discrepancy between the CTPA and the X/Q scan result.

CTPA

CTPA was the reference standard in this study. All CTPAs were assessed by the radiologist on-call. Standard contrast enhanced CTPAs were performed using a multi-detector row CT-scanner according to state-of-the-art protocols for the diagnosis and evaluation of PE (15). Patients were scanned during a single breath-hold, in caudocranial direction, from the upper level of the diaphragm to a level slightly above the aortic arch (pitch of 1, 120 kV, 150-200 mAs). One hundred milliliters of contrast was administered intravenously. An imaging delay of 20 seconds was used and overlapping images were reconstructed every 3 mm. PE was confirmed by the presence of a constant intraluminal defect in (sub) segmental or more proximal branches of a pulmonary artery.

Perfusion scintigraphy

Six-view perfusion lung scintigraphy was performed within 24h of referral following the guidelines of the Society of Nuclear Medicine (SNM 2004) (16). Images were

obtained immediately after the administration of 148-155 MBq of technetium-99m macroaggregated albumin particles (MAA) after several deep breaths. According to the PISAPED protocol, care was taken to inject the radioactive bolus with the patient positioned as closely as possible to the sitting position in order to preserve the effect of gravity on the regional distribution of pulmonary blood flow (10). The effective radiation dose varied per MBq dose, ranging from 0.55-1.1 mSv.

Chest radiographs (X)

In examining the chest radiographs, the PISAPED readers considered the size and shape of the heart and hilar arteries, position of the diaphragm, presence or absence of pulmonary parenchymal abnormalities (consolidation, atelectasis, edema), and pleural effusion. Chest radiographs were rated as abnormal if one or more of the following were present: enlargement of the heart or hilar vessels; elevated diaphragm (unilateral or bilateral); pleural effusion (including intrafissural liquid); increased lung density (focal or diffuse); pulmonary edema; oligemia with or without pleonemia in the contralateral lung; consolidation suggestive of infarction; emphysema; or fibrothorax.

X/Q-scan

The X/Q- scans were centrally adjudicated according to the PISAPED criteria (10) (Table 1) and compared with the CTPA. For our analysis we used the results of the chest X-ray combined with Q-scan (X/Q-scan). All images at time of the diagnosis were stored on CD-Rom or comparable storage. All X/Q-scans were analyzed by two trained nuclear physicians, who were blinded of clinical information or CTPA result. In case of disagreement, a consensus reading was carried out with a third reviewer. In case of abnormalities on the perfusion scan, the findings were combined with the result of the chest radiograph (X/Q-scan).

The readers interpreted the Q-scans according to PISAPED criteria (Table 1). Abnormal perfusion scans were classified as 'PE present' when single or multiple wedge-shaped perfusion defects were present, irrespective of abnormalities on the chest X-ray, aiming to reduce the number of non-diagnostic scans. PE was considered as 'PE absent' in case of either no perfusion defects of any kind or perfusion defects which are smaller or equal in size and shape to the following chest radiograph abnormalities: cardiomegaly, enlarged aorta, hilar and mediastinum, elevated diaphragm blunting of the costophrenic angle, pleural thickening, intrafissural collection of pleural effusion. Also, if the perfusion defects were not wedge-shaped regardless matching chest

radiograph abnormalities, X/Q-scan was considered as 'PE absent'. Wedge-shaped areas of overperfusion are usually not seen. In all other cases the X/Q-scan was considered non-diagnostic. These patients would, theoretically, require additional testing (Table 1, criteria adapted from Miniati et al (10)).

Table 1. PISAPED Scintigraphic Criteria (Prospective Study of Acute Pulmonary Diagnosis) (10).

PE present	
Abnormal: PE	One or more wedge-shaped perfusion defects, with or without matching chest X-ray abnormalities. Wedge-shaped areas of overperfusion usually coexist.
PE absent	
Normal:	No perfusion defects of any kind
Near normal:	Perfusion defects smaller or equal in size and shape to the following chest X-ray abnormalities: – cardiomegaly – enlarged aorta, hila and mediastinum – elevated diaphragm blunting of the costophrenic angle – pleural thickening – intrafissural collection of liquid
Abnormal: no PE	Perfusion defects not wedge-shaped with or without matching chest X-ray abnormalities. Wedge-shaped areas of overperfusion are usually not seen
Non-diagnostic	
Cannot classify as PE+ or PE-	

Statistical analysis

Normally distributed variables are presented as mean and standard deviations (SD) and non-normally distributed variables are expressed as medians with (interquartile-) ranges. The proportion of patients in each X/Q category was calculated, as well as the sensitivity, specificity and positive and negative predictive values, with 95% confidence intervals (CI). To express inter-reader agreement the multi-reader kappa (κ) coefficient was calculated. Sensitivity, specificity, positive and negative predictive values of X/Q were calculated in comparison to CTPA. All analyses were performed using SPSS, version 19.0 (SPSS, Chicago il. USA).

Results

A total of 78 patients with suspected PE and a likely clinical probability or abnormal D-dimer test result were included. The Q-scan result was missing in one patient and in another patient the timeframe between the CTPA and Q-scan was > 24 hours. Consequently, these patients were excluded. Table 2 shows the baseline characteristics of the 76 participants, who underwent CTPA and X/Q-scan. Twenty-six patients (34%) had a likely clinical decision rule, 68 patients (90%) had an abnormal D-dimer test result. Twenty-five patients (33%) were diagnosed with PE based on the CTPA.

Table 2. Clinical characteristics of patients with suspected PE (likely clinical probability or abnormal D-dimer test result), who underwent with CTPA and X/Q-scan.

Characteristic	
Number of patients, n	**76**
Female, n (%)	48 (64)
Age, years, median (IQR)	40 (29-45)
Body Mass Index, mean (SD)	27 (5.9)
Duration of complaints in days, median (IQR)	3 (1-10)
COPD, n (%)	1 (1.3)
Heart failure, n (%)	2 (2.6)
Use of estrogen containing drugs, n (%)	21 (28)
Clinical symptoms of DVT, n (%)	8 (11)
Tachycardia, n (%) #	14 (18)
hemoptysis, n (%)	4 (5.3)
Immobilization or surgery in last 4 weeks, n (%)	21 (28)
Active cancer, n (%)	6 (7.9)
Previous episode of VTE, n (%)	7 (8.0)
Likely Wells score or Revised Geneva Score	26 (34)
D-dimer level > 500 μg L^{-1}, n (%)	68 (90)

COPD chronic obstructive pulmonary disease, CTPA computed tomography pulmonary angiogram DVT deep venous thrombosis, N number, SD standard deviation, VTE venous thromboembolism, X/Q-scan chest X-ray combined with perfusion scintigraphy.

X/Q

The interobserver agreement was almost perfect (κ=0.89). After consensus reading, 21 patients (28%, 95% CI 19-38%) were categorized as 'PE present' with X/Q, 53 patients (70%, 95% CI 64-84%) were categorized as 'PE absent' and in two patients (2.6%, 95% CI 0.8-9.0%), the scan was classified as non-diagnostic (Table 3).

Overall agreement for the diagnosis of PE between the CTPA and the X/Q-scan was present in 59 of 76 patients (78%, 95% CI 67-86%) (Table 3). The sensitivity and specificity of the X/Q-scan were 60% (95% CI 41-77%) and 86% (95% CI 74-93%), respectively. The PPV of X/Q was 71.4% (95% CI 50-86%) and the NPV was 83.0% (95% CI 71-91%), respectively (Table 3).

In nine patients, PE was detected with CTPA whereas X/Q-scan scored 'PE absent'. Eight of these cases had segmental or more proximal PE and one patient had subsegmental PE. All these patients received anticoagulant therapy. On the other hand, PE was ruled out by CTPA, but classified as 'PE-present' on X/Q-scan, in six patients. Three months follow-up in those patients was uneventful despite the fact that anticoagulant therapy had not been started.

Table 3. Overall agreement of the CTPA and Chest X-ray/perfusion scan (X/Q) according to PISAPED (10).

		CTPA		
X/Q		PE	No PE	**total**
	PE present, n (%)	15 (20)	6 (8)	21 (28)
	PE absent, n (%)	9 (12)	44 (58)	53 (70)
	Non diagnostic, n (%)	1 (1)	1 (1)	2 (3)
	Total, n (%)	25 (33)	51 (67)	76 (100)

CI confidence interval, CTPA computed tomography pulmonary angiogram, PE pulmonary embolism, PISAPED Prospective Study of Acute Pulmonary Diagnosis

Sensitivity	60% (95% CI 41-76%)
Specificity	86% (95% CI 74-93%)
Positive predictive value	71% (95% CI 50-86%)
Negative predictive value	83% (95% CI 71-90%)

Discussion

In our cohort of young patients suspected of PE with likely clinical probability or abnormal D-dimer, X/Q-scans read according to PISAPED criteria did not reliably categorize segmental perfusion defects as 'PE absent' or 'PE present' for PE. The PPV was 71% (95% CI 50-86%), and NPV of 83% (95% CI 71-91%) by using CTPA as standard. Therefore, X/Q-scan as a diagnostic test for PE was not accurate enough to either confirm or exclude PE.

Our results differ from previous reports. Sostman and colleagues compared both the PISAPED criteria and the PIOPED II criteria with CTPA, using data of 889 perfusion scans (9). Compared to CTPA, they found a sensitivity of the PISAPED criteria of 83.3% (95% CI, 76.0-88.7%) and a specificity of 97.0% (95% CI, 95.5-98.0%) among patients less than 50 years. The PPV and NPV were 96% and 95 %, respectively. There were no patients with a non-diagnostic scan in this cohort. The reason why we cannot reproduce these data on our cohort is unclear. However, since they have validated the PISAPED criteria retrospectively in scans using the PIOPED II protocol, there was no care taken that the patients received the radioactive bolus while they were positioned in a sitting position, according to the PISAPED protocol (10). Besides, in this study, patients were stratified according to their pre-test probability by using the Wells score, but not in combination with a D-dimer test-result. However, whether this explains the large difference between the accuracy of the PISAPED criteria is not known.

Previous studies, investigating the efficiency of a chest radiograph and Q-scan showed, high levels of the PPV, ranging from 82-100% (7;8;17). In these studies, the chest X-ray was also used as a substitute for ventilation scintigraphy, and was interpreted in a similar fashion when it was combined with the Q-scan. PE was considered present in case of one or more segments of X/Q mismatches, regardless the shape of the perfusion defect. Although adequate predictive values were obtained in these studies, the number of non-diagnostic results was also high (ranging from 31-49% (7;8;17)).

PISAPED criteria classified patients as 'PE present' or 'PE absent' based on the shape of the perfusion defect, irrespective of the presence of chest X-ray abnormalities. Therefore fewer non-diagnostic test results were to be expected, which is confirmed by our results (2 out of 77). However, the wedge shape perfusion defect that had to be specifically present for the Q-scan being classified as 'PE present' may have caused the high number of false negative test results (9 of 53 patients with 'PE absent' were diagnosed with PE by CTPA).

The near perfect interobserver agreement of the X/Q-scans using the PISAPED criteria (κ=0.89), which is in line with the literature (Sostman et al. reported κ=0.903) (9), suggests a good consistency in the evaluation, which strengthens our results. Among patients diagnosed with PE on the X/Q-scan and with a negative CTPA result (n=6), none had a suspected or recurrent PE during the next 3 months, despite the lack of anticoagulant therapy. Additionally, among patients classified as 'PE absent' by the X/Q, and having PE on CTPA, all but one patient had segmental or larger PE with a CTPA. One of these patients had central PE, which leads to large areas of hypoperfusion and makes wedge-shaped perfusion defects harder or even impossible to detect.

Our finding that CTPA detects more PE than the Q-scan, is in line with the literature (18). The proportion of patients with PE was comparable to other management studies on the diagnostic work-up of PE (36% and 45%) (1;19). Our study has implications regarding the role of the Q-scans in patients with suspected acute PE. The advantages of CTPA secure a place for CTPA as a first-line diagnostic imaging test in appropriately selected patients (1). However, the advantages of Q-scanning, which are in addition to the lower radiation dose and avoidance of iodinated contrast material, lower costs, can also be considered. Despite an increased use of Q-scans appears warranted, especially in a young and healthy population (20), our data show that the PISAPED criteria seem neither a safe nor an accurate alternative for CTPA. However, the accuracy of X/Q-scan strategy, prospectively assessed and using other criteria (i.e. modified PIOPED II criteria), remains to be shown. If in a prospectively conducted investigation X/Q-scan shows a high sensitivity and specificity, clinical care might be enriched by X/Q-scan next to the CTPA. Currently, however, CTPA is the gold standard for detecting or excluding PE, regardless the patients' age.

The conclusions of this study are strengthened by its prospective and multicenter design, in patients with a risk stratification including a clinical decision rule and a D-dimer, which enhance the extrapolation of our findings. Some limitations of our study warrant consideration. First is the moderate sample size. We discontinued this study after the first 78 included patients, since it appeared from the analysis that further continuation of the study was futile. This was on the basis of the NPV and PPV of the X/Q-scan, which seemed to fall short compared to CTPA. We believe that the conclusions of the diagnostic accuracy of the X/Q-scan according to the PISAPED criteria would not change with a larger sample size. In addition, we did not perform follow-up in all participants. However, since the event rate of VTE after a negative CTPA results is negligible (1), we consider this strategy as safe. Besides, in the patients with a negative CTPA result and

'PE present' on the X/Q-scan, we did perform follow-up retrospectively. None of these patients experienced (suspected) VTE within three months after inclusion.

In conclusion, our results demonstrate that in patients aged < 50 years with a likely clinical probability of PE or abnormal D-dimer test result, a diagnostic strategy of X/Q-scan according to the PISAPED criteria is insufficient to reliably exclude or confirm the diagnosis of PE.

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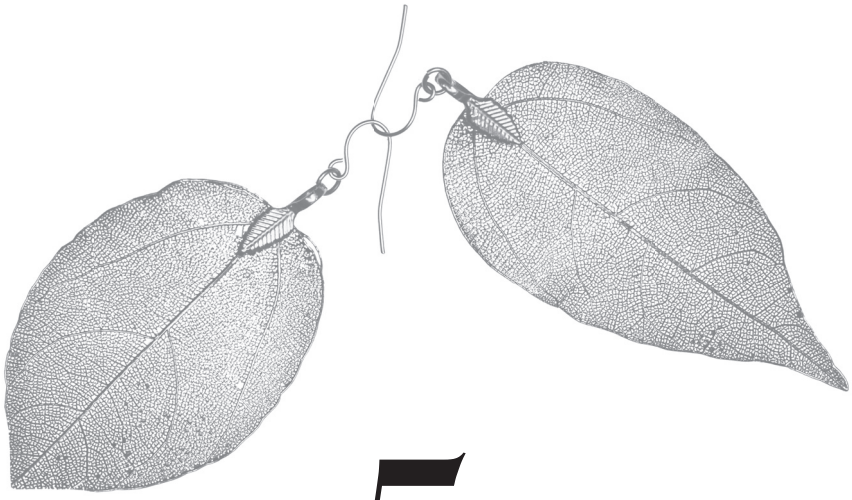

CHAPTER 5

The accuracy of D-dimer testing in suspected pulmonary embolism varies with the Wells score

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Abstract

Background: In patients suspected for pulmonary embolism (PE), D-dimer testing is often used in combination with the Wells score to exclude pulmonary embolism, with a fixed D-dimer positivity threshold of 500 μg/L. We evaluated whether its diagnostic accuracy varies with the Wells score.

Methods: Data were collected in a multicentre cohort study of consecutive patients with clinically suspected PE. CT-scan results and follow-up were used as the clinical reference standard. We estimated D-dimer sensitivity, specificity and area under the ROC curve (AUC) for subgroups of patients, defined by having no, one or two items (including the subjective item: 'alternative diagnosis less likely than PE') positive on the Wells score.

Results: Data from 723 patients could be analysed, of which 177 (24%) patients had zero items on the Wells score, 300 (41%) had one item positive, and 136 (19%) had two items positive, including the subjective item. The overall diagnostic accuracy of the D-dimer test, as expressed by the AUC, was 0.92 (95% CI: 0.82 to 0.99) in the subgroup of patients with a zero Wells score. This AUC was significantly higher than the AUC in the subgroup with one item positive (0.78; 95% CI 0.72 to 0.84) and the subgroup with two items positive (0.78; 95% CI 0.70 to 0.86). The estimated sensitivity for the D-dimer test at the 500 μg/L positivity threshold was 1.00, 0.98 and 1.00 in the three subgroups respectively. Specificity was significantly different, at 0.49, 0.30 and 0.16 respectively.

Conclusion: The diagnostic accuracy of D-dimer testing varies significantly across subgroups defined by the Wells score. The D-dimer test positivity threshold could be adapted to keep specificity more comparable across all values on the Wells score.

Introduction

Although the incidence of pulmonary embolism (PE) increases with age from 1 per 10,000 in childhood to nearly 8 per 1000 in older-aged patients (1), the prevalence of objectively proven PE in patients with suspected PE is relatively low: between 20-30% (2;3). Computerized tomographic (CT-) scanning in suspected PE has a high sensitivity, ranging between 64-100%, with a specificity between 89-100% (4), however CT-scans have also adverse effects, such as an increased lifetime risk of malignancy from radiation exposure and the risk of contrast nephropathy (5;6). These concerns force physicians to use a diagnostic strategy in suspected PE that results in the lowest possible number of CT-scans.

The overall sensitivity of the D-dimer test in detecting PE, using a cut-off value of 500µg/L is estimated at nearly 100%; its reported specificity, however, varies between 30-40% (7;8). Standardised clinical decision rules (CDRs) are therefore additionally used in suspected PE. One frequently used, is the Wells score, which consists of items obtained from history (risk factors for PE), physical examination (such as heart rate and signs of deep venous thrombosis (DVT)) and a subjective item, where the physician can judge whether an alternative diagnosis is more likely than PE (9). Recently, the simplified version of the Wells score (all items are assigned one point) was found to have a performance similar to that of the original rule in combination with a high sensitive D-dimer test (3;7). An 'unlikely' Wells score combined with a negative D-dimer test safely excludes PE in 20-40% of patients with suspected PE (10). Of the remaining patients in whom a CT-scan should be performed in order to either exclude or confirm PE, only 20-30% has a positive CT-scan for PE (11). CT-scanning is thus indicated in case of a 'likely' Wells score or a positive D-dimer test (3).

It is well known that the diagnostic accuracy of a test can vary with the strength of clinical suspicion (12). In that case, previously reported accuracy estimates may not be generalizable to all subgroups. We investigated if this is also the case in D-dimer testing in suspected PE. We compared the accuracy of the D-dimer in subgroups of patients with 0, 1 or 2 items of the Wells score positive.

Methods

For this purpose we performed an analysis of data from a prospective multicentre cohort study in patients with clinically suspected PE, reported in detail elsewhere (13). In brief, the study population consisted of consecutive in- and outpatients in whom acute PE was suspected. The dichotomized Wells score (cut-off value 4), simplified Wells score (cut-off value 1), and dichotomized Revised Geneva Score (RGS) (cut-off value 5) and simplified RGS (cut-off value 2) were calculated in each patient and combined with a high-sensitivity quantitative D-dimer test. A CT-scan was performed in patients with a 'likely' outcome of at least one of the CDRs, or if the D-dimer was elevated (> 500 μg/L). In case of an unlikely CDR with all scores and a normal D-dimer result, no CT-scan was performed. Patients were followed for 3 months by telephone; they were instructed to return to the hospital if symptoms of PE or DVT occurred and imaging diagnostic tests were done if PE or DVT was suspected (13).

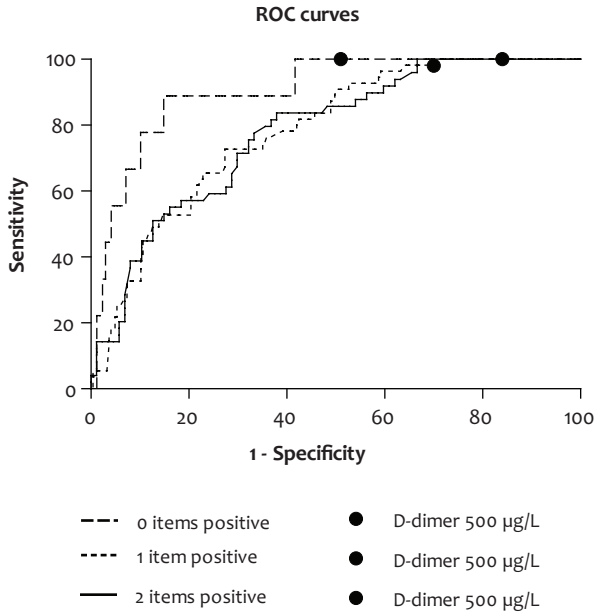
The mean age of the 807 included patients with suspected PE was 52 years; 61% were females. A D-dimer result was available in 723 (90%), of whom 156 patients had PE (22%). Median duration of symptoms was 2 days (inter quartile range 1-7); the mean body mass index was 26 (standard deviation 5).

We defined 3 groups of patients, based on the number of positive items on the Wells score. The first group had none of the Wells items positive. The second group had only 1 item positive; since our analysis focused on patients with a low pre-test probability, it did not matter which item was positive. Finally we assessed patients with 2 positive Wells items, 1 of which was the subjective item, as it is known that when physicians are aware of a positive D-dimer, they are more likely to consider the subjective item 'alternative diagnosis less likely than PE' as positive, regardless of the clinical situation (14). Consequently, in clinical practice, there sometimes is only one item positive officially, combined with a 'false positive' subjective item (14).

To express the diagnostic accuracy of the D-dimer in each subgroup, we calculated the area under the Receiver Operating Characteristics curve (AUC). To evaluate the significance of difference in the AUC, the z-test statistic was used. We also calculated the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratio of the 500 μg/L D-dimer cut-off in each group. All analyses were performed using SPSS software, version 19.0 (SPSS Inc, Chicago, Ill). A significance level of 0.05 was used in all analyses.

A total of 177 patients had zero positive items on the Wells score, of whom 9 patients had PE (5%). The AUC of the D-dimer test in this subgroup was 0.91 (95% CI 0.82-0.99) (Figure 1). Another 300 patients had one item positive: this was PE as the most likely diagnosis in 64%, being immobilized within 4 weeks prior to enrolment in 9%, malignancy in 7%, heart rate above 100 beats per minute in 11%, clinical suspicion of DVT in 3%, and 3% had haemoptysis. In this subgroup of 300 patients 55 had PE (18%). The AUC of the D-dimer test in this subgroup was significantly lower than in the group with zero items positive: 0.78 (95% CI 0.72-0.84; p=0.020) (Figure 1).

Figure 1. Receiver operating characteristic curves illustrating the diagnostic performance of the D-dimer in combination with Wells scores of 0, 1 and 2 items scored as positive.



The areas under the curve were 0.91 (95% confidence interval (CI) 0.82-0.99), 0.78 (95% CI 0.72-0.84) and 0.78 (95% CI 0.70-0.86) respectively.

A total of 136 patients had 2 items positive, including the subjective item. Of these patients 49 had PE (36%). The AUC in this subgroup was also significantly lower than in the subgroup with a zero score: 0.78 (95% CI 0.70-0.86; p=0.031). The AUC of the D-dimer test was not significantly different between the patients with one and those with 2 Wells items positive (p=0.42) (Figure 1).

The sensitivity of D-dimer at the conventional 500 μg/L cut-off in patients with a zero Wells score was 100% (95% CI 69%-100%). This estimated sensitivity was comparable with that in patients with 1 (98%, 95% CI 90%-100%) or 2 items positive (100%, 95% CI 93%-100%). However, the specificity was lower with increasing number of items positive: 49% (95% CI 42%-75%), 30% (95% CI 25%-37%) and 16% respectively (95% CI 10%-25%). In addition, the positive predictive value differed significantly between the 0, 1 and 2 item groups: 10%, 24% and 33% ($p < 0.0001$). The negative predictive value did not: 100%, 99% and 100% ($p=0.5$).The positive likelihood ratio in patients with 0, 1 and 2 Wells items positive was 2.0, 1.4 and 1.2, respectively. The negative likelihood ratio, however, was 0.0 for all groups.

Discussion

We showed that there is a significant difference in the diagnostic accuracy of the D-dimer test depending on the Wells score. The overall accuracy is significantly lower in subgroups with higher Wells score. At the current cut-off value, D-dimer specificity is more than halved in patients with two items positive compared to those with a zero Wells score.

Since the accuracy of the D-dimer test varies, one could consider adapting the D-dimer positivity threshold to make the behaviour similar in subgroups defined by the Wells score. Previous studies have demonstrated that a D-dimer cut-off value, adapted to the clinical probability category of the patient, has a better accuracy in excluding PE than using a single D-dimer cut-off value, regardless of the clinical probability (15-17). In those studies, the proposed cut-off value was kept at 500 μg/L for patients with an intermediate clinical suspicion of PE, but doubled (1000 μg/L) in patients with a low clinical suspicion, and halved (250 μg/L) in patients with a high clinical suspicion of PE. In a study by Kabrhel and colleagues, for example, the conventional cut-off of 500 μg/L had an overall sensitivity of 94% (95% CI 91-97) at a specificity of 58% (95% CI 56-60), and a NPV of 99.5% (95% CI 99.1- 99.7). When probability-dependent cut-offs were used, the overall sensitivity became 88% (95% CI 83-92), specificity was 75% (95% CI 74-76), and NPV was 99.1% (95% CI 98.7- 99.4) (15).

Despite the statistical significance of the differences in accuracy, the subgroups in the current analysis were of moderate size, especially the one of patients with zero positive items, making estimates in subgroups somewhat imprecise. In 84 patients no D-dimer was performed (13). The reason for these missing D-dimer tests is unclear, but

it is possible that these patients had a 'likely' result on the Wells rule, in which case a D-dimer test was not necessary to indicate CT-scan as the next diagnostic step (7). Since we also included patients with 2 items positive (including the subjective item counting for 3 points), we have also included patients with a 'likely' clinical probability according to the Wells rule in this group of patients (3).

In conclusion, the diagnostic accuracy of D-dimer testing varies significantly across subgroups defined by the Wells score. In particular, specificity is significantly lower in subgroups with one or more positive items of the Wells score. At the current cut-off value, D-dimer specificity is more than halved in patients with two items positive compared to those with none of the Wells items positive. These findings could be taken into account in improving the diagnostic strategy in patients with suspected PE.

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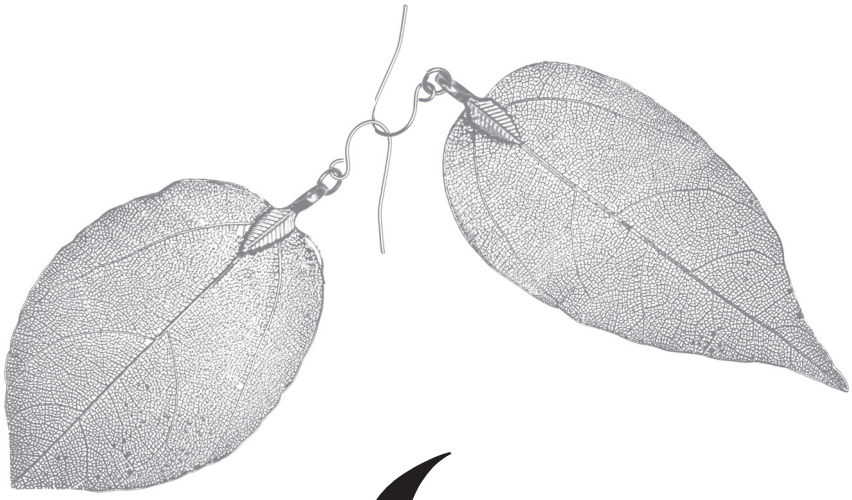

CHAPTER 6

Combining Wells score including the D-dimer results in less need for CT-scanning in patients with suspected pulmonary embolism

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Abstract

Introduction: The combination of an "unlikely" clinical decision rule and a negative D-dimer test result safely excludes pulmonary embolism (PE) in 30% of presenting patients. We aimed to simplify this diagnostic approach and to increase its efficiency.

Methods: We analysed data of a multicentre study of 723 consecutive patients with suspected PE. After constructing a logistic regression model including the D-dimer test result and Wells score items, we identified the most prevalent combinations of influential Wells items and subsequently developed a new clinical decision rule. The performance of this new clinical decision rule was externally validated in a separate dataset including 3306 patients with suspected PE.

Results: The prevalence of PE was 22%. Three Wells items were identified as significantly adding incremental value to the D-dimer test result: two clinical items (haemoptysis and clinical signs of deep vein thrombosis) and the subjective item (PE most likely). Based on the most frequent combinations of these three items we identified two groups: 1) none of these three items positive (41%), and 2) at least one of these items positive (59%). When applying a 1000 μg/L D-dimer threshold in group 1 and 500 μg/L in group 2, PE could be excluded without CT-scanning in 36%, whereas the false-negative rate was 1.2% (95% 0.04-3.3%). Alternatively, when a lower threshold of 900 μg/L and 400 μg/L was used, PE was excluded in 31%, and the false negative rate was 0.4% (95% 0.1-2.3%). In the validation cohort, the proportion of patients in whom PE could be excluded without CT-scanning, was 46% and 42% with false negative rates of 1.9% (95% CI 1.2-2.7%) and 1.4%, (95% CI 0.9-2.3%) for the two combinations of cut-off levels, respectively.

Conclusion: Combining items of the Wells rule with the D-dimer test result resulted in a simplified clinical decision rule, which additionally reduced the need for CT-scanning in patients with suspected PE. A prospective evaluation of this strategy would be required before implementation in clinical practice.

Introduction

The clinical presentation of patients with suspected acute pulmonary embolism (PE) is nonspecific and varies widely (1;2). The proportion of objectively proven PE by computerized tomography pulmonary angiography (CTPA)-scan in patients with suspected PE is relatively low: 20% to 30% of all patients undergoing CT-scanning for a clinical suspicion of PE (3;4). CT-scanning, being widely available among hospitals, has become the first-line imaging modality in patients with suspected PE (5), but is also associated with an increased lifetime risk of malignancy from radiation exposure and the risk of contrast nephropathy (6). These concerns encourage clinicians to seek a diagnostic strategy that safely reduces the number of CTPAs.

In the past decade, standardised clinical decision rules have been derived and implemented in clinical practice to determine the pre-test probability of PE. The most frequently validated and most commonly used clinical decision rule is the Wells rule (7). This score incorporates seven objective items from clinical history and physical examination and one subjective item, allowing the physician to indicate whether or not an alternative diagnosis is more likely than the presence of acute PE (Table 1) (7). The Wells rule was developed by selecting variables significantly associated with PE from an extended list of 40 items. These items were initially evaluated in univariate logistic regression analysis; significant variables that were retained after a step-wise backward elimination procedure in multivariable logistic regression were selected for the final clinical decision rule (7). Since unadjusted odds ratios calculated this way are known to have an upwards bias with lower values in replication studies, Gibson and colleagues derived and validated a simplified Wells score, assigning one point to all variables. The corresponding clinical decision rule uses a cut-off of one point; all patients with two points or more are referred for CT-scanning (Table 1) (8;9). This simplified Wells clinical decision rule showed to be as effective and safe as the original Wells rule (10). It probably is also easier to memorize, potentially leading to fewer mistakes in the acute care setting.

The Wells rule is used in combination with a high-sensitive D-dimer test (4;11). The sensitivity of the D-dimer, combined with a clinical decision rule, using a cut-off value of 500 µg/L was estimated at nearly 100%; its specificity, however, is only 30% to 40% (11;12). In patients with suspected PE, about 20% to 40% have an 'unlikely' result with the Wells score and a normal D-dimer test result (< 500µg/L). In these patients, PE can be safely excluded without CT-scanning (4;10).

The Wells clinical decision rule-D-dimer combination leads to CT-scanning in all patients with a slightly elevated D-dimer, even in patients with a Wells score of zero, although the accuracy of D-dimer testing has been demonstrated to be substantially different in this subgroup (13). In clinical practice, D-dimer-testing is often performed on a low threshold, regardless the Wells score (11). This results in more patients being referred for CTPA, which increases the number of CTPAs negative for the presence of PE, and decreases the proportion of patients in whom PE can safely be excluded without imaging. The aim of this study was therefore to derive a new clinical decision rule, combining the Wells items and D-dimer testing, with sensitivity similar to that of the original clinical decision rule but with an enhanced specificity, in order to safely reduce the number of (negative) CTPAs.

Methods

Development set

To derive a new clinical decision rule, we analyzed data from 807 patients with clinically suspected PE included in a prospective multicentre cohort study, of which the design is reported in detail elsewhere (10). Briefly, the study population consisted of consecutive in- and outpatients in whom acute PE was clinically suspected. Clinically suspected acute PE was defined as sudden onset of dyspnea, deterioration of existing dyspnea, or sudden onset of pleuritic chest pain. Patients were identified in seven academic and non-academic hospitals in the Netherlands.

The attending physicians performed the clinical evaluation and collected demographic data and additional relevant information at baseline (10). For each included patient, the dichotomized Wells score (cut-off value 4) based on information obtained from history and physical examination. For study purposes, a high-sensitivity quantitative D-dimer test was performed in all patients (10). In case of an "unlikely" classification and a normal D-dimer result, PE was considered to be excluded (10). A CTPA-scan was performed in patients with a "likely" classification or in case the D-dimer test was abnormal (> 500 μg/L). The diagnosis of PE was confirmed by the presence of at least one filling defect in the pulmonary artery tree (10).

Patients were followed for three months and instructed to return to the hospital if symptoms of PE, DVT or bleeding events occurred and objective, imaging diagnostic tests were done if PE or DVT was suspected (10).

Validation set

For the validation set, data from a large prospective multicenter cohort study was used (4). This study evaluated the clinical effectiveness of an algorithm based on the dichotomized Wells score, D-dimer testing and CTPA-scanning in patients with suspected PE. The study design and results are reported elsewhere (4). In short, between November 2002 and August 2004, all consecutive in- and outpatients with clinically suspected acute PE in 12 hospitals in the Netherlands were eligible for this study. The institutional review boards of all participating hospitals had approved the study protocol.

The study group consisted of 3,306 patients. All underwent a sequential diagnostic work-up, consisting of clinical probability calculation, a D-dimer test, and CTPA-scanning. At admission, the clinical probability was calculated by the treating physician using the Wells score. According to the protocol, a D-dimer test was performed only in patients with a Wells score of 4 or less. PE was excluded by either an 'unlikely' Wells score (≤ 4) combined with a D-dimer test ≤ 500 μg/L; or by a negative CTPA-scan in all other patients. PE was considered confirmed by a positive CTPA.

Patients were followed up by their family physicians and were interviewed by telephone by one of the study coordinators at the end of a three month follow-up period. The primary outcome measure was the estimated three-month thromboembolic risk in patients in whom PE was considered ruled out by the initial diagnostic work-up, and who had not received anticoagulants during follow-up (4).

Statistical analysis

We used multivariable logistic regression analyses, in which we added the original Wells items to the D-dimer test result, using PE as the dependent variable. The accuracy of the resulting model was evaluated by calculating the area under the Receiver Operating Characteristics curve (AUC).

We then calculated the frequency of the informative Wells variables. Based on the most frequent combinations and multivariable modelling, we aimed to develop a simple classification of the total group of patients based on the retained, most influencing Wells items. In each of the resulting subgroups we then identified a D-dimer threshold that would lead to a sensitivity rate comparable to that of the original Wells rule. Sensitivity of the new clinical decision rule was estimated using the proportion of patients with a positive clinical decision rule, relative to all patients with PE, as confirmed by CTPA. Specificity is estimated as the proportion of patients with a negative clinical decision rule

result, relative to all patients without PE. The positive predictive value (PPV) was defined as the proportion of patients with a negative clinical decision rule with PE confirmed by CTPA relative to all positive clinical decision rules; the negative predictive value (NPV) was defined as the proportion of patients with a clinical decision rule unlikely with PE excluded by CTPA relative to all clinical decision rule classified as unlikely. Additionally, we calculated the false negative rates, defined as those patients who had PE in the diagnostic investigation or during follow-up. Besides, we assessed the number of patients who experienced DVT during follow-up. The clinical utility was assessed by calculating the proportion of patients in whom further diagnostic testing could be safely withheld. The safety as well as the clinical utility of the new clinical decision rule was compared to that of the original Wells rule at a cut-off ≤ 4 in combination with a normal D-dimer result (≤ 500 μg/L). The 95% confidence interval (CI) for the three months PE incidence rate in both the scores (for the Wells score in combination with a normal D-dimer test result) was calculated. A clinical decision rule was considered acceptable if the confidence interval around the observed diagnostic failure rate would not exceed 3% (14).

All p-values were two-tailed and statistical significance was defined as $p < 0.05$, except where indicated otherwise. All analyses were performed using SPSS software, version 19.0 (SPSS Inc, Chicago, Ill).

Results

The development set consisted of 807 patients with clinically suspected PE. In 84 patients was no D-dimer test available, consequently these patients were excluded. Of the remaining 723 patients, 156 patients (22%) had PE. The mean age was 52 years (SD 17) and 441 patients (61%) were female, mean body mass index was 26 kg/m^2 (SD 5), and 92 female patients (13%) used estrogen containing drugs. With regard to the comorbidity, 67 patients (9%) had chronic obstructive pulmonary disease, 38 patients (5%) had heart failure and 90 patients (12%) had a malignancy. When using the regular Wells rule combined with the conventional D-dimer threshold, the number of patient in whom PE could be excluded was 160 (22%; 95% CI 19% to 25%). The PPV and NPV of this algorithm were 0.28 (95% CI 0.24-0.31) and 0.99 (95% CI 0.99-1.00), respectively.

Items of the new clinical decision rule

Table 1 shows the multivariable logistic regression model, fitted to the data in the development set, using the original Wells items. This table additionally depicts the coefficients for the same model, also including the D-dimer test result. When including the D-dimer test result in all items, only three of the seven Wells items were significantly associated with PE (at $p < 0.2$): two clinical items (haemoptysis, clinical signs of DVT) and the subjective item (PE most likely). All other items (history of DVT or PE, malignancy, immobilisation, and tachycardia) did not provide incremental value, conditional on the D-dimer test result.

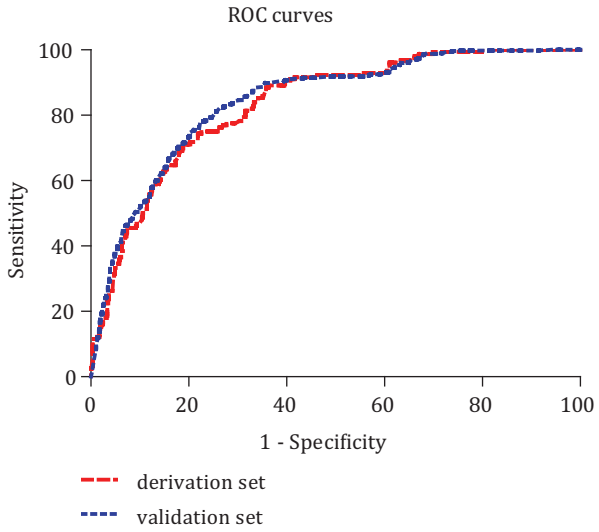
Table 1. Multivariable logistic regression model, fitted to the data in the development set, using the original Wells items and the Wells items including the D-dimer result.

			Wells items	Wells items and D-dimer test result
Wells items and points		**N (%)**	**OR (95% CI:)**	**OR (95% CI:)**
Clinically suspected DVT	3	39 (5%)	3.94 (1.93-8.03)	2.99 (1.41-6.33)
Active malignant condition	1	90 (12%)	1.08 (0.91-1.90)	0.94 (0.51-1.74)
Previous DVT or PE	1.5	35 (5%)	3.30 (1.56-6.99)	2.25 (0.96-5.28)
Alternative diagnosis less likely than PE	3	399 (55%)	2.65 (1.76-3.98)	2.43 (1.56-3.77)
Heart rate ≥ 100 beats per minute	1.5	152 (21%)	1.59 (1.03-2.55)	1.29 (0.80-2.07)
Immobilization/surgery in past 4 weeks	1.5	145 (20%)	1.92 (1.23-3.00)	1.27 (0.77-2.09)
Haemoptysis	1	37 (5%)	2.86 (1.36-6.03)	2.84 (1.29-6.24)
D-dimer test result			-	1.58 (1.42-1.75)

CI confidence interval, DVT deep venous thrombosis, N number, PE pulmonary embolism

The corresponding model, including these three variables and the D-dimer test result had an AUC of 0.83 (95% CI 0.80-0.87) (Fig 1).

Figure 1. Receiver operating characteristic curves illustrating the diagnostic performance of the two clinical items (haemoptysis, clinical signs of deep venous thrombosis) and the subjective item (pulmonary embolism most likely), combined with the D-dimer test result in the derivation and validation cohort. The areas under the curve were 0.83 (95% confidence interval (CI) 0.80-87), 0.84 (95% CI: 0.83-0.86) and respectively.



Four combinations of the three remaining Wells items could be identified: (1) none of these items positive (n=298, 41%), (2) only the subjective item positive, none of the other two items positive (n=354, 49%) (3) one or two clinical items positive (n=26, 3.6%) (4) the subjective and one or more clinical items positive (n=45, 6.2%). Based on these frequencies, we then defined two groups (group 1) none of these items positive (41%), (group 2) the subjective item and/or one of the clinical items positive (59%) (Table 2).

Table 2. The most prevalent (> 2%) combinations of the variables of the Wells rule in the derivation cohort and the validation cohort.

Combination of variables	Derivation cohort	Validation cohort
PE is most likely diagnosis n (%)	345 (49)	1402 (50)
None of the items positive, n (%)	298 (41)	1135 (41)
PE is most likely diagnosis plus:		
Hemoptysis, n (%)	18 (2.5)	78 (2.8)
clinical signs of DVT, n (%)	23 (3.2)	69 (2.5)

DVT deep venous thrombosis, N number, PE pulmonary embolism

Based on this model, a novel clinical decision rule could be constructed that corresponds to the use of a variable D-dimer threshold, depending on the type and number of items positive. We calculated two different D-dimer cut-off levels: one for patients with none of these items positive (group 1), and one for the other subgroup (one or more of the three items positive) (group 2).

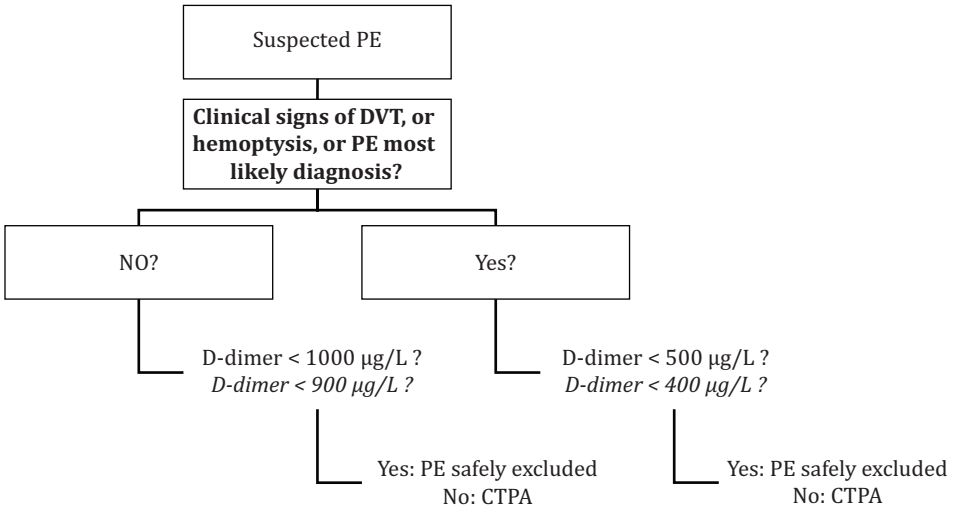
We assessed the cut-off levels of 1000 μg/L and 500 μg/L for the two groups, respectively: 1000 μg/L for group 1, and 500 μg/L for group 2. Using these cut-off levels we found the D-dimer to be negative in 83 patients in group 1 and 176 patients in group 2, respectively. This new rule had a positive predictive value of 22% at a negative predictive value of 99% for group 1 versus 37% and 99% for group 2. Overall, PE could be excluded in 259 patients (36%, 95% CI 32-39). Additionally, one patient with malignancy experienced DVT during follow-up, with none of the items positive and a D-dimer test result of 980 μg/L . Compared to the conventional method of the original Wells rule, combined with a normal D-dimer test result (cut-off value 500 μg/L), the number of patients in whom PE could be excluded increased from 160 to 259 (absolute increase 14%, relative increase of 62% (99/160)). The false negative rate increased from 0.6% (1/160, 95% CI 0.10-2.4%) to 1.2%, (3/259 95% CI 0.04-3.3).

We alternatively evaluated lower cut-off levels, leading to fewer negatives, but also a lower failure rate: 900 μg/L for group 1, and 400 μg/L for group 2. The PPV was 21% and 35%, at a NPV of 99% and 100%, for group 1 and 2, respectively. Using these cut-off levels we found the D-dimer test to be negative in 162 and 63 patients in the two groups respectively. PE could safely be excluded in 225 patients (31%, 95% CI 28 to 34%), with a false negative rate of 0.4% (1/225, 95% CI 0.1-2.3%). For this patient,

none of the three items was positive. None of the patients experienced DVT. Compared to the conventional algorithm, the number of patients in whom PE could be excluded increased from 160 to 225 patients (absolute increase 8.9%, relative increase 41% (65/160)). The false negative rate decreased from 0.6% (1/160, 95% CI 0.2-3.4) to 0.4% (1/225, 95% CI 0.10-2.4%).

Table 3 lists the test characteristics in terms of sensitivity, specificity, PPV and NPV of the new diagnostic strategy for the CDR combined with 1000/500 µg/L or 900/400 µg/L D-dimer cut-off levels. In Figure 2 the diagnostic steps of the new strategy are illustrated.

Figure 2. Diagnostic work up for suspected pulmonary embolism (PE), a combination three clinical items and two different cut-off points of the D-dimer.



CT computerized tomography, DVT deep venous thrombosis, PE pulmonary embolism

Validation set

The validation sample consisted of 3,306 patients with clinically suspected PE. In 515 patients with an unlikely clinical probability of PE, D-dimer test results were recorded only qualitatively and were therefore missing for this analysis. In another six patients, one of the Wells items was missing. Consequently these patients were excluded from

further analysis. Of the remaining 2785 patients, 491 patients were diagnosed with PE (17.6%). The clinical characteristics were similar to those of the patients in the derivation cohort. When using the original Wells rule combined with a conventional normal D-dimer test result, the number of patient in whom PE could be excluded was 989 (35%; 95% CI: 34% to 37%). The PPV and NPV of this algorithm were 0.28 (95% CI 0.26-0.30) and 0.99 (95% CI 0.99-1.00), respectively (Table 3).

Performance of the new clinical decision rule

In 1135 (41%) patients of the validation set, none of the informative Wells items was positive; in the other 1649 patients (59%) one or more items were positive (Table 2). The corresponding model, including these three variables and the D-dimer test result had an AUC of 0.84 (95% CI 0.83-0.86) (Fig 1).

Applying the cut-off levels of 1000 μg/L for group 1, and 500 μg/L for group 2, the D-dimer test was negative in 782 and 500 patients, respectively. Using the cut off level of 1,000 μg/L for group 1, the PPV and NPV were 21% and 98%, respectively. For group 2, in which we used the lower, 500 μg/L cut-off, the PPV was 34% and the NPV 98%. Overall, PE could be excluded in 1295 patients (46%, 95% CI 45-48%) with a false negative rate of 1.9% (24/1295, 95% CI 1.2-2.7%). Compared to the conventional algorithm, the number of patients in whom PE could be excluded increased from 989 to 1295 (absolute increase 11%, relative increase of 31%). The false negative rate increased from 0.5% (5/989, 95% CI 0.2-1-2%) to 1.9% (24/1295, 95% CI 1.2-2.7%).

With the lower D-dimer positivity cut-offs (900 μg/L for group 1 and 400 μg/L for group 2), the PPV was 21% and 32%, the NPV 98% and 99%, Using these cut-off levels, the D-dimer test was negative in 762 and 403 patients, respectively. PE could safely be excluded in 1165 patients (41%, 95% CI 40-43%), with a false negative rate of 1.4% (17/1165, 95% CI 0.9-2.3%). Compared to the conventional algorithm, the number of patients in whom PE could be excluded increased from 989 to 1165 patients (absolute increase 7.0%, relative increase 18% (176/989). However, the false negative rate increased from 0.5% (5/989, 95% CI 0.2-1-2%) to 1.4% (17/1165, 95% CI 0.9-2.3%) (Table 3).

Table 3. Test characteristics of the new diagnostic strategy combined with D-dimer cut-off values 1000/500 ug/L * and 900/400 µg/L **, and the conventional Wells score with the the D-dimer test (cut-off 500 ug/L).

	New CDR including D-dimer cut-off levels 1000/500 ug/L *	**New CDR including D-dimer cut-off levels 900/400 ug/L ****	**Wells score unlikely (</=4) and D-dimer cut-off 500 ug/L**
Derivation cohort, n = 723			
Number (%) of patients in whom PE can be excluded	259 (36)	225 (31)	160 (22)
Sensitivity (95% CI)	0.98 (0.95-0.99)	0.99 (0.97-1.00)	0.99 (0.97-1.00)
Specificity (95% CI)	0.45 (0.41-0.49)	0.40 (0.36-0.44)	0.28 (0.25-0.32)
PPV (95% CI)	0.33 (0.29-0.37)	0.31 (0.27-0.35)	0.28 (0.24-0.31)
NPV (95% CI)	0.99 (0.97-1.00)	1.00 (0.98-1.00)	0.99 (0.97-1.00)
Validation cohort, n = 2785			
Number (%) of patients in whom PE can be excluded	**1295 (64)**	**1165 (42)**	**989 (36)**
Sensitivity (95% CI)	0.95 (0.93-0.97)	0.97 (0.95-0.98)	0.99 (0.98-1.00)
Specificity (95% CI)	0.56 (0.53-0.57)	0.50 (0.48-0.52)	0.43(0.41-0.45)
PPV (95% CI)	0.32 (0.29-0.34)	0.29 (0.27-0.31)	0.28 (0.26-0.30)
NPV (95% CI)	0.98 (0.97-0.99)	0.99 (0.98-0.99)	0.99 (0.99-1.00)

CDR clinical decision rule, NPV negative prospective value, PPV positive prospective value, PE pulmonary embolism.

Combining the results of the two cohorts

The number of patients in whom PE could be excluded in the 3508 patients in total of the two cohorts together, when assessing 1000 µg/L for group 1, and 500 µg/L for group 2, was 1554 patients (44%, 95% CI 43-46%), with a failure rate of 0.7% (27/3508, 95% CI 0.5-1.1%). Compared to the conventional algorithm the number of patients in whom PE could be excluded increased from 1149 (37%) to 1554 patients (absolute increase 7%, relative increase 35% (405/1149). The false negative rate increased from 0.5% (6/1149, 95% CI 0.2-1-1%) to 0.7% (27/3508, 95% CI 0.5-1.1%).

When using 900 µg/Land 400 µg/L for group 1 and 2 respectively, this number was 1390 patients (40% 95% CI 38.9-41.2%), with a false negative rates of 0.5% (18/3508, 95% CI 0.3-0.8%).

Compared to the conventional method of the original Wells rule, combined with a normal D-dimer test result (cut-off value 500 µg/L), the number of patients in whom PE could be excluded increased from 1149 (37%) to 1390 patients (absolute increase 3%, relative increase 21% (241/1149). The false negative rate did not differ 0.5% (5/989, 95% CI 0.2-1-2%) versus 0.5% (18/3508, 95% CI 0.3-0.8%).

Discussion

We derived a simple clinical decision rule in which Wells items and the D-dimer test are incorporated. Conditional on the D-dimer result, only a few of the Wells items proved to be of incremental value. The resulting rule therefore, was based on these three items and the D-dimer test result, with a different D-dimer threshold for those with no items positive versus those with one or more items positive. With this new clinical decision rule, approximately 36% (using the 1000/500 µg/L cut-off value) and 31% (using the 900/400 µg/L cut-off value) of patients with suspected PE can be withheld from further diagnostic imaging, a proportion substantially higher to that observed with the original Wells rule (22%).

In primary care, physians already have access to a validated clinical decision rule for DVT, including 7 clinical items and the D-dimer, with a maximum of 13 points (16;17). A positive D-dimer result contributes for 6/13 points. Using this rule, the proportion suspected DVT referred for imaging tests could be reduced from 100% to 77%, at the expense of not referring 0.7% of all DVT cases. However, it is only recently demonstrated that for patients with suspected PE in primary care, the traditional Wells score followed by a D-dimer test safely excludes PE (18). Additionally, several studies addressed that using a higher cut-off level of the D-dimer, results in higher specificity without a relevant fall in sensitivity. Kline and colleagues recently doubled the threshold of the D-dimer, in a prospective study with 678 patients with suspected PE and an unlikely pretest probability (19). They found the threshold of 1000 µg/L to be safe to exclude PE in patients with a Wells score of ≤ 4 points. Similarly, in patients with suspected DVT, this study group has showed that in 860 patients with a first episode of suspected DVT, a D-dimer cut-off of 1000 µg/L is as safe as the conventional cut-off point of 500 µg/L in those with a low clinical probability (20). Other previous studies also demonstrated that a D-dimer cut-off value, adapted to the clinical probability category of the patient, has greater utility for exclusion of PE compared to the use of one D-dimer cut-off value regardless of the clinical probability (21;22). The proposed cut-off

value was kept at 500 µg/L for patients with an intermediate clinical suspicion of PE, but was doubled in patients with a low clinical suspicion, and halved in patients with a high clinical suspicion of PE. In a study by Kabrhel and colleagues, the conventional cut-off of 500 µg/L had an overall sensitivity of 94% (95% CI 91-97) and a specificity of 58% (95% CI 56-60). These rates were 88% (95% CI 83-92) and 75% (95% CI 74-76), respectively, when probability-dependent cut-offs were used (21).

Combining the items of the Wells rule with the D-dimer result resulted in a clinical decision rule with fewer items, one that has a sensitivity similar to that of the original Wells score / D-dimer combination, but substantially increased specificity. We showed the performance for two sets of cut-off points for the D-dimer test result: 1,000 plus 500 µg/L on the one hand, and 900 and 400 µg/L on the other. Obviously, the lower the cut-off level, the safer the strategy is. It is commonly accepted that the confidence intervals of the proportions of patients with PE at baseline or after three months with a diagnostic strategy for PE may not exceed 3% (13). The upper level of the confidence interval for the false negative rate of the novel decision rule, using 1000 µg/L and 500 µg/L, was 2.7%, and 3.3% in the validation set. Using the combination of cut-off levels of 900 and 400 µg/L, the upper levels of the 95% CI were 2.3% and 2.7% in the derivation set and validation set, respectively. Nevertheless, the false negative rates with this novel clinical decision rule are higher than applying the conventional Wells score with a D-dimer test result at a cut-off 500 µg/L. However, these false negative rates may not directly translate to failure rates if this strategy is applied in practice. There may be false positive CT-scans for PE, some of the PE cases during follow-up could be new thrombotic events and it has been suggested that not all PE cases confirmed by imaging are consequential (21;22). On the other hand, these false negative rates may be too high to allow this strategy to fully replace the current diagnostic strategy without further evaluation. Management studies could document the actual failure rate as well as any practical challenges when implementing this novel decision rule.

The conclusions of this study are strengthened by its large sample of patients, and its multicenter design, which enhance the extrapolation of our findings to other clinics. Limitations include that a D-dimer test was not performed in 84/807 patients of the derivation cohort, and that 515 patients of the validation set were excluded, because no qualitative D-dimer test was available. Furthermore, although our analysis was based on prospectively collected data and validated in an independent cohort, this analysis was done retrospectively. Therefore, our strategy would benefit from a prospective validation in a management study.

In summary, we have shown that combining the Wells items with the D-dimer test result in patients with suspected PE, using different thresholds for those with no Wells items positive than in the others, leads to a simple decision rule with comparable sensitivity, but substantially higher specificity, thereby increasing the number of patients in whom CT-scanning be withheld. This strategy needs further evaluation in management studies.

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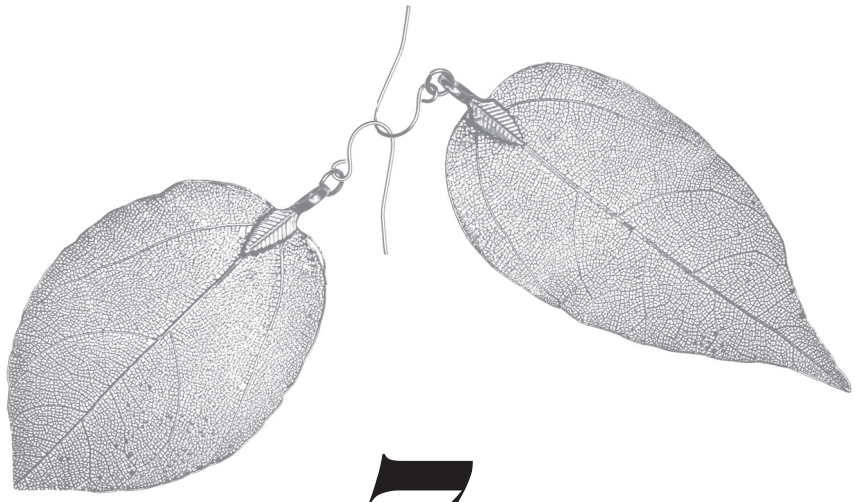

CHAPTER 7

Clinical impact of findings supporting an alternative diagnosis on computed tomography pulmonary angiography in patients with suspected pulmonary embolism

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Abstract

Background: Computed tomography pulmonary angiography (CTPA) is commonly used as the first-line imaging test in the diagnostic work-up of patients with suspected pulmonary embolism (PE). Other CTPA findings may provide an alternative explanation for the signs and symptoms in this group of patients; however, the clinical impact of these findings is not clear.

Methods: In 203 consecutive patients with suspected PE, we prospectively evaluated the clinical implication of abnormalities on CTPA. Alternative diagnoses were defined on clinical grounds prior to performing CTPA; afterwards, all findings were systematically registered. Diagnostic and therapeutic consequences were assessed using a priori defined criteria.

Results: Of the total of 203 patients, 61 (30%) had no abnormality on CTPA. Thirty-nine (19%) patients were diagnosed with PE. Before CTPA, alternative diagnoses were suspected in 97 (48%) patients. Findings supporting an alternative diagnosis were detected in 88 (43%) patients. In 28 patients this was a new finding; in 18 patients, a conclusive and previously unknown alternative diagnosis for the complaints was made based on the outcome of the CTPA. Overall, findings supporting alternative diagnoses had therapeutic consequences in 10 (4.9%) patients. Incidental findings (nodules/lymph nodes) requiring diagnostic procedures were present in 17 (8.4%) patients, of which one (0.5%) had a therapeutic consequence.

Conclusion: In patients undergoing CTPA for suspected PE, findings supporting alternative diagnoses were found in almost half of the patients. However, in only few patients this had therapeutic consequences. Hence, CTPA should principally be used to find or exclude PE in high probability patients but not to establish an alternative diagnosis.

Introduction

Since the last decade, computed tomography pulmonary angiography (CTPA) has been increasingly used as first choice imaging test to confirm or exclude pulmonary embolism (PE) (1). Compared to the previous reference standard (ventilation perfusion scintigraphy and pulmonary angiography) advantages of CTPA are that it is easily accessible, quick and non-invasive. Besides, CTPA has high sensitivity, ranging from 80% to 100% with a specificity of 96% to 100% (2;3). Another potential advantage of CTPA is its possibility of detecting additional findings that explain the patient's complaints or symptoms if PE is excluded (4;5). However, CTPA also harbors a risk of finding incidental findings, such as intrapulmonary nodules or enlarged lymph nodes. Although these findings may be suggestive of a malignant disease, in the majority of patients, follow-up of these incidental findings likely involves visitations, invasive procedures, repeated CTPAs and therefore repeated exposure to radiation and contrast medium, and can be therefore burden for the patient (4). Especially, the exposure to radiation following repeat imaging is an important risk factor for developing a malignancy (6;7). The reported proportion of nodules that are actually malignant is approximately 1% (8). Screening with low-dose chest CT has not been proven to decrease the rate of detection of advanced cancer or to affect mortality resulting from lung cancer (8;9).

Still, some clinicians use CTPA to detect a potential alternative diagnosis, even if the clinical suspicion of PE is low (10). Several studies showed that CTPA will yield a reliable finding supporting an alternative diagnosis in 25-52% of patients with suspected PE (4;5;11). However, it is unclear whether these findings supporting alternative diagnoses, mostly pneumonia, could also at forehand be established by clinical presentation, laboratory results and the chest radiograph (12). In this cohort study we assessed the clinical impact of findings supporting alternative findings on CTPA ordered in the diagnostic work-up for PE, in terms of diagnostic or therapeutic consequences. Furthermore, we investigated whether findings supporting alternative diagnoses were already established or highly suspected before CT-scanning.

Methods

Patients

Consecutive in- and outpatients with a clinical suspicion of acute PE in whom CTPA was performed at the Academic Medical Center, Amsterdam, the Netherlands between

August 2008 and April 2009 were eligible for this analysis. Patients with severely impaired renal function (creatinine clearance <30 ml/min using the Cockroft-Gault formula), who were younger than 18 years of age, or were pregnant were excluded. The study protocol was approved by the institutional ethical review boards.

Study design

The pretest clinical probability of PE was considered 'unlikely' in case of a Wells score ≤ 4 and 'likely' in case of a Wells score > 4 points (13). Patients categorized as 'PE unlikely' underwent D-dimer testing. A CTPA was performed in all patients with an abnormal D-dimer test result (> 500 µcg/L) and all patients classified as 'PE likely' (14).

Evaluation of the possibility or presence of alternative diagnoses was performed on three occasions:

1. Before CT-scanning, the ordering physician was requested to inform the emergency radiologist to explicitly mention an alternative diagnosis other than PE, based on signs, symptoms, physical examination, laboratory results and chest radiograph.
2. After scanning, the CTPA was assessed by the radiologist. Patients were treated by the attending physician based on the CTPA results in combination with other clinical information. The treating physician was asked immediately after hearing the results of the CTPA to judge whether a finding supporting an alternative diagnosis on CTPA could indeed explain the signs and symptoms of the patient and whether the findings had diagnostic or therapeutic consequences. All additional diagnostic tests and therapeutic consequences were separately recorded.
3. Finally, for this analysis, we evaluated whether findings or diagnoses documented at the time of inclusion had been revised three months later.

CTPA analysis

CTPA for diagnosing or excluding PE was performed using a 64-slice MDCT scanner (Siemens Sensation 64, Forchheim, Germany). Scan parameters were: collimation 64 * 0.6 mm with 100 kV and 200 mAs, rotation time 0.5, with pitch of 1.4 and a 4D automatic tube current modulation (CARE dose 4D Automatic Exposure Control, Siemens, Erlangen, Germany). Intravenous contrast medium (Ultravist® 300, Bayer Pharma AG, Berlin, Germany; 100 ml at 4 ml/s) was administered via an 18G peripheral canula, followed by a saline chase of 40 ml at 4 ml/s. Images were reconstructed at 1 mm axial, sagittal and coronal slices in soft kernel with additional coronal maximum intensity projection (MIP) reformats. All studies were read by the attending radiologist

or resident with second read by an experienced emergency radiologists using a picture archiving and communication system PACS (Impax 4.5, AGFA Gevaert, Mortsel, Belgium) using standard window settings with possibility to change these settings without restrictions. A CTPA was considered to be of non-diagnostic quality to detect PE if there was insufficient opacification (subjective interpretation of available contrast in the pulmonary arteries, Hounsfield units < 200) of the vessels or in case of major artifacts. For CTPA evaluation a structured reporting format was used by the radiologists.

CTPA findings

1. Findings supporting an alternative diagnosis

'Findings supporting an alternative diagnosis' were defined as all findings that *potentially* provided an alternative diagnosis for the patient's signs and symptoms (e.g. chest pain, shortness of breath, hypoxemia, or tachycardia). This included pneumonia, pleural effusion, tumor (noted on the report as new mass suspicious for malignancy or progression of known malignancy, possibly combined with adenopathy), significant atelectasis, bronchiolitis, pericardial effusion, (progressive) chronic obstructive pulmonary disease (COPD), heart failure or other diagnoses. Significant atelectasis was only determined if it was not secondary to pleural effusion. In case multiple findings were found on one CTPA, all findings were reported and the most likely finding to explain the patient's symptoms was registered as a finding supporting an alternative diagnosis.

This classification was irrespective of the assessment whether or not the finding truly explained the signs and symptoms of the patient, only that it *potentially* could explain the symptoms (group A, Table 2 and Figure 1). For instance: a pneumonic infiltrate was present, and classified as an alternative finding. However, judging more strictly, the infiltrate could be deemed too small to explain the clinical status. Therefore, an additional differentiation was made, selecting only those CT scans with findings that *sufficiently* explained the signs and symptoms of the patient as was concluded by the treating physician (group B, Table 2 and Figure 1). Furthermore, we classified the findings as "new" if the CTPA findings were not visible on the chest radiograph before CT-scanning.

2. Incidental findings

Incidental findings on CTPA included pulmonary nodules and enlarged lymph nodes either mediastinal or hilar. ~~Findings that were considered significant~~ included (1) any lymph node larger than 1 cm in short axis diameter and not associated with pneumonia;

(2) any lymph node larger than 3 cm in diameter; or (3) presence of multiple mediastinal or hilar lymph nodes. ~~A pulmonary lymph node~~ was only defined as a new finding if no mass or nodule was evident on previous imaging reports or if no history of malignancy, mass, or nodule was noted in the patient's local medical record. A pulmonary mass > 1 cm, which was not described as a nodule or lymph node was not considered an incidental finding, but categorized as the finding supporting the alternative diagnosis '*tumor*'.

3. Other findings

Findings that were not considered as findings supporting an alternative diagnosis and required less urgent or no follow-up included: previously known or non-progressive emphysema (changes described as emphysematous or consistent with emphysema or chronic obstructive pulmonary disease); mild atelectasis (read as atelectasis, collapse, or volume loss described as dependent or involving fewer than 3 pulmonary segments); previously known, unchanged systemic disease such as sarcoidosis, systemic scleroderma or tuberculosis, cardiomegaly; skeletal findings (degenerative changes and other nonmalignant anomalies in skeletal structures); other pulmonary process (any other pulmonary process not already recorded, such as scarring or calcifications).

Consequences of findings detected on the CTPA

A finding was considered to have diagnostic consequences in case one or more of the following procedures was performed: a thoracentesis, bronchoscopy, sputum culture, consultation of a pulmonologist or cardiologist or performance of other diagnostic tests. A therapeutic consequence was classified when antibiotics, diuretics, corticosteroids or chemotherapy was administered or if thoracentesis was performed – as a direct consequence of the CTPA or following a diagnostic thoracentesis. Both diagnostic and therapeutic consequences were only considered if a diagnosis was newly found at the current clinical episode and was not already known before CT-scanning (Figure 1).

Statistical analysis

Normally distributed variables are presented as mean and standard deviations (SD) and non-normally distributed variables are expressed as medians with ranges. Exact 95% confidence intervals (CI) of proportions were calculated using SPSS software, version 19.0 (SPSS Inc, Chicago, Ill).

Results

Patient characteristics

A total of 203 consecutive patients with suspected PE were included. Mean age was 57 years (SD 17 years), 77 (38%) were male, 26 (13%) patients had a history of COPD, 10 (4.9%) patients had a history of heart failure and in 59 (29%) an active malignancy was present (Table 1).

Table 1. Clinical characteristics.

Characteristic	Value
Number of patients	**203**
Age, mean in years (SD)	57 (17)
Male, n (%)	78 (38)
COPD, n (%)	26 (13)
Heart failure, n (%)	10 (4.9)
Malignancy, n (%)	46 (22)
Smoking, n (%)	79 (39
Inpatient, n (%)	116 (57)

COPD – chronic obstructive pulmonary disease, N – number, SD – standard deviation

Suspected alternative diagnoses prior to CTPA

Before CT-scanning, alternative diagnoses were considered by the treating physician in 97 (48%) patients. Most prevalent of the differential diagnoses were: pneumonia in 37 (18%), isolated pleural fluid in 12 (5.9%), (progression of) tumor in 7 (3.4%), and COPD in 7 (3.4%) patients.

CTPA findings

PE was diagnosed in 39 patients (19%); 61 patients (30%) had no abnormalities on CTPA.

1. Findings supporting alternative diagnoses

CTPA findings supporting an alternative diagnosis that potentially explained the patient's symptoms (Group A), were found in 88 patients (43%, 95% CI 37-50%) (Table 2 and Figure 1); 3 patients also had PE. Among these alternative diagnoses were one or more pneumonic infiltrates (n=28, 14%), significant pleural effusion (n=27, 13%), and

Table 2. Prevalence of radiographic findings, findings supporting alternative diagnoses, and incidental findings in the diagnostic work-up of pulmonary embolism (PE) in 203 CTPA scans, stated as numbers (% of the total cohort of 203 patients, 95% confidence interval).

PE*	**39 (19, 14-25)**					
No abnormality	**61 (30, 24-36)**					
Findings supporting alternative diagnoses*	**Group A****	**Group B*****	**Unknown prior to CTPA Group A**	**Unknown prior to CTPA Group B**	**Diagnostic consequences**	**Therapeutic consequences**
Total	**88 (43, 37-50)**	**56 (28, 22-34)**	**28 (14, 9.7-19)**	**18 (8.8, 5.7-14)**	**11 (5.4, 3.1-9.4)**	**10 (4.9, 2.7-8.8)**
Pneumonic infiltrates	***28*** *(14, 0.7-19)*	***21*** *(10, 6.8-15)*	***9*** *(4.4, 2.3-8.2)*	***6*** *(3.0, 1.4-6.3)*	***3*** *(1.5, 0.5-4.2)*	***4*** *(2.0, 0.8-4.9)*
Pleural effusion	***27*** *(13, 9.3-18)*	***17*** *(8.3, 5.3-13)*	***4*** *(2.0, 0.8-4.9)*	***2*** *(1.0, 0.3-3.1)*	***0*** *(0)*	***2*** *(1.0, 0.3-3.1)*
(progression of) Tumor/ metastases	***10*** *(4.9, 2.7-8.8)*	***3*** *(1.5, 0.5-4.2)*	***3*** *(1.5, 0.5-4.2)*	***2*** *(1.0, 0.3-3.1)*	***2*** *(1.0, 0.3-3.1)*	***0*** *(0)*
Large atelectasis	***5*** *(2.5, 1.1-5.6)*	***2*** *(1.0, 0.3-3.1)*	***3*** *(1.5, 0.5-4.2)*	***2*** *(1.0, 0.3-3.1)*	***1*** *(0.5, 0.1-2.7)*	***1*** *(0.5, 0.1-2.7)*
Bronchiolitis	***4*** *(2.0, 0.8-4.9)*	***3*** *(1.5, 0.5-4.2)*	***3*** *(1.5, 0.5-4.2)*	***2*** *(1.0, 0.3-3.1)*	***1*** *(0.5, 0.1-2.7)*	***1*** *(0.5, 0.1-2.7)*
Pericardial effusion	***2*** *(1.0, 0.3-3.1)*	***1*** *(0.5, 0.1-2.7)*	***2*** *(1.0, 0.3-3.1)*	***1*** *(0.5, 0.1-2.7)*	***1*** *(0.5, 0.1-2.7)*	***1*** *(0.5, 0.1-2.7)*

(Exacerbation of) Chronic Obstructive Pulmonary Disease	***7*** *(3.0, 1.7-6.9)*	***5*** *(2.5, 1.1-5.6)*	***2*** *(1.0, 0.3-3.1)*	***2*** *(1.0, 0.3-3.1)*	***2*** *(1.0, 0.3-3.1)*	***1*** *(0.5, 0.1-2.7)*
Heart failure	***5*** *(2.5, 1.1-5.6)*	***4*** *(2.0, 0.8-4.9)*	***2*** *(1.0, 0.3-3.1)*	***1*** *(0.5, 0.1-2.7)*	***1*** *(0.5, 0.1-2.7)*	***1*** *(0.5, 0.1-2.7)*
Incidental findings*					**Diagnostic consequences**	**Therapeutic consequences**
Total	**23 (11, 7.7-16)**	-	-	-	**17 (8.4, 5.3-13)**	**1 (0.5, 0.1-2.7)**
Nodule	**10** (4.9, 2.7-8.8)	-	-	-	**7** (3.4, 1.7-6.9)	**1** (0.5, 0.1-2.7)
Enlarged lymph nodes	**13** (6.4, 3.8-11)	-	-	-	**10** (4.9, 2.7-8.8)	**0** (0)

PE, pulmonary embolism; CI, confidence interval; n, number; CTPA , computed tomography pulmonary angiography.
*Patients may be classified as having more than one outcome: PE and/or alternative diagnosis and/or incidental finding, etc.
**Group A: findings supporting an alternative diagnosis that *potentially* explained the signs and symptoms of the patient
***Group B: findings supporting an alternative diagnosis that *sufficiently* explained the signs and symptoms of the patient, as was concluded by the treating physician

(progression of) tumor/metastases (n=10, 4.9%). These were new findings in 28 out of the 88 patients (Figure 1 Table 2).

Of these 88 patients with findings supporting an alternative diagnosis, the findings were scored as sufficiently explaining the symptoms in 56 of the CTPAs (56/203 (28%, 95%CI 22-34%)). Of these, 18 were new findings (Table 2, Figure 1).

2. Incidental findings

An incidental finding was found in 23 patients (11%, 95% CI 7.6-16%), of which 17 (8.3%, 95% CI 5.3-13%) required further diagnostic evaluation (5 diagnostic punctures, 5 consultations of a pulmonologist, 7 follow-up by radiologic imaging). In one patient the diagnostic evaluation of the lymph node had therapeutic consequences because of a diagnosis of cancer (chemotherapy).

3. Other findings

In 74 patients (36%, 95% CI 30-43%) minor findings were seen on CTPA, which were considered unrelated to the clinical signs and symptoms and did not require follow-up. These findings included residual abnormalities due to previous infections, mild emphysema, mild atelectasis, pre-existing systemic disease (tuberculosis, sarcoidosis, mixed connective tissue disease and CREST syndrome), post-operative and post-radiation therapy changes, skeletal changes and minimal and insignificant parenchymal findings (scarring, fibrosis, aspecific small isolated nodules and small bullae). In 30 patients, these findings were diagnosed in addition to PE, an alternative diagnosis or an incidental finding.

Diagnostic and therapeutic consequences

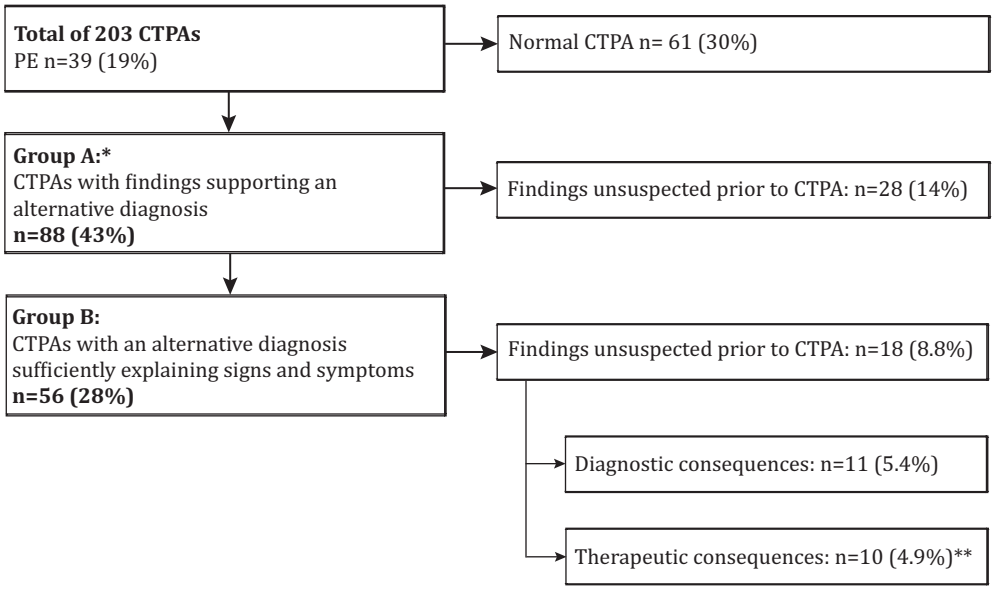
In 11 patients (5.4%, 95% CI 3.1-9.1%), CTPA abnormalities had diagnostic consequences (Figure 1), mostly bronchoscopy, thoracentesis, sputum culture, cardiac evaluation or an MRI-scan. These diagnostic tests resulted in (change of) treatment in 5 patients.

Start or change of therapy was a direct result of the CTPA findings in 10 patients (4.9%, 95% CI 2.7-8.8%; Table 2, Figure 1). The therapeutic consequences were initiation of antibiotics in 7 patients, diuretics in 2 patients and corticosteroids in one patient. Of these 10 patients, the findings were an indirect consequence after a diagnostic step in 5 and were a direct consequence of the CTPA in another 5 patients.

Comparison between diagnoses at baseline and three month follow-up

After three months, 13 patients (6.4%, 95% CI 3.8-11%) had died; none of the deaths were suspected to be due to PE. In the remaining 190 patients, the initial diagnosis (PE, finding supporting an alternative diagnosis or no abnormality) was unchanged in 187 patients (98%, 95% CI 96-99%) and had been adjusted by the treating physician in 3 patients (1.6%, 95% CI 0.6-4.2%). In one patient, the diagnosis of PE was changed into 'artifact' after re-evaluation by two different radiologists. Two diagnoses of tumor (newly found masses) were changed after puncture into 'inflammation secondary to a foreign body' and 'scar tissue', respectively. None of the patients was evaluated for deep venous thrombosis or PE during follow-up.

Figure 1. Flowchart of findings supporting an alternative diagnosis and the subsequent results in diagnostic and therapeutic consequences. Percentages in brackets reflect percentage of the total number of patients (203).



* 3 of these patients also had PE
** the findings were an indirect consequence after a diagnostic step in 5 and were a direct consequence of the CTPA in another 5 patients.

Discussion

This study demonstrates that in patients with suspected PE, CTPA is able to detect findings supporting an alternative diagnosis in 28% of the patients. However, two-thirds of these findings were already known or suspected before CTPA was performed. The findings supporting alternative diagnoses had therapeutic consequences in only 5% of all patients. Incidental findings on CTPA, such as lymph nodes or nodules resulted in further diagnostic steps in 8% of the patients with suspected PE, with limited therapeutic consequences.

Several studies addressed the issue of possible alternative diagnoses in patients who underwent CT-scanning for suspected PE. The proportion of alternative diagnoses ranged between 25-52% (4;5;11;15-17) and was comparable with our findings. Hall and colleagues found an alternative diagnosis in 33% of 589 patients, and an incidental finding requiring follow-up in 24%, far outnumbering the rate of PE in their study, which was 9% (4). A retrospective analysis of a large multicenter clinical management study on PE investigated the frequency of alternative diagnoses on CTPA in 512 consecutive patients (5). In 130/512 patients (25%, 95% CI 9.5-18%) without PE an alternative diagnosis was considered likely. However, whether these alternative diagnoses observed on the CTPA were already identified before CT-scanning and whether these findings were clinically significant in terms of actual therapeutic consequences was not assessed. To our knowledge, our prospective study is the first that assessed the proportion of findings supporting alternative diagnoses as well as the clinical impact in terms of diagnostic and therapeutic consequences. Furthermore, we systematically collected information on alternative diagnoses prior to CTPA, thus reducing the risk of bias by knowledge of the CTPA result. Not only were the majority of findings supporting alternative diagnoses already known prior to CTPA, these findings led to therapeutic actions in only 5% of all presenting patients . This indicates that the findings supporting alternative diagnoses can be established in the majority of cases using history, clinical presentation, laboratory results, and chest radiograph, and places the perceived additional value of CTPA for the diagnosis of PE over other imaging modalities (such as perfusion scintigraphy) in perspective.

Although guidelines do not recommend to perform CTPA in case of an ‘unlikely’ clinical decision rule and a normal D-dimer test-result, this advice is often not followed for several reasons (14;18-19). One of these reasons may be that some clinicians hope that CTPA will help them find an alternative diagnosis in a patient with a low

likelihood of PE. In our study, 8% of the CTPAs showed an incidental finding requiring repeated exposure to radiation and contrast or an invasive procedure, with no life saving consequence in terms of early detection of a malignancy. This, together with the relatively low yield of previously unsuspected alternative diagnoses with therapeutic consequences, makes it at least arguable to liberally use CTPA with the additional aim to detect an alternative diagnosis in patients with a low clinical suspicion of PE in terms of 'net clinical benefit'.

Some aspects of this study merit consideration. First, this study was conducted at a single tertiary care referral center, and results may not be generalizable to other settings. However, the prevalence of PE was similar to that of other PE studies in which clinical probability combined with the D-dimer (14) were used and it is likely that the rate of incidental findings would be comparable if similar evaluation and CTPA protocols and equipment were used. Furthermore, there may be significant variability between radiologists reporting. In our study, we used the observation of the radiologist on call, without an independent second radiologist confirming the diagnosis on the CTPA in the majority of cases. Although all CTPAs were assessed according to a pre-specified protocol, it cannot be ruled out that some of our patients were misclassified as having PE, an alternative finding or an incidental finding. However, this obviously reflects routine clinical practice of the diagnostic process of suspected PE. Another limitation is the moderate sample size of this study. As a result, the different findings supporting alternative diagnoses were rather small. However, the 95% CIs of the main results were rather narrow; we therefore think it unlikely that a larger sample size would lead to a materially different conclusion. We did not study the impact of CTPA on the confidence of physicians in the finding supporting an alternative diagnosis and consequential demands of the patients. It is intrinsically difficult to check validity of pretest therapeutic intentions, as verification could be influenced by the test findings. We can only speculate whether the CTPA in certain patients helped in converting a suspicion into confirmation of an alternative diagnosis, and its implications. Furthermore, the distinction we make between a liberal definition of findings supporting an alternative diagnosis including *potentially explaining* findings (group A), and a strict definition including only patients with *sufficiently explaining* findings (group B) is arbitrary. We, however, think this distinction makes our interpretations a more accurate reflection of clinical practice. It shows that there is a considerable group of patients in which it is difficult to prove that the observed finding supporting an alternative diagnosis is indeed an explanation for the complaints. When we used either the liberal or the strict definition, our main

findings did not change. Lastly, it was not possible to obtain a standard reference test for every suggested finding supporting an alternative diagnosis. As approximately 98% of the diagnoses of the surviving patients at baseline did not change at 3-month follow-up, we think that this study is a valid reflection of clinical practice.

In conclusion, although CTPA yields findings supporting alternative diagnoses in a considerable proportion of patients with suspected PE, these resulted in change or initiation of therapy in only 5% of the total population. Besides, incidental findings requiring diagnostic follow-up were found in 23 patients (11%). Hence, CTPA should primarily be used to find or exclude PE in patients in whom the clinical probability is high, based on clinical decision rule and the D-dimer test result, and not to establish a finding supporting an alternative diagnosis.

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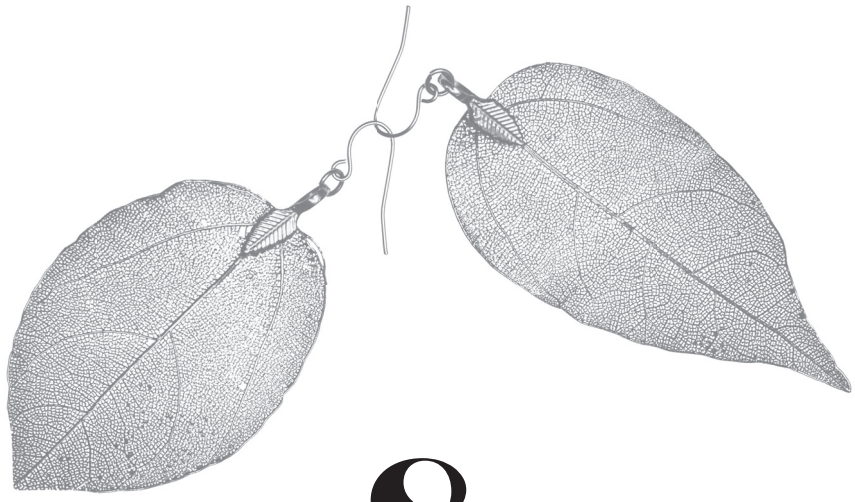

CHAPTER 8

Urinary prothrombin fragment 1+2 in patients with venous Thrombosis and myocardial infarction

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Abstract

Background: Patients with venous-thromboembolism (VTE) and myocardial infarction (MI) have elevated prothrombin fragment 1+2 (F1+2) levels. In patients with postoperative VTE, urinary F1+2 (uF1+2) was higher than in individuals without VTE. To explore the relationship between plasma and uF1+2 we performed a pilot study in patients with thrombotic events and healthy controls.

Methods: In 40 patients with VTE or MI, and 25 age- and sex-matched healthy controls, F1+2 and D-dimer levels were measured in urine and plasma within 48 hours after diagnosis. In addition, in all subjects renal function was assessed.

Results: Plasma and uF1+2 levels were positively correlated. Compared to controls, patients with VTE had higher levels of both plasma F1+2 (271 versus 160 pmol L^{-1}, $p < 0.05$) and uF1+2 levels (38 versus 28 pmol L^{-1}), the latter, however, was not statistically significant. Patients with acute MI had similar F1+2 levels as controls in both plasma and urine. Differences in urinary F1+2 levels could not be attributed to differences in concentrations of creatinin or albumin in spot urine samples.

Conclusion: Although urine F1+2 levels may be associated with postoperative venous thrombosis, we found no clear association with acute VTE or MI.

Introduction

In the acute phase of venous and arterial thrombosis, D-dimer and F1+2 plasma levels are both elevated, which reflects thrombin generation (1;2). F1+2 can be measured in the urine by enzyme-linked immuno sorbent assay (ELISA) (3). Recently, F1+2 levels were assessed in urine samples of patients, prior and 3 days after a total hip replacement (4). Interestingly, increased urinary F1+2 (uF1+2) level predicted postoperative venous thromboembolism (VTE) after total hip replacement, whereas low levels of uF1+2 were found in patients who had bleeding complications after surgery (4). uF1+2 may be an interesting marker for thrombin generation in epidemiological studies, in which citrated plasma, necessary for plasma F1+2 or D-dimer measurement, is often not stored. The concentration of plasma F1+2 is increased in patients with acute VTE (4;5). The test is less sensitive and specific compared to the D-dimer assays, which precludes clinical use. To our knowledge it is not fully known how F1+2 undergoes renal clearance [3,4]. To explore the relationship between plasma and uF1+2 we performed a pilot study in patients with thrombotic events and healthy controls.

Forty consecutive patients > 18 years presenting with an objectively confirmed diagnosis of VTE or MI and 25 controls in the Academic Medical Centre and Slotervaart Hospital in Amsterdam, the Netherlands, between August and December 2010 were included. The study protocol was approved by the Medical Ethics Review Committee, and all participants provided written informed consent. DVT was diagnosed with compression ultrasonography and PE was diagnosed with multi-slice CT-scan. MI was diagnosed when either one of the following criteria were met: the presence of ECG changes, defined as ST-segment elevation or ST-segment depression or T-wave abnormalities, and/or based on biochemical marker evidence, defined as CKMB (mass,C) levels ≥ 15 ug L^{-1}, and/or Troponin I levels ≥ 0,04 ug L^{-1}. Controls were gender- and age-matched, 1:1, to the VTE and MI patients and consisted of visitors of the AMC and Slotervaart hospital. Selection was based on the male/female ratio and age (maximum difference of 5 years) of the cases. MI and VTE were the only exclusion criteria of the controls. Since the age of MI and VTE patients was not completely similar, a total of 25 controls were included instead of 20.

Within 48 hours after diagnosis, blood samples for F1+2 and D-dimer were drawn and collected in tubes containing 0.109 mol L^{-1} trisodium citrate. Within 1h after collection, platelet-poor plasma was obtained by twice centrifugation for 15 min at 1500g and 15°C. The plasma was stored in 2-mL cryovials containing 0.5 mL of

plasma at -80°C. Simultaneously, spot urine samples were collected and plasma and urine F1+2 levels were determined using a commercially available ELISA (Enzygnost, Siemens healthcare Diagnostics, Marburg, Germany) D-dimer levels were determined with a particle-enhanced immunoturbidimetric assay (Innovance D-Dimer, Siemens Healthcare Diagnostics, Marburg, Germany).

To be able to adjust for the concentration of creatinin and albumin in the spot urine samples and micro-albuminuria, we analyzed microalbumin and creatinin using immunoturbidimetry and spectrofotometry respectively (both P800, Roche diagnostics).

Results are presented as mean ± standard deviation or median with inter-quartile range (IQR), depending on the observed distribution. All statistical analyses were performed in SPSS version 16.0 (SPSS Inc. Chicago, IL, USA).

Results

Mean age was 65 years (SD 18) and 38% was female. Both age and gender-distribution were comparable as the groups were matched by these variables. Also ethnicity, BMI, smoking habits, and urine creatinine and albumin levels were not different between the groups. Of the patients who were diagnosed with VTE, 8 patients had PE and 12 patients had DVT.

A correlation was found indeed between the F1+2 levels in the plasma and urine (regression coefficient 0.463, $r^2 = 0.214$, $p < 0.001$). Compared to controls, patients with VTE had higher levels of both plasma F1+2 (271 versus 160 pmol L^{-1}, $p < 0.05$) and plasma D-dimer (5.12 versus 0.38 mg L^{-1} fibrinogen equivalent units (FEU), $p < 0.01$). Urinary F1+2 Levels in VTE patients were comparable to uF1+2 levels in controls. In MI patients, plasma F1+2 and D-dimer levels were comparable to the control group ($p=0.87$ and $p=0.49$, respectively) (Table 1). Also uF1+2 levels did not differ between MI patients and control persons. In all subjects, urine levels of D-dimer were not detectable. To account for concentration of the spot urine samples we calculated uF1+2 / urine creatinine ratios. This yielded similar results (Table 1). Subsequently, we adjusted for (micro) albuminuria by dividing uF1+2 by microalbumin / creatinine ratio. These assessments showed similar results in the 3 groups (Table 1).

Table 1: F1+2 and D-dimer results of the different patients groups and controls.

	Controls n=25	**VTE n=20**	**MI N=20**
Plasma F1+2 (pmol L^{-1}) median (IQR)	160 (120-254)	271 * (201-541)	157 (115-268)
Urine F1+2 (pmol L^{-1}) median (IQR)	28 (15-46)	38 (23-71)	25 (16-80)
Plasma D-Dimer (mg L^{-1} FEU) median (IQR)	0.38 (0.19-0.65)	5.12 ** (1.81-8.45)	0.47 (0.28-0.60)
Urine D-Dimer (mg L^{-1} /L FEU)	Undetectably low	Undetectably low	Undetectably low
Urine creatinin (mmol L^{-1}) mean (SD)	10.5 (7.6)	11.5 (5.8)	12.1 (9.2)
Urine microalbumin (mg L^{-1}) median (IQR)	11 (4-22)	11 (8-18)	14 (2-52)
u albumin/u creatinin (mg L^{-1} / mmol L^{-1}) median (IQR) *	0.57 (0.31-1.22)	0.85 * (0.65-1.88)	0.63 (0.35-2.95)
u F1+2 / u creatinin (pmol L^{-1} /mmol L^{-1}) median (IQR)	3.1 (2.0-4.2)	3.9 (2.5-7.9)	3.0 (2.0-6.2)
(u F1+2) x (u creatinin / microalbumin) (pmol) x (mmol L^{-1} / mg L^{-1}) median (IQR)	48.3 (23.3-90.9)	42.2 (22.0-122.5)	28.4 (10.6-54.0)

*p <0.05 ** p < 0.01
FEU = fibrinogen equivalent units, IQR = inter quartile range, MI = myocardial infarction, SD = standard deviation, U = urine, VTE = venous thromboembolism

Discussion

This pilot study shows that plasma levels of F1+2 are elevated in patients with acute VTE and not in MI patients, but uF1+2 levels in VTE and MI patients were similar to the uF1+2 levels in controls. This is in contrast with the uF1+2 levels predicting postoperative VTE after orthopaedic surgery (4;5). The group of patients who developed VTE 3 days after surgery, had a higher median uF1+2 level of 127.3 (IQR 19-1200 pmol L^{-1}) than VTE patients in this analysis (4). This difference might be due to the orthopaedic procedure, after which there is also a large wound area.

The limitations of our study merit some considerations. There was a difference in time to inclusion between the MI and VTE patients. Patients with acute MI were first referred to an intervention centre for the required procedure. Upon return within 48

hours patients were enrolled, whereas patients with VTE were included straight after the diagnosis. Given that the T½ of F1+2 is approximately 90 minutes, this difference in time to inclusion might have played a role in the results (6). Consequently, the use of intravenous or subcutaneous heparin in patients with MI in the first 48 hours administered could have lowered the plasma and urinary D-dimer and F1+2 levels. However, in prospective studies no clear effect of unfractionated heparin on plasma F1+2 was observed (7). Results might also have been influenced by the concentration of the spot urine samples and micro albuminuria. When adjusted for urinary micro-albumin and creatinine levels, however, similar results were found. This study was designed as a small pilot study to investigate whether there would be robust differences of urinary F1+2 levels between patients with VTE, MI and healthy controls. Consequently, we had a small study sample. Last, to our knowledge, the pre-analytical phase for measurement of F1+2 in urine samples has not been thoroughly investigated, and F1+2 determination may have been influenced by other proteins or proteases present in urine.

Although uF1+2 levels are associated with postoperative VTE, we found no clear associations with acute VTE or MI and therefore a role of uF1+2 as predictor in epidemiological studies seems limited.

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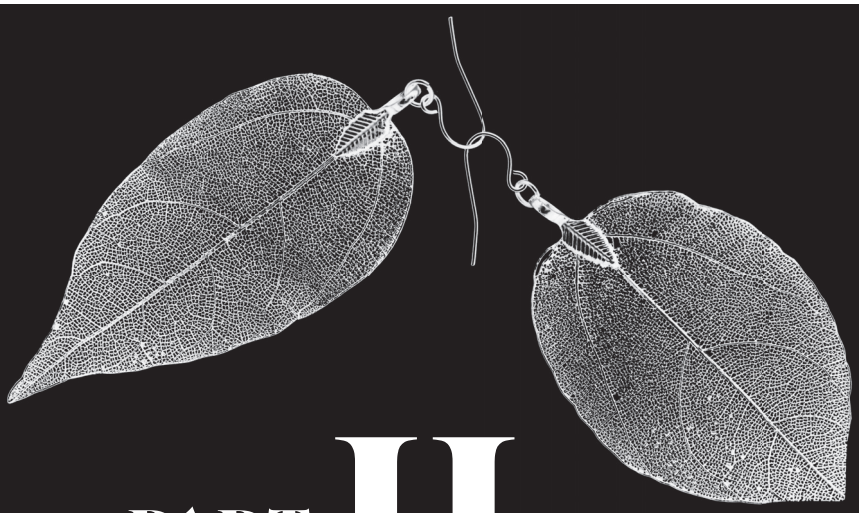
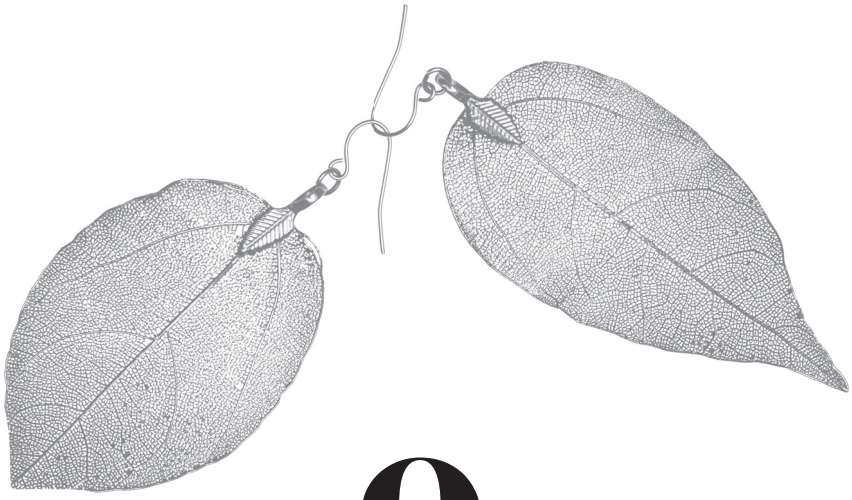


PART II

Treatment and prognosis of pulmonary embolism



CHAPTER 9

How to prevent, treat, and overcome current clinical challenges of VTE

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Abstract

Venous thromboembolism (VTE) is most commonly initially treated with low molecular weight heparin (LMWH), fondaparinux, or unfractionated heparin, in combination with vitamin-K antagonists (VKA) for the long-term treatment. VKA have some drawbacks however, which has led to the development of new anticoagulants. Most of these new drugs can be administered orally, and they have been investigated in many phase III clinical trials. The benefits of the anticoagulants are the stable therapeutic effect, little interactions with other medication and food, and therefore no regular monitoring is required. The duration of anticoagulant treatment for VTE is usually 3-12 months, and depends on the balance between the risks of recurrent thrombosis, major bleeding, and the patient's preference. Clinical decision rules to assess the risk of recurrence to tailor the duration of anticoagulant treatment, are being investigated. The beneficial aspects of novel anticoagulants may prolong the duration of treatment. VTE treatment should be adjusted in special patient groups, such as in case of malignancy, renal failure, pregnancy, or extreme bodyweight. This article gives an overview of current and future aspects of the treatment of VTE.

Introduction

Pulmonary embolism (PE) and deep-vein thrombosis (DVT) are considered to be two manifestations of the same condition: venous thromboembolism (VTE) – which has an incidence of 1-3 per 1000 of the general population per year, and is the third most common cardiovascular disorder in industrialized countries. With the aging of the current population, the incidence is expected to increase further (1;2). Anticoagulant treatment in patients with VTE is highly effective, as it reduces the incidence of recurrent disease from about 25% to about 3% during the first 6-12 months of therapy (3). Since 1960, treatment with oral vitamin K antagonists (VKA) remained the mainstay of long-term anticoagulation therapy for hemodynamic stable patients with VTE, for both prevention of thrombus extension, and recurrence of the disease (3). There are well-known disadvantages notable with the use of VKA. Although VKA administration usually can be started immediately after diagnosis, the slow onset and offset of action often requires bridging with parental or subcutaneous anticoagulant drugs, which challenges outpatient treatment (4). The initial treatment with low molecular weight heparin (LMWH), fondaparinux or unfractionated heparin (UFH) can only be stopped after the International Normalized Ratio (INR) remains above 2.0 for at least 24 h (4), which usually takes 5-10 days (5;6). LMWH or fondaparinux are usually preferred to intravenous UFH because they rarely require monitoring and are both associated with fewer recurrent thrombotic events, and less major bleeding (7). However, dose adjustments for severe renal impairment and extreme obesity are not standardised for LMWH, and there is no antidote unlike for UFH, which can be directly reversed with protamine sulphate. A rare but serious complication of UFH, LMWH, and in extreme rare situations of fondaparinux, is heparin-induced thrombocytopenia (HIT) (8;9). Besides the need for additional bridging, other drawbacks of VKA therapy include the interactions with other drugs and food, and the narrow therapeutic window, which leads to a great inter-individual variability in dose-response rate. The risk for either under- and overtreatment consequently is high and therefore routine monitoring and dose adjustments are necessary (10). Patients taking VKA spend at least one third of the time outside the therapeutic INR range (11). Therefore, the development of new anticoagulants in the last decade was welcome. In contrast to VKA these new drugs, (in-)direct Factor Xa and thrombin inhibitors, have less disadvantages, as they all have predictable pharmacological profiles (Table 1) (12;13). Currently, many clinical trials with new anticoagulants have been published or are on-going. Factor Xa inhibitors

most advanced in clinical development are rivaroxaban, apixaban, idrabiotaparinux and edoxaban, Dabigatran is the most advanced thrombin inhibitor (12;13). Critically, there is a lack of information on the appropriate antidote, and on reliable monitoring for special circumstances, such as in case of a major bleeding or when an urgent invasive procedure is required (14).

Initial anticoagulant treatment is different for patients with massive PE with hemodynamic instability and a high mortality risk. Systemic thrombolysis is recommended as first-line treatment, because of the short-term resolution of emboli and the beneficial hemodynamic effect of thrombolysis (4;15-17). However, the available evidence on the benefit of thrombolytic therapy in patients with massive PE is modest, let alone in patients with right ventricular dysfunction and a normal blood pressure (submassive PE). Embolectomy (surgically, by aspiration of the clot, or by angioplasty) is indicated in patients with PE and arterial hypotension in whom thrombolysis has failed or is contraindicated (4). However, a randomized clinical trial to compare the efficacy of the surgical and the catheter-based techniques has not been performed (4).

Table 1; Pharmacokinetic and pharmacodynamic properties of novel anticoagulants. *From phase II studies with Idraparinux. **After a single bolus, from phase I studies.

	Steady state levels	**Ttpeak (hours)**	**½ life (hours)**	**excretion**
Dabigatran	After 3 days	2	14-17	80% kidneys 20% biliary system
Rivaroxaban	After the first dosage	2-4	5-9 young 9-13 elderly subjects	66% kidneys 28% intestines
Apixaban	After 3 days	1	12	25-29% kidneys 46-56% intestines
Edoxaban	After 2 days	1-3	9-11	35-39% kidneys
Idrabiotaparinux	3-4 months*	1.5 h	120 h** 60 days*	Idraparinux: Mainly kidneys

If anticoagulant or thrombolytic therapy is contraindicated, VTE can also be treated with an inferior vena cava (IVC) filter. Patients with an IVC filter are recommended to receive a conventional course of anticoagulant therapy when the risk of bleeding is diminished (4;18). No randomized trials or prospective cohort studies have been performed to evaluate IVC filters as monotherapy of VTE, without concurrent anticoagulation.

Consequently, the use of IVC filters is restricted to patients with VTE who have a temporary contraindication to anticoagulant treatment (4).

In this state of the art, the results from large clinical trials with new anticoagulants will be outlined. Additionally, the optimal duration of anticoagulant treatment of VTE will be discussed; with a focus on special patient groups, such as cancer, renal failure, obesity and antiphospholipid syndrome, as well as the use of anticoagulant treatment in pregnant women.

Clinical implementation of novel anticoagulants

Over the last decade, a new generation of anticoagulants has emerged, with favourable characteristics to their predecessors, the VKAs. These novel anticoagulants directly inhibit one specific coagulation factor, and have stable pharmacokinetic and pharmacodynamic properties. Due to the absence of major interactions with food or other drugs, they do not require frequent monitoring. Several phase III trials have shown efficacy and safety for prophylaxis and treatment of VTE, and for the prevention of stroke in atrial fibrillation, as the following chapter further describes.

Dabigatran

Dabigatran is a novel direct thrombin inhibitor, administered orally as a prodrug, dabigatran etexilate. Its properties are listed in Table 1 (19;20). Dabigatran is licensed for the prevention of VTE after planned knee or hip surgery, following the results of several phase III studies. Both dabigatran 150 mg and 220 mg administered once daily were shown to be non-inferior to enoxaparin 40 mg subcutaneous once daily, and bleeding risks were similar (the RE-MODEL trial, see Table 2) (21). In the RE-MOBILIZE study, with a higher enoxaparin dosage of 30 mg twice daily, both dosages of dabigatran were found to be inferior to enoxaparin, without a difference in the major bleeding risk (22). Furthermore, the same dosages of dabigatran were as effective and safe as enoxaparin 40 mg once daily for the prevention of VTE after hip replacement (The RENOVATE and RENOVATE-II) (23;24).

In patients with acute VTE, dabigatran was also non-inferior to VKA in preventing recurrent VTE (in the RECOVER trial). Subjects were randomized double-blind to 6 months of treatment with either dabigatran 150 mg bid or warfarin (target INR 2-3). LMWH was administered to all patients at the beginning of treatment. Dabigatran had the same recurrence rate of VTE and the same major bleeding rate as warfarin (Table 2) (25). Results of two other studies for the (extended) treatment of VTE with dabigatran are eagerly awaited (http://clinicaltrials.gov, NCT00329238, NCT00558259).

Dabigatran was also assessed for the prevention of stroke in atrial fibrillation. The RE-LY study included 18,000 patients, randomised between dabigatran 110 mg or 150 mg bd, and warfarin (target INR 2-3). The study had a double blind, double-dummy design, and subjects were treated for 2 years. Dabigatran 110 mg bid gave a significant lower incidence of major bleeding than warfarin, and a similar occurrence of stroke or systemic embolism (Table 2). The higher dosage of dabigatran 150 mg bd was as safe as warfarin in terms of bleeding risk, but more effective in the prevention of stroke or systemic embolism. Notable side effect was dyspepsia, occurring in 12% of all dabigatran recipients (26). Based on these results, dabigatran was registered for the prevention of stroke in atrial fibrillation, in Canada and USA. The licensed dosage was 150 mg twice daily, an adjusted dose of 75 mg twice daily was suggested for patients with severe renal impairment. The 75 mg dose was however not assessed in the RE-LY study, in which patients with a creatinine clearance of < 30 mL per minute were excluded.

Rivaroxaban

One of the most advanced direct factor Xa inhibitors is rivaroxaban, a novel oral anticoagulant known for causing steady state levels after the first dose. See Table 1 for its other properties (27;28). Rivaroxaban 10 mg once daily has been shown superior to LMWH in preventing VTE after knee and hip surgery, with similar bleeding risks as 40 mg enoxaparin once daily (the phase III RECORD studies) (29;30) (Table 2). A meta-analysis of eight randomised controlled trials involving rivaroxaban for VTE prophylaxis underlined these results (31). The combined endpoint of the VTE rate and all cause mortality was lower for rivaroxaban than for enoxaparin (RR 0.56, 95% CI 0.39-0.80), and both drugs had comparable risks of major (RR 1.65, 95% CI 0.93-2.93) and clinically relevant non-major bleeding (RR 1.21, 95% CI 0.98-1.50) (31). Rivaroxaban has therefore been registered for the prevention of VTE after elective orthopaedic surgery in both Europe and Canada, for a dosage of 10 mg once daily.

The EINSTEIN investigators showed that rivaroxaban 20 mg once daily was as effective and safe as VKA for treating acute DVT. Recurrences of VTE were similar for both drugs, as was the incidence of the total of major and clinically relevant non-major bleeding (Table 2). In contrast to other new anticoagulants or VKA, rivaroxaban does not require additional LMWH at the onset of treatment. The trial was therefore designed as open-label (32). In the first 3 weeks patients received a higher dose of 15 mg rivaroxaban twice daily, followed by 20 mg once daily for the rest of the treatment period. In the EINSTEIN-Extension study, patients were randomized double-blind to the same dosage of rivaroxaban, or placebo for the extended treatment of symptomatic VTE.

Subjects had either participated in the original EINSTEIN acute DVT study, or had taken VKA for 6 -12 months. Rivaroxaban significantly reduced the recurrence of VTE, without a different risk of major bleeding (Table 2). The net clinical benefit, the composite of recurrent VTE or major bleedings, was 2.0% for the rivaroxaban group and 7.1% for the placebo group (HR 0.28, 95% CI 0.15 to 0.53, p <0.001). The EINSTEIN-PE study in patients with pulmonary embolism is still ongoing.

Rivaroxaban was also investigated for the prevention of stroke in patients with atrial fibrillation. The double-blind, double-dummy ROCKET AF trial contained a relatively vulnerable patient population, with an average age of 73 years, and a 90% incidence of a CHADS 2 score of ≥ 3. Rivaroxaban 20 mg once daily was non-inferior in comparison to warfarin (target INR 2-3) for the prevention of stroke and systemic embolism, and the risk for major bleeding was also comparable in both treatment arms. The discontinuation of treatment was relatively high for the total study population (22%), and less than 57.8% of the warfarin treated subjects had an INR in the therapeutic range (33;34).

Apixaban

Apixaban is an oral anticoagulant that directly inhibits factor Xa, its details are described in Table 1 (35). Apixaban was shown to be superior to enoxaparin for VTE prevention after both hip and knee replacement surgery. The occurrence of the composite of major and clinically relevant bleeding was similar for both drugs (see Table 2) (36;37). For the treatment of symptomatic deep vein thrombosis with apixaban, only dose-ranging studies have been performed (7). Further results from phase III studies will follow (AMPLIFY and AMPLIFY-EXT) (38). In the AVERROES study, in which apixaban 5 mg bid was evaluated vs. aspirin (80-320 mg) for patients with non-valvular atrial fibrillation and who were unsuitable for VKA treatment, the prevalence of stroke and/or systemic embolism was significantly lower in the apixaban study group, while major bleeding rates were similar for both treatment arms (Table 2). Apixaban resulted in more minor bleeding events than aspirin (HR for apixaban 1.24, 95% CI 1.00-1.53). The double-blind double-dummy study was stopped prematurely because of the efficacy of apixaban (39). The ARISTOTLE study that compares apixaban to warfarin in patients with atrial fibrillation is currently ongoing (38).

Edoxaban

Another novel oral direct factor Xa inhibitor is edoxaban (Table 1) (40). There are no available results from phase III studies for the prevention of VTE after elective hip or knee replacement. The HOKUSAI study currently investigates the efficacy and safety of

edoxaban vs. warfarin for the treatment of symptomatic VTE in a randomised, double-blind, double-dummy design. All patients are initially treated with 5-12 days of (LMWH) heparin (http://clinicaltrials.gov, NCT00986154).

Edoxaban has been assessed in a phase II study for the prevention of stroke in atrial fibrillation, with various dosages. The highest doses, 30 mg and 60 mg bid, resulted in significant more bleeding events in comparison to warfarin. The dosages of 30 mg and 60 mg once daily had similar outcomes as the vitamin K antagonist, for bleeding as well as thrombosis (41).

Idrabiotaparinux

Idrabiotaparinux was created by biotinylation of idraparinux, enabling reversal by means of avidin, its unique antidote. It indirectly inhibits activated FXa via selective antithrombin binding and therefore this pentasaccharide inhibits thrombin generation via both the extrinsic and intrinsic pathway, is administered subcutaneously, and has a very long half-life, which facilitates a once weekly dosing (42). Idrabiotaparinux shares it pharmacokinetic and pharmacodynamic properties with idraparinux, some of which are notable. It takes substantial time before the anticoagulant reaches steady state levels, after which its half-life expands to 60 days. Whether or not this increases the risk of bleeding after a long treatment period, is not clear. It may require dose adjustments for patients with long-term therapy (see also Table 1) (43). There are no studies performed with idrabiotaparinux for the prevention of VTE. Idrabiotaparinux was compared to idraparinux in the EQUINOX study for the treatment of DVT (Table 2). Idraparinux was shown effective and safe in comparison to VKA in the treatment of DVT (Van Gogh DVT study) (44). During 6 months of treatment, idrabiotaparinux 3 mg once weekly was as efficient and safe as idraparinux 2.5 mg once weekly, in terms of recurrent VTE and major bleeding, although the composite of all bleedings and major bleedings was higher for idraparinux than previously found in the Van Gogh trial (45). The CASSIOPEA study is investigating the treatment of pulmonary embolism with idrabiotaparinux in comparison to standard therapy with warfarin. In this double-blind, double-dummy, parallel group trial subjects will be treated for 3 or 6 months. Primary outcome will be the recurrence of VTE at 3 months. Secondary outcome will be the recurrence of VTE at 6 months, and bleeding risk (http://clinicaltrials.gov, NCT00345618). The BOREALIS-AF was designed to investigate whether idrabiotaparinux could prevent the occurrence of stroke or other systemic embolism in patients with atrial fibrillation. Unfortunately this trial was terminated prematurely due to financial issues.

Table 2. Results from phase III clinical trial programs for most advanced novel anticoagulants. Dosages of novel anticoagulants are mentioned in the corresponding chapter.

Novel anticoagulant	VTE prevention after orthopaedic surgery*		VTE treatment**		Stroke prevention in AF**	
	Total VTE events	Major Bleeding	VTE recurrence	Major Bleeding	Stroke plus systemic embolism	Major bleeding
Dabigatran	*Knee surgery* 36.4% vs 37.7% (p=0.017 for non-inferiority)	*Knee surgery* 1,5% vs 1,3% (p=0.82)	2.4% vs 2.1% (p < 0.001 for non-inferiority)	1.6% vs 1.9% (p < 0.001 for non-inferiority)	1.1% vs 1.7% (RR 0.7 95% CI 0.5-0.8)	3.1% vs 3.4% (p=0.31)
	Hip surgery 6.0% vs 6.7% (p < 0.001 for non-inferiority)	*Hip surgery* 2.0% vs 1.6% (p=0.6)				
Rivaroxaban	*Knee surgery* 9.6% vs 18.9% (p=0.01)	*Knee surgery* 0.6% vs 0.5% (p=0.77)	HR 0.68, 95% CI 0.44-1.04	8.1% for both treatments	2.12% vs 2.42%, p=0.117	3.6% vs 3.45%, p=0.58
	Hip surgery 1.1% vs 3.7% (p<0.001)	*Hip surgery* 0.3% vs 0.1% (p=0.18)	*Extended treatment#* HR 0.18, 95% CI 0.09-0.39	*Extended treatment#* 0.7% vs none (p=0.11)		
Apixaban	*Knee surgery* 15% vs 24%, p < 0.001	No data available	No data available	No phase III data available	1.5% vs 4.0%*** HR 0.43, 95% CI 0.30-0.62	1.5% vs 1.2%***, p=0.33
	Hip surgery RR 0.36, 95% CI 0.22-0.54					
Idrabiotaparinux	No data available	No data available	2.3% vs 3.2**** (p value not mentioned)	5.2% vs 7.3**** (p=0.29)		

VTE: venous thromboembolism. AF: atrial fibrillation. *versus enoxaparin 40mg qd **versus LMWH/VKA (INR 2-3) except for ***versus aspirin 80-320 mg ****versus idraparinux 2,5 mg weekly #versus placebo

Challenges in daily practice

The introduction of new anticoagulants in clinical practice presents several challenges. First, the favourable results of the phase II and III trials may not necessarily sustain in clinical practice, where patients with high risk of thrombosis or bleeding will be treated. Also, new anticoagulants still have an increased risk of bleeding, and in case of a major hemorrhage or the need for an emergency intervention, the anticoagulant effect should be directly and completely reversed. Today, a proper method to reverse novel anticoagulants is unknown (46).

Although these agents may not require routine monitoring, this may still be needed for special conditions. In a debate published in 2010, both parties (for and against) agreed that laboratory testing should be performed in specific circumstances (47;48). Examples are extreme bodyweight, renal impairment, or potential drug interactions. Also in the case of major bleeding or a possible overdose, or when emergency surgery is necessary, monitoring of the anticoagulant effect may provide relevant information prior to any reversal attempts. Furthermore, assessing compliance with anticoagulant treatment will become more difficult without monitoring. Finally, the information regarding the pharmacokinetic and pharmacodynamic properties of these drugs comes from a selected study population. In clinical practice, patients who would have been disqualified for such studies may not have a similar response. It remains to be shown whether these novel anticoagulants remain as beneficial and safe for their clinical implementations. Results regarding long term effects are therefore eagerly awaited.

Duration of treatment

Long-term anticoagulant therapy is required to prevent (symptomatic) extension of the thrombus and recurrence of the disease. The continuation of treatment is based on the balance between recurrent VTE and anticoagulant-related major bleeding, and the preference of patients (3;49). International guidelines on the treatment of VTE base the duration of treatment first of all on the existence and absence of an underlying cause, classifying VTE in unprovoked or provoked by risk factors such as surgery, malignancy, pregnancy or the puerperium (4). Furthermore, provoked VTE can be categorised in VTE caused by temporary or reversible risk factors, and VTE caused by persistent risk factors. In general, when a persistent risk factor is present such as malignancy, treatment should be continued as long as the risk factor is present (4;50). In patients with VTE caused by temporary and reversible risk factors, treatment duration of three months is recommended, as the incidence of recurrence is low (0% versus 19% for unprovoked VTE, two years after stopping treatment) (51).

When thrombotic events are unprovoked, VTE recurs in about a quarter of patients within 5 years (52-54). Based on the number of VTE episodes, as well as the consequences of VTE and anticoagulant-related major bleedings, anticoagulant treatment should be continued for at least 3-12 months, when risk factors for bleeding are absent and good anticoagulant monitoring is achievable (55-57). In clinical practise, most patients are treated 6-12 months (58). The decision to prolong treatment and even consider indefinite treatment, should be based on the individual recurrence and bleeding risk, together with the preference of patients (3;4;58). Agnelli et al. (55) clearly showed that the recurrence rate after stopping anticoagulant treatment, is comparable between three months (5.1%, 95% CI 3.2-7.5) and 12 months of therapy (5.0%, 95% CI 3.1-7.8).

The introduction of new anticoagulants may shift the balance to longer treatment duration. Extension of anticoagulant treatment with rivaroxaban, for instance, reduced the recurrence of VTE with acceptable bleeding rates in comparison with placebo (32). It should be noted that data on bleeding risk for the new anticoagulants is based on trials where high bleeding risk patients were excluded. Efficacy and safety data from clinical practice are needed before definite conclusions can be drawn. If the risk of bleeding is proven lower in daily practice for novel anticoagulants, prolonging anticoagulant treatment may be beneficial.

Ideally, a more individual treatment approach may be applied, where the risk of recurrence is based on patient specific characteristics. Gender, D-dimer levels measured shortly after cessation of anticoagulant therapy, and residual thrombosis in the leg veins seem all associated with a higher risk of recurrence. The PROLONG study showed that an abnormal D-dimer level, measured after the cessation of anticoagulant therapy, correlated with a higher recurrence rate (adjusted HR 1.70, p=0.045) (59). Thus far, two studies have attempted to improve the prediction of the recurrence risk by the use of risk assessment models. First, Rodger et al. designed a clinical decision rule to predict the risk of a recurrence VTE after 5-7 months of VKA (60). They concluded that for women, it might be safe to discontinue anticoagulant therapy after 5-7 months, when a maximum of one of the following features is present: post- thrombotic signs, D-dimer level ≥ 250μg/L, BMI ≥ 30 kg^{-1}, or age ≥ 65 years (60). More recently, another risk assessment model was developed by Eichinger et al., (52) based on 929 patients with unprovoked VTE and without thrombophilic factors. Only the combination of the location of initial VTE, male gender, and peak thrombin levels were found to discriminate well between low- and high risk of recurrence of VTE. Age, BMI, and Factor V Leiden did not enter the final risk models (Table 3) (52). On the other hand, treatment duration

will also be affected by an increased bleeding risk, but a bleeding risk prediction model of anticoagulant treatment in patients with VTE has not been assessed. Consequently, a precise instrument to weigh benefit and risk of anticoagulant treatment is urgently needed.

Table 3. Multivariable Cox Regression prediction models for recurrent VTE, including D-Dimer (A) and Peak Thrombin Levels (B) (51) (with permission).

Variable	Hazard Radio	95% CI	P
Model A			
Male vs female sex	1.90	1.31-2.75	<0.001
Pulmonary embolism vs distal thrombosis	2.60	1.49-4.53	<0.001
Proximal vs distal thrombosis	2.08	1.16-3.74	0.01
D-dimer (per doubling)	1.27	1.08-1.51	0.005
Model B			
Variable			
Male vs female sex	2.05	1.36-3.09	<0.001
Pulmonary embolism vs distal thrombosis	2.32	1.32-4.09	0.004
Proximal vs distal thrombosis	1.88	1.03-3.44	0.04
Peak thrombin (per 100 nmol/L)	1.38	1.17-1.63	<0.001

Treatment in specific circumstances

General guidelines do not apply to all patient groups, and the balance between recurrence of thrombosis and the risk of bleeding may vary with special circumstances, leading to a different choice of anticoagulant, dose regime, or duration of therapy.

Pregnancy

Pregnancy and the postpartum period are associated with an increased risk of VTE, which is the leading cause of maternal mortality in the developed world (61;62). The increased risk of VTE during pregnancy results from procoagulant changes in the haemostatic and fibrinolytic systems, in combination with venous stasis in the lower extremities (63;64). Pregnant patients with VTE are treated with LMWH, because this agent does not cross the placenta in contrast to VKA, exposure to which is associated with small negative effects on neurodevelopment in the first trimester and gives an unacceptable risk of hemorrhage during delivery. VKA can, only if necessary, be safely administered in the 17th to 36th week of the pregnancy. As a result of increased renal perfusion, clearance of

LMWH increases during pregnancy. Most centres, therefore, measure the anti-factor Xa (anti FXa) levels at regular intervals to monitor the therapeutic effect. However, there seems to be a wide variation in LMWH dosage and monitoring, together with a low rate of recurrences, and there is controversy to the clinical representation of the anti-FXa levels. It is therefore questionable whether anti-Xa monitoring is really mandatory (65-67). Another point of discussion is whether monitoring of platelets in patients using LMWH is required in order to assess the presence of HIT, a rare side effect of LMWH with an even lower incidence during pregnancy (65;66).

In pregnant women with HIT or with a history of HIT, the heparinoid danaparoid sodium can be administered, although only limited data exist describing use during pregnancy (68). In these cases of (a history of) HIT, platelet monitoring could be useful, but evidence about the frequency of monitoring is lacking.

LMWH should preferably be discontinued 24 h before the expected time of labour. However, in case of a very high risk of recurrent VTE, e.g. if the VTE occurred after week 36 of the pregnancy, unfractionated heparin (UFH) should be considered. Ideally, UFH should be discontinued four to 6 h prior to elective induction or caesarean section, in order to limit the duration of time without therapeutic anticoagulation. Additionally, a retrievable inferior vena cava (IVC) filter could be inserted within a week of elective induction or caesarean section (69). In the postpartum period, the duration of the anticoagulant therapy should be administered for at least 6 weeks, either with LMWH or VKA, a total duration of at least 3 months (70).

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by vascular thrombosis and/or pregnancy morbidity in the presence of circulating antiphospholipid antibodies, lupus anticoagulant, anticardiolipin or anti-β2-glycoprotein 1. Patients with APS have an increased risk of VTE recurrence ranging from 10-70% (71-73). Patients with APS are usually treated with VKA, with an INR range between 2.0 and 3.0 (15). The optimal duration of anticoagulant treatment for prevention of recurrent VTE in patients with APS is unclear, but considering the high recurrence rate, a minimal duration of one year is generally recommended, depending on the circumstances of the thrombotic event and the risk of bleeding (71;74).

Cancer

Patients with cancer and particularly those with metastatic disease have a high risk of VTE with an incidence of 4-20%, which is caused by the prothrombotic effects of the tumor and treatment with chemotherapy and radiotherapy (75-77). In patients with

cancer, VTE is an important cause of morbidity and mortality, and may be a predictor of worse prognosis (78).

It is generally recommended that patients with cancer and thrombosis are treated with LMWH for at least 6 months, because the risk of recurrent VTE is reduced to 9% with LMWH compared to a 17% recurrence rate with VKA (79). The risk of major hemorrhage with LMWH and VKA in patients with cancer and VTE are comparable (79). After 6 months of LMWH, indefinite anticoagulant therapy is recommended as long as the cancer is active (50). Whether LMWH is still more effective than VKA in the prevention of VTE after the first 6months is under investigation. At present, the relative benefits and risks of continuing LMWH beyond 6 months versus switching to oral VKA remains a clinical judgment per individual patient.

Obesity

Obese subjects have a lower proportion of highly vascular and lean body mass as a percentage of total body weight. It is therefore possible that in obese subjects treatment with LMWH could lead to an overdose, since LMWH treatment is based on body weight. Conversely, arbitrary dose reduction or capping could lead to sub-therapeutic anticoagulation and increased risk of recurrent VTE. Therefore, there is an ongoing debate whether the dose should be increased linearly, adjusted for weight or capped at some point at a maximum allowable dose. Furthermore, extreme bodyweight is a risk factor for VTE (80-83). Obese subjects with VTE are mostly excluded from clinical trials and therefore the information on the efficacy and safety of anticoagulants is scarce and inconclusive (84). Three studies showed that there is no need to adjust the currently recommended dose of therapeutic dalteparin and tinzaparin in obese people with (near) normal renal function (85-87). However, monitoring may not have been properly assessed, as Bazinet et al. found that the increase of anti FXa levels with higher body mass index is not significant (88). Whether these discrepant results depend on the pharmacokinetic properties of the different LMWHs remains to be determined (89).

Renal Insufficiency (RI)

As in patients with obesity, patients with RI are excluded in most clinical trials, so the optimal dose of the (new) anticoagulants and monitoring in the setting of RI is lacking. Anticoagulant treatment in patients with RI is also challenging because of the associated hypercoagulable state and increased risk of bleeding (90;91). Most LMWHs, with the exception of tinzaparin sodium, undergo renal clearance. In patients with non severe renal insufficiency, (glomerular filtration rate (GFR) > 30mL^{-1}), and VTE, dose-adjustment of LMWH according to anti-Xa levels is necessary, due to the risk of accumulation of LMWH

(88;92). However, due to the inter-individual variation of LMWH accumulation, no simple dosing scheme can be recommended (92).Therapeutic subcutaneous bemiparin is currently investigated among others severe RI (GFR < $30mL^{-1}$), but to date, no data have been evaluated yet (93). Due to the accumulation of LMWH in patients with severe RI (GFR < $30mL^{-1}$) (92), UFH is indicated as bridging therapy (4). UFH can be administered subcutaneously as an unmonitored, fixed, weight-based dose (5;94;95). Although VKA are predominantly metabolized by the liver, renal failure can decrease non-renal clearance and alter the bioavailability of and response to VKA. Therefore, a dose reduction of 10-20% is required, depending on the severity of the renal failure (90;91).

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CHAPTER 10

Acute pulmonary embolism. Part 2: treatment

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Abstract

The clinical presentation of pulmonary embolism (PE) varies widely, ranging from only limited symptoms to severe cardiogenic shock. Treatment of PE comprises initial therapy with low-molecular-weight heparin (LMWH), fondaparinux, or unfractionated heparin, and long-term treatment, most commonly with vitamin-K antagonists (VKAs). Methods of risk stratification, to determine whether a patient will benefit from thrombolysis, are currently under investigation. However, at present, insufficient evidence exists that hemodynamically stable patients who demonstrate echocardiographic right ventricular strain (submassive PE) benefit from thrombolysis. By contrast, thrombolysis is a widely accepted treatment strategy for patients with hemodynamic shock (massive PE). The duration of VKA treatment is commonly 3-12 months and depends on the type of PE and on the balance between the risks of recurrent PE, major bleeding, and patient's preference. In patients with a malignancy, treatment with LMWH during the first 6 months after diagnosis of PE is recommended. Several new oral anticoagulants, such as factor IIa and factor Xa inhibitors, are now being investigated. For prevention of recurrent PE in situations where anticoagulation is contraindicated, a temporary inferior vena cava filter might be useful. Some patients with PE can be safely treated at home, but few outcome studies in this setting have been published.

Introduction

Despite the long history of research on the diagnosis and prognosis of pulmonary embolism (PE), the disease remains a cause of high mortality with a case-fatality rate without treatment of up to 15% in normotensive patients, rising to 58% in patients with cardiogenic shock, which exceeds mortality for acute myocardial infarction (1). The incidence of venous thromboembolism (VTE) – comprising PE and deep-vein thrombosis (DVT) – is high, particularly among old individuals (>75 years) and is, therefore, a major health problem (2-4). The clinical presentation of PE varies widely. Some patients are asymptomatic or have only limited symptoms caused by small, and often peripheral, emboli. Others experience the more severe complaints of dyspnea, tachycardia, pain on exertion, syncope, or cardiogenic shock, which are caused by multiple, larger, or more-centrally located emboli. Patients with a high thromboembolic load, low cardiac reserve, or both often experience rapid hemodynamic deterioration. The patient's risk of death mainly depends on the presence of absence of hemodynamic instability and the severity of underlying diseases (1;5). The epidemiology and diagnosis of PE are discussed in detail in Part 1 of this Review (4).

The landmark randomized trial by Barritt and Jordan, published in 1960, was the first to demonstrate that patients with PE benefit from anticoagulant therapy (6). This treatment can be administered intravenously as unfractionated heparin (UFH), subcutaneously as low-molecular-weight heparin (LMWH), fondaparinux, or UFH, or orally as vitamin-K antagonists (VKAs). Furthermore, novel oral anticoagulants, such as selective factor IIa or Xa inhibitors, are currently under investigation and could potentially facilitate and improve the treatment of VTE. Although PE can be effectively treated, short-term and long-term sequelae characterize its clinical course. In Part 2 of this Review, we discuss the initial and long-term treatment of PE, including the use of established and novel anticoagulants. We also consider the treatment of PE in patients with comorbid conditions, such as cancer and the antiphospholipid syndrome, and in pregnant women.

Initial therapy for PE

The choice of initial therapy for patients with PE depends on their risk of severe hemodynamic complications or mortality during the first weeks after diagnosis. Risk stratification is necessary to identify patients who would benefit from a more aggressive approach to treatment than is usually taken.

Risk stratification

When an embolus occludes one or more of the pulmonary arteries, impaired blood flow and increased right ventricular (RV) afterload can lead to RV dysfunction, which, in combination with hypotension, carries a high mortality risk. Depending on the hemodynamic situation, patients with PE and subsequent RV dysfunction can roughly be divided in two categories: high-risk individuals with 'massive' PE, who have a systolic blood pressure ≤ 90 mmHg or a pressure drop of ≥ 40 mmHg for at least 15 min; and lower-risk patients with 'submassive' PE, whose blood pressure is preserved, but whose RV function is impaired (7). Of note, the term 'massive' in this context denotes hemodynamic instability caused by the thrombi, rather than the degree of obstruction. For example, patients can develop a large saddle embolus (that is, a clot that occupies the arterial bifurcation and blocks both branches) without becoming hypotensive. Conversely, patients with several diffusely located peripheral emboli can be hemodynamically unstable. Although massive PE is rare, representing less than 5% of cases, mortality is higher in patients with massive PE than in normotensive patients with PE (1;8). In the Management Strategy and Prognosis in Pulmonary Embolism Trial (MAPPET) registry (9), PE-related mortality in patients with cardiac arrest, cardiogenic shock, and arterial hypotension was 60%, 23%, and 14%, respectively.

Several tools have been investigated to identify RV dysfunction in normotensive patients with acute PE. The prevalence of RV dysfunction among patients with PE has been reported as 27-40% as assessed by echocardiography and 22-70% as assessed by CT scans (8;10). The presence of RV dysfunction as demonstrated with these imaging tools, however, has a limited positive predictive value (PPV) for mortality (5-12% (10;11) and 10% (12) for echocardiography and CT, respectively). The use of these techniques is also restricted by the lack of standardized criteria for the diagnosis of RV dysfunction and the often limited use of echocardiography in this setting.

In addition to these imaging techniques, biomarkers, such as troponins (I or T) and N-terminal pro-brain natriuretic peptide (NT-proBNP), have been evaluated for their sensitivity and predictive value, either alone or in combination, for risk stratification of patients with PE (13;14). In a meta-analysis assessing normotensive patients with PE, 21% had elevated troponin levels and mortality among these patients was 18% (odds ratio [OR] 5.9, 95% CI 2.68-12.95) (14). In addition, Ten Wolde et al. reported that the PPV of BNP level > 21.7 pmol/l for PE-related death was 17% (95% CI 6-33%) (15). The negative predictive value for an uneventful outcome of a BNP level of < 21.7 pmol/l was

99% (95% CI 93-100%). Combining the tests for NT-proBNP and troponin T increases the PPV to 33% (16).

Despite the increased risk of adverse outcomes in patients with RV dysfunction or elevated levels of cardiac biomarkers, the use of these risk stratification tools is limited by the many different cut-off values that have been reported in the literature and the high prevalence of these clinical features among normotensive patients with PE (low specificity for adverse outcomes). Selecting patients for thrombolysis on the basis of elevated biomarker levels or RV dysfunction seen on echocardiograms or CT scans can, therefore, lead to misclassification and expose a substantial proportion of patients to a high risk of major bleeding (17). We advocate treating these patients in a similar way to low-risk patients, until further research has demonstrated that risk stratification is effective and without the disadvantages that currently limit its use.

Low-risk patients

Patients with PE who do not have signs of hemodynamic instability or RV dysfunction have the lowest short-term mortality risk among those with the disease (16). Initial therapy for these individuals comprises either subcutaneous LMWH or fondaparinux, (18) or UFH given intravenously or, very rarely, subcutaneously (Table 1) (19;20).

Table 1. Drugs and dosages for the initial treatment of PE[89].

Drug	Dosage
Fondaparinux	Body weight < 50 kg: 5.0 mg Body weight 50-100 kg: 7.5 mg Body weight > 100 kg: 10.0 mg Administered subcutaneously daily
Unfractionated heparin	Bolus of 5,000 U followed by intravenous infusion adjusted to the aPTT
Low-molecular-weight heparin	0.6-1.0 IU/ml (depending on the patients' body weight) for once-daily or twice-daily administration If monitored, a target range of 1.0-2.0 IU/ml is recommended

Abbreviations: aPTT, activated partial thromboplastin time; PE, pulmonary embolism.

However, LMWH or fondaparinux are usually preferred because, when compared with intravenous UFH, they rarely require monitoring and are both associated with fewer recurrent thrombotic events (3-month recurrence rate: LMWH 3.0% versus UFH 4.4%, OR 0.68, 95% CI 0.42-1.09 (20); fondaparinux 3.8% versus UFH 5.0%, absolute

difference 1.2%, 95% CI 3.0-0.5%) (21), and because LMWH results in a lower incidence of major bleeding (LMWH 1.3% versus UFH 2.1%, OR 0.67, 95% CI 0.36-1.27) (20). UFH is preferred in patients with an increased risk of bleeding or those for whom thrombolysis is being considered, because its short-acting effect can be directly reversed with protamine sulfate. UFH is also indicated in patients with severe renal impairment (creatinine clearance < 30 ml/min) because most LMWHs, with the exception of tinzaparin sodium, undergo renal clearance (22;23). UFH could also be indicated in patients with extreme obesity, for whom the correct dose of LMWH is unpredictable and necessitates laboratory monitoring (activated partial thromboplastin time can only be used for UFH, not for LMWH). Although monitoring of LMWH or fondaparinux is possible with an anti-factor-Xa assay, this test is not available in the majority of hospitals.

Patients with a history of surgery, trauma, or a gastrointestinal bleed or ulcer in the previous 4 weeks, or those with a predisposing factor, such as thrombocytopenia, are at increased risk of major bleeding when receiving anticoagulant medication. In general, the risk of major bleeding during initial anticoagulant therapy is 1.4% for LMWH and 2.3% for UFH (24).

Heparin-induced thrombocytopenia (HIT, reduced platelet count) is a rare, but serious, complication of UFH therapy, (2.7%, 95% CI 1.3-5.1%) and, to a lesser extent, of LMWH (0%, 95% CI 0-1.1%) (25). HIT is extremely rare when fondaparinux is used and this agent has a very low cross-reactivity with HIT-antibodies *in vitro* (26). The risk of this prothrombotic condition is higher in women than in men (OR 2.37, 95% CI 1.37-4.09, p=.0015) (27) and in surgical patients compared with those receiving medical (nonsurgical) treatment (OR 1.61, 95% CI 1.24-2.08, p=0.0003), with ORs for the orthopedic and cardiac subgroups of 1.51 (p=0.009) and 1.92 (p=0.006), respectively (28). For patients with strongly suspected or confirmed HIT, whether or not complicated by thrombosis, an alternative anticoagulant, such as lepirudin, argatroban, bivalirudin or danaparoid, can be given. VKA therapy should be avoided until after the platelet count has substantially recovered (29).

Patients with submassive PE

For normotensive patients with PE who have right ventricular (RV) dysfunction – so-called 'submassive' PE – the benefit of thrombolysis is undefined (1). These patients are, therefore, initially treated in the same way as low-risk patients with 'nonmassive' PE (that is, those who are hemodynamically stable with no RV dysfunction). However, risk stratification to investigate if thrombolytic therapy might be useful in patients with

submassive PE is currently under investigation. Thrombolytic therapy accelerates clot lysis, when compared with nonthrombolytric therapy, resulting in faster restoration of lung perfusion and a decrease in RV overload. The short-term mortality in patients with submassive PE who do not undergo thrombolysis but receive regular therapy varies from 0% to 5%, which is significantly lower than in patients with massive PE (30;31).

To date, two randomized, placebo-controlled trials have evaluated the efficacy of thrombolytic therapy in patients with submassive PE. Konstantinides and colleagues showed that early treatment with heparin plus alteplase (recombinant tissue plasminogen activator) could improve the clinical course of patients with acute submassive PE (n=256) when compared with heparin alone, and particularly reduced the need for emergency escalation of treatment (32). However, the latter finding has been debated owing to its subjectivity; physicians were permitted to break the randomization code before the decision to escalate treatment, and patients undergoing thrombolysis with alteplase might then have been treated differently to those receiving heparin alone. In this study, no difference in mortality between the treatment groups was reported (32). This trial was included in a meta-analysis, together with five other studies focusing on hemodynamically stable patients (n=494) (33). Again, no difference in mortality between patients treated with thrombolysis and patients treated with heparin alone was found (3.3% versus 2.4%, OR 1.16, 95% CI 0.44-3.05) (33).

A more-recent exploratory analysis of 58 hemodynamically stable patients showed that treatment with heparin plus a single bolus of tenecteplase was feasible and was associated with a significant reduction in right to left end-diastolic dimension ratio during the 7-day follow-up (p=0.043) when compared with treatment with heparin plus placebo (34). Moreover, the use of the combined anticoagulant and thrombolytic therapy raised no safety concerns (34). However, clinical benefit was not an end point in this study and needs to be further investigated. To this end, the clinical benefit of thrombolysis in normotensive patients with PE, RV overload, and elevated troponin levels is being investigated in the ongoing Pulmonary Embolism Thrombolysis (PEITHO) trial (35). In the absence of clear benefit of thrombolysis in patients with submassive PE, these patients should still be treated in the same way as low-risk patients (36).

Patients with massive PE

Patients with massive PE are at high risk of adverse events, such as hypotension, hypoxia, and RV dysfunction, as well as cardiac morbidity and mortality. Given the short-term resolution of emboli and the suggested beneficial hemodynamic effect of thrombolysis,

together with the often critical clinical status of the patient, systemic thrombolysis is currently widely accepted as the first-line treatment in hemodynamically unstable patients with PE (1;18;37;38). The thrombolytic drug (urokinase, streptokinase, or tissue-type plasminogen activator) is usually administered systemically (Table 2). However, the available evidence on the benefit of thrombolytic therapy in patients with massive PE is modest and ambiguous, particularly with regard to long-term benefit during the months following presentation.

Table 2. Thrombolytic regimens for PE*.

Thrombolytic agent	Regimen
Tissue plasminogen activator	100 mg intravenously for 2 h
Streptokinase	250,000 U intravenously during the initial 30 min, then 100,000 U/h for 24 h‡
Urokinase	4,400 U/kg intravenously during the initial 10 min, then 4,400 U/kg/h for 12 h

*aPTT should be measured when infusion of the thrombolytic therapy is complete. Heparin should be resumed without a loading dose when the aPTT is less than twice its upper limit of normal ([8]). Regimens with short infusion times (2 h) are recommended over those with a prolonged infusion time (24 h) ([18;90]). Thrombolytic therapy should be administered intravenously instead of placing a pulmonary catheter ([8]). ‡Monitor closely for hypotension, anaphylaxis, asthma, and allergic reactions. Abbreviations: aPTT, activated partial thromboplastin time; PE, pulmonary embolism.

To date, only one randomized controlled trial of thrombolysis in patients with massive PE (n=8) has been published (39). This trial was stopped prematurely by the ethics committee, because survival was significantly greater among patients who received thrombolysis than in those allocated to heparin. The evidence on the effect of thrombolytic therapy in massive PE is further called into question by the fact that, in most studies of this intervention, no distinction is made between patients with hemodynamic instability and those who were normotensive. Wan et al. conducted a meta-analysis of five studies focusing on patients with massive PE and cardiac shock (n=254) (40). The investigators found that thrombolysis was associated with a significant reduction in recurrent PE and death compared with heparin (OR 0.45, 95% CI 0.22-0.92) (40). By contrast, however, data from 108 patients with massive PE who were enrolled in the International Cooperative Pulmonary Embolism Registry (ICOPER) showed no difference in mortality or recurrence of PE at 90 days between those receiving thrombolytic therapy and those receiving heparin (41). 90-day mortality was 46.3% (95% CI 31.0-64.8%) in patients

receiving thrombolytic therapy and 55.1% (95% CI 44.3-66.7%) among those who did not undergo thrombolysis (41).

The drawback of thrombolysis is the risk of bleeding. According to the most recent meta-analysis and Cochrane collaboration review, which were published in 2004 and 2006, respectively, the risk of major bleeding with thrombolytic therapy is nonsignificantly increased compared with treatment with heparin alone (40;42). The incidence of intracranial hemorrhage associated with thrombolytic therapy has been reported to be around 3% (1). Catheter-directed thrombolytic therapy is another available strategy, but evidence is lacking for the efficacy of this treatment in patients with acute PE (43;44).

Embolectomy is indicated in patients with arterial hypotension in whom thrombolysis has failed or is contraindicated owing to a high risk of bleeding (18). Embolectomy can either be performed surgically or by using percutaneous catheters (45;46). Surgical removal of the embolus is performed by a median sternotomy and opening of the pulmonary artery, with extracorporal support of the circulation, followed by either aspiration or mechanical removal of the clot(s) (47). Catheter-based embolectomy can be either rheolytic or rotational. Rheolytic embolectomy involves maceration of the embolus with pressurized saline, whereas in rotational embolectomy a rotating device on the catheter is used to fragment the embolus. Both catheters subsequently aspirate the embolus. Balloon angioplasty is an alternative to rheolytic and rotational embolectomy; the balloon compresses the embolus against the vessel wall and fragments the thrombus with distal embolization (46).

The choice between surgical or catheter-based embolectomy depends on the availability of resources and expertise of the physician, since surgical embolectomy can only be performed in large, specialized centers. A comparison between the surgical and the catheter based techniques has not been performed and, more importantly, neither has a randomized clinical trial to investigate the comparative efficacy of these approaches. Catheter-based embolectomy should, therefore, be restricted to patients in whom thrombolysis is indicated, but is not feasible, except in centers were adequate expertise is available (18).

Patients with a high risk of bleeding

PE can be treated by interrupting the vena caval flow using an inferior vena cava (IVC) filter if anticoagulant or thrombolytic therapy is contraindicated or the patients has a high risk of bleeding. IVCs allow blood to flow while preventing large emboli from travelling

from the pelvis or lower extremities to the lung (48). Absolute contraindications to thrombolysis include hemorrhagic stroke, closed head trauma, and ischemic stroke within the previous 3 months (49).

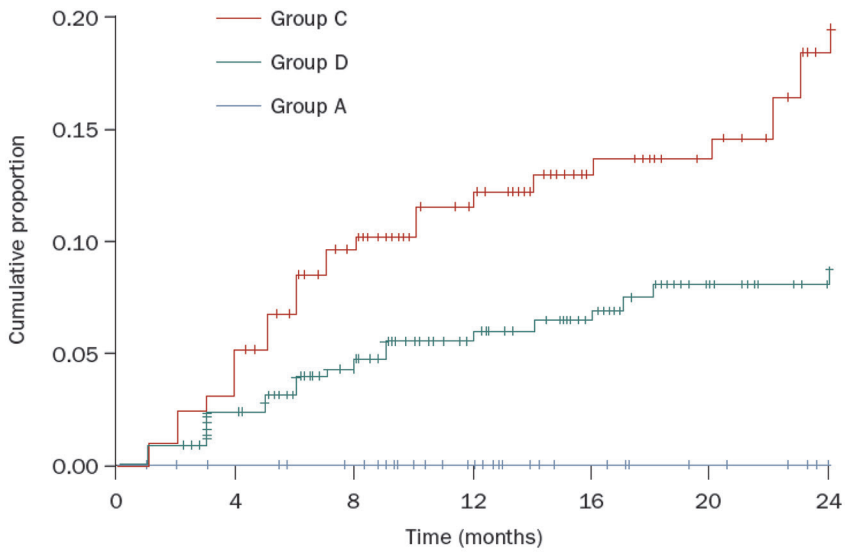
IVC filters can be permanent or retrievable. Retrievable filters can be removed through the jugular vein; however, those that have been in place for a few weeks can be overgrown by cells from the IVC wall, with a risk of IVC injury if the filter is dislodged (50). Retrievable IVC filters can be removed up to 1 year after placement. However, removal of the filter becomes more complicated as the duration of placement increases (51;52). Patients with an IVC filter are recommended to receive a conventional course of anticoagulant therapy when the risk of bleeding is diminished, for example when a surgical procedure was uncomplicated or with increasing postoperative duration (18;53). Currently, insufficient data exists to allow a comparison between the safety and efficacy of various types of IVC filters. In the randomized PREPIC trial (54), the incidence of PE in patients with DVT who received a permanent IVC filter in addition to anticoagulant treatment was reduced after 12 days, and after 2 and 8 years when compared with anticoagulant therapy alone. However, combined therapy led to an increase in the incidence of recurrent DVT. Total mortality and the incidence of post-thrombotic syndrome were the same in both groups (54). No randomized trials or prospective cohort studies have been performed to evaluate IVC filters as monotherapy, without concurrent anticoagulation, in patients with PE. Consequently, the use of IVC filters is restricted to patients with PE who have a temporary contraindication to anticoagulant treatment. If a permanent IVC filter is inserted and the patient's bleeding risk is acceptable, long-term anticoagulant treatment is indicated (18).

Long-term treatment

In all patients with PE, long-term anticoagulant treatment is required to prevent (symptomatic) extension of the thrombus and recurrence of the disease. Treatment with an orally administered VKA is still the mainstay of long-term anticoagulation therapy. VKA administration can usually be started immediately after diagnosis of PE – together with LMWH, UFH, or fondaparinux – and the effective range of anticoagulation (International Normalized Ratio [INR] 2-3) is reached after 5-10 days. Initial treatment with LMWH, UFH, or fondaparinux can only be stopped after the INR remains above 2.0 for at least 24 h (18). The risk of recurrent PE after stopping long-term anticoagulant therapy is approximately 10% in the first 2 years after treatment has begun (38;55) Recurrence risk is primarily determined by the patient's intrinsic risk (18). If the

thrombotic episode was provoked by a reversible risk factor, such as surgery or trauma, the incidence of recurrent VTE after stopping VKA therapy is lower at 2 years than if VTE was unprovoked (0% versus 19%; Figure 1) (56).

Figure 1. Cumulative proportions of recurrent thrombosis after cessation of anticoagulant therapy. Group A: patients with surgery in the previous 6 weeks. Group C: patients with no indentifiable clinical risk factor. Group D: patients with non-surgical risk factors for venous thromboembolism. Data for group B are not included becaue it was a small group with no recurrences.



Number at risk							
Group C	193	184	153	133	110	98	81
Group D	279	269	235	209	185	155	139
Group A	86	82	79	71	61	58	53

In 1995, Schulman and colleagues showed that 6 weeks of treatment with VKA resulted in a higher recurrence rate of VTE compared with treatment for 6 months (57). Subsequently, two studies of patients with VTE showed that the rates of recurrence and major bleeding were comparable after 3 months and 6 months of therapy (Table 3)

(58;59) In addition, Agnelli and colleagues found that 12 months of treatment with a VKA resulted in similar rates of recurrence (~16%) to those of 3 months of treatment (Table 3) (60). Rates of major bleeding were 1.5% and 3% for patients who received 3 months and 12 months of therapy, respectively (60). Most major bleeding episodes occur in the first 3 months of treatment (56). In addition, the risk of a major bleeding rises with patient age (61). Consequently, the decision to continue treatment beyond 12 months should be individually determined, taking the patient's preferences into consideration, and should be reassessed at periodic intervals (18).

Table 3. Outcomes of short-term and long-term treatment in patients with PE.

		Major hemorrhage (%)			Recurrence of VTE (%)		
Study	**n**	**3 months**	**6 months**	**12 months**	**3 months**	**6 months**	**12 months**
Campbell et al. (58)	749	0	2	NR	8	7	NR
Pinede et al. (59)	736	2	3	NR	8	9	NR
Agnelli et al. (60)	267	1.5	NR	3	16	NR	16

NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

On the basis of the frequency, as well as on the consequences, of recurrent VTE and anticoagulant-related major bleeding, duration of treatment for provoked PE is recommended to be 3 months. For patients with unprovoked PE, in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, long-term treatment is recommended for a period between 3 and 12 months. In clinical practice, therefore, most patients with unprovoked PE will be treated for 6-12 months. In case of recurrent PE, treatment with VKA should have an indefinite duration (18).

Although long-term treatment with heparin (>6 months) can induce osteoporosis, the incidence of bone fractures potentially attributable to this complication is extremely low and is comparable with that for treatment with warfarin (62).

Biomarkers for recurrent VTE

Considering the high risk of recurrence associated with PE, and the increased bleeding risk with treatment, tailoring the duration of anticoagulation to the individual patient is important (19;63) Several biomarkers have been investigated for this purpose; plasma D-dimer level and presence of residual thrombus are the most-promising candidates.

Elevated D-dimer levels have been associated with an increased risk of recurrence of VTE (relative risk 2.19, 95% CI 1.10-4.35) (64;65) Eichinger and colleagues found that patients with a D-dimer level below 250 μg/l had a low risk of VTE recurrence and those with levels above 250 μg/l had a high risk of recurrence (cumulative probability of recurrence at 2 years 3.7% [95% CI 0.9-6.5%] and 11.5% [95% CI 8.0-15.0%], respectively), independent of the presence of thrombophilic risk factors (65). In the PROLONG study (66), D-dimer level was used as a risk stratification tool for determining the duration of anticoagulation therapy. In total, 608 patients with a first unprovoked event underwent D-dimer testing 1 month after discontinuation of anticoagulation therapy. An abnormal D-dimer test result was recorded for 223 patients, who were then randomly assigned to either resume or discontinue VKA treatment. The recurrence rates in the two groups were 2.9% and 15.0%, respectively (adjusted hazard ratio [HR] 4.26, 95% CI 1.23-14.6, p=0.02) (66). However, thromboembolism also recurred in 6.2% of patients with normal D-dimer levels who discontinued anticoagulation therapy (66). Although a clear benefit of continuation of treatment could be observed for patients with an abnormal D-dimer level, the risk-benefit ratio of stopping anticoagulation for patients with a normal D-dimer is uncertain. Therefore, the application of the D-dimer measurement for individual risk stratification is uncertain at the present time (66).

Residual thrombus in a leg vein also seems to be associated with an increase in the risk of recurrent VTE (67), but this risk disappears after controlling for the influence of the D-dimer level (68). In a large study of patients with VTE, women with two or more clinical findings (hyperpigmentation, edema or redness of either leg, D-dimer level ≥ 250 μg/l while taking warfarin, BMI ≥ 30 kg/m^2, or age ≥ 65 years) had an annual risk of recurrence of 14%, but unfortunately no combination of clinical predictors was useful in men (69). Clearly, given the number of unresolved issues, a need exists for a randomized trial comparing various durations of anticoagulation and evaluating a biomarker-based approach to predicting PE recurrence (55).

Treatment in specific circumstances

Pregnancy

Pregnancy and the postpartum period are associated with an increased risk of PE, which is the leading cause of maternal mortality in the developed world (70;71). The increased risk of VTE during pregnancy results from procoagulant changes in the hemostatic and fibrinolytic systems (72) in combination with venous stasis in the lower extremities (73). Pregnant women with acute PE should be treated with LMWH, because this agent

does not cross the placenta. Since drug clearance increases during pregnancy, as a result of increased renal perfusion (74), the effect of therapy should be monitored each month by measuring anti-factor-Xa levels. VKAs do cross the placenta and are associated with congenital malformations, so they should be avoided during pregnancy. In the postpartum period, therapy can be switched to a VKA, which should be administered for at least 6 weeks. In women receiving adjusted-dose LMWH or UFH, discontinuing heparin therapy for 24 h before elective induction of labor is recommended (70;75).

Cancer

Patients with cancer, and particularly those with metastatic disease, have a high risk of VTE because of the prothrombotic effects of the tumor and treatment with chemotherapy and radiotherapy (76;77). Patients with malignancy and thrombosis should be treated with long-term LMWH, because the risk of recurrent VTE associated with LMWH is 9%, whereas the recurrence rate associated with VKAs is 17% in the first 6 months after the thrombotic event (78). However, the risk of major hemorrhage is similar for LMWH and VKAs in patients with cancer and PE (78). Considering the persistently high rate of PE recurrence, these patients should receive anticoagulant treatment for as long as the cancer is active (Figure 2).

Antiphospholipid syndrome

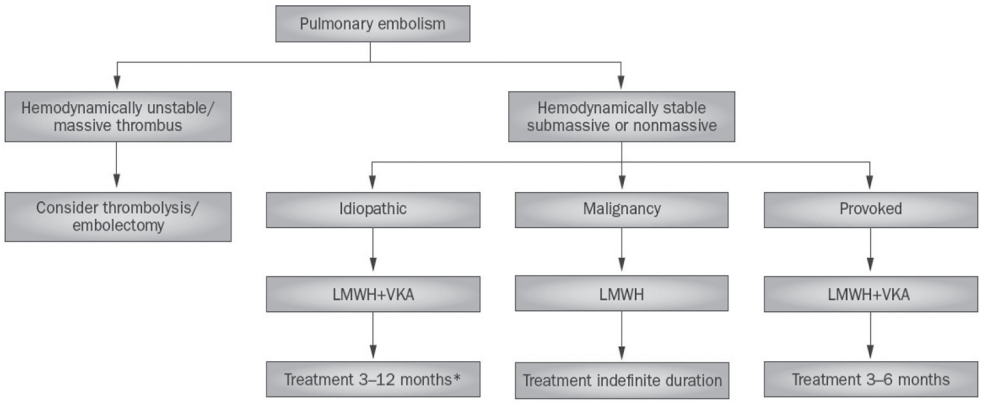
Patients with VTE and the antiphospholipid syndrome (APS), which is described in Part 1 of this Review (4), have an increased risk of VTE recurrence ranging from 10% to 70% (79-81). The optimal duration of anticoagulation for prevention of recurrent thrombosis in patients with antiphospholipid antibodies is unknown. The general consensus is to treat patients with APS and PE in the same way as patients with submassive PE, aiming at a target INR of 2-3, but with a duration of anticoagulation therapy of 1 year (38).

Home treatment

Owing to potential hemodynamic instability, the risk of adverse outcome, or the presence of complicating comorbidities, patients with PE are usually admitted to the hospital for administration of initial therapy and monitoring. However, some patients might have only mild symptoms at presentation, with a low expected risk of adverse outcome. In these patients, hospital admission could possibly be avoided, as for many individuals with DVT. Furthermore, with the introduction of LMWH in place of UFH, monitoring of initial anticoagulant treatment is no longer necessary. Home treatment involves patients self-administering anticoagulant therapy under physician guidance, in combination with nurse-led outpatient clinics for those patients who require assistance or monitoring. Risk stratification could be helpful in determining the best treatment

setting for each individual patient. The absence of ventricular dysfunction or low levels of cardiac biomarkers such as troponin (> 0.07 mg/l) and NT-proBNP (> 600 ng/l) (16) may indicate a low risk of morbidity and mortality and identify patients who could safely benefit from being treated at home.

Figure 2. Overview of treatment strategies for patients with pulmonary embolism. *Consider prolonged treatment after counseling of the patient.



Abbreviations: LMWH, low-molecular-weight heparin; VKA, vitamin-K antagonist.

Otero et al. performed a randomized clinical trial to compare the efficacy and the safety of early discharge in patients with acute symptomatic PE classified as being at low risk of death (based on a low prediction rule score and the absence of RV dysfunction) (87). Patients were randomly assigned to early discharge after 3 days in the hospital or to standard hospitalization. During the 3-month follow-up, the incidence of nonfatal recurrences of PE and hemorrhagic complications did not differ significantly between the two groups. However, the study was terminated early, after 132 patients were enrolled, owing to unexpectedly high short-term mortality in the early-discharge group as compared with the standard-hospitalization group (2.8% [95% CI 0.8-9.6%] versus 0%, p=0.30) (87). Agterof et al. investigated the safety of home treatment of hemodynamically stable patients with PE (n=152) with low (< 500 ng/l) levels of NT-proBNP, who were discharged from the hospital within 24 h of presentation (88). No deaths, occurrence of major bleeding, or recurrences of VTE took place in the first 3 months after hospital discharge. During the first 10 days, seven patients were

readmitted; in three cases, readmission was necessitated by complaints that could be related to PE. The patients who were treated at home did not experience anxiety (as assessed by the Hospital Anxiety and Depression scale) and considered home treatment to be convenient (88). This study suggests that home treatment in patients with acute PE after risk stratification could be feasible, but more studies are needed to better assess the safety of this strategy.

New anticoagulants

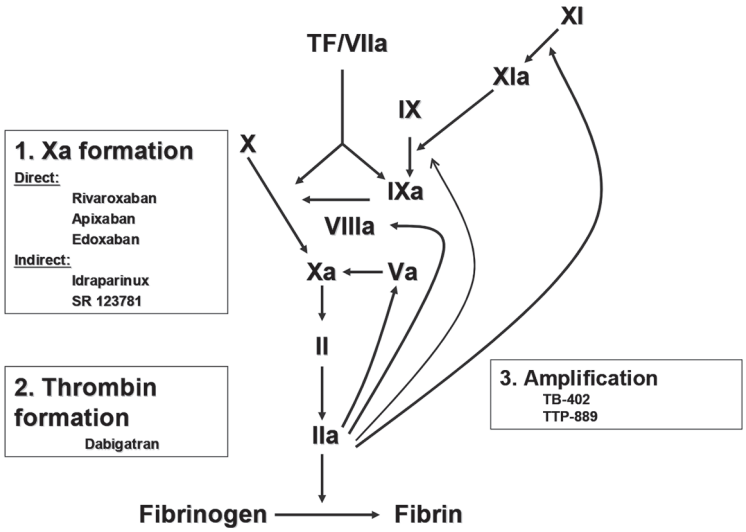
Oral VKAs, which indirectly inhibit several steps in the coagulation pathway, have been the most commonly used anticoagulants since the 1950s. However, during the past decade, several new oral anticoagulants (Figure 3) have been investigated that more selectively inhibit coagulation factors, such as factor IIa (thrombin) or factor Xa (activated factor X) (82;83). Potential advantages of direct factor IIa and factor Xa inhibitors are oral administration and fact that dose titration or monitoring is not required. Also, owing to their specificity, fewer clinical drug interactions are expected. Nevertheless, the absence of an appropriate antidote for these drugs and the need for monitoring their use in specific circumstances (for example, in patients with renal impairment) are problems that still need to be solved (36).

The oral factor IIa inhibitor dabigatran was investigated in the RE-COVER trial (84), in which 2,539 patients with acute VTE were treated for 6 months with either dabigatran or warfarin. 541 of these patients had PE and the results for these patients were similar to those for the total group of patients with VTE. Dabigatran was found to be as effective as warfarin in the prevention of VTE. The rates of recurrent VTE were 2.4% and 2.1%, respectively (HR with dabigatran 1.10, 95% CI 0.65-1.84). Major bleeding occurred in 1.6% and 1.9% of patients in the dabigatran and warfarin groups, respectively (HR with dabigatran 0.82, 95% CI 0.45-1.48) (84). Therefore, a fixed dose of dabigatran seems as effective as warfarin for the treatment and prevention of VTE recurrence and has a safety profile that is similar to that of warfarin (84).

Idraparinux, a subcutaneous, long-acting pentasaccharide inhibitor of factor Xa, is being evaluated in the randomized, double-blind CASSIOPEA trial (85). 3-month or 6-month treatment with idraparinux (3.0 mg subcutaneously, once-weekly) will be compared with warfarin for the treatment of acute PE. This trial is expected to be completed in October 2010. In addition, the efficacy and safety of the direct factor Xa inhibitors rivaroxaban and apixaban are being evaluated for long-term prevention of recurrent VTE in patients with acute DVT and PE. The results of these investigations will

soon be available. Edoxaban, which is also an oral direct factor Xa inhibitor, is currently in phase III investigation for the treatment of VTE. Other oral direct factor Xa inhibitors are in an earlier phase of development. The compound YM-150 is being tested in trials involving patients undergoing surgery and among those with coronary artery disease. In phase II clinical trials of patients undergoing primary hip replacement surgery, a dose-related response to YM-150 was reported, confirming the results of preclinical thrombosis models (86). Currently, several other phase II, II/III, and III trials of this compound are ongoing or recruiting patients. The phase III trials will assess the efficacy of YM-150 in the prevention of VTE in a large number of patients.

Figure 3. Novel anticoagulants, such as factor IIa, factor Xa, and amplification-loop inhibitors, in the coagulation cascade. Some drugs are still under investigation for the treatment and prophylaxis of venous thromboembolism. Coagulation factors are represented by their roman numerals.



Conclusions

Untreated PE is associated with high mortality. Initial therapy for PE usually comprises LMWH or fondaparinux. Only hemodynamically unstable patients with PE should receive thrombolysis or thrombectomy. VKAs are still the preferred long-term treatment and

should be used for a period of 3-12 months, depending on whether the PE was provoked or unprovoked. Longer treatment should be considered after individual counseling of the patient. An IVC filter should only be placed when a contraindication for anticoagulant treatment exists. Pregnant women and patients with cancer should be treated with LMWH instead of VKAs. Several new anticoagulants are currently under investigation, including the factor IIa inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban and idraparinux. These agents could potentially replace VKAs and LMWH for the prevention and treatment of VTE. Whether home treatment of patients with PE is safe has not yet been established.

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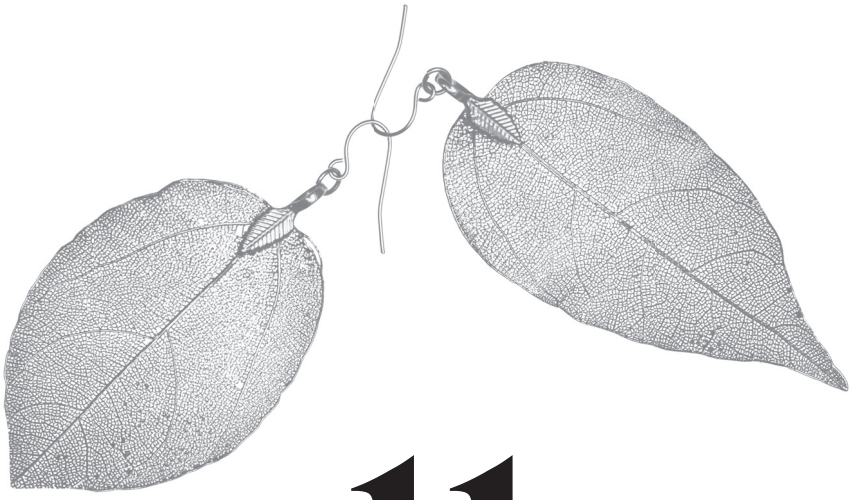

CHAPTER 11

Clot resolution after 3 weeks of anticoagulant treatment of pulmonary embolism: comparison of computed tomography and perfusion scintigraphy

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ABSTRACT

Introduction: Little is known about the natural history of clot resolution in the initial weeks of anticoagulant therapy in patients with acute pulmonary embolism (PE). Clot resolution of acute pulmonary embolism (PE) was assessed with either computed tomography pulmonary angiography (CT-scan) or perfusion scintigraphy (Q-scan) after 3 weeks of treatment.

Methods: This was a predefined safety analysis of the Einstein PE study, including PE patients, randomized to either enoxaparin with vitamin K antagonists or rivaroxaban. A similar scan as at baseline was repeated after 3 weeks. The percentage of pulmonary vascular obstruction (PVO) was calculated based on a weighted semi-quantitative estimation of obstruction. Clot resolution was assessed blindly by calculating the relative change after 3 weeks.

Results: PE was diagnosed in 264 patients with CT-scan and in 83 with Q-scan. Baseline characteristics were comparable. At baseline, the mean PVO assessed with CT-scan (PVO-CT) and with Q-scan (PVO-Q) were both 21% (Standard deviation (SD) 13%) (p=0.9). The mean relative decrease in PVO was 71% (SD) 33%) for PVO-CT, compared to 62% (SD 36%) for PVO-Q (p=0.02), while complete resolution was observed in 44% (116/264; 95% CI 38-50%) and 31% (26/83; 95% CI 22-42%) with of CT-scan and Q-scan, respectively (p=0.04). No difference in clot resolution between enoxaparin/VKA and rivaroxaban was found.

Conclusion: In patients with acute PE, only 3 weeks of anticoagulant treatment leads to complete clot resolution in a considerable proportion of patients and normalization is more often observed with CT-scan than with Q-scan.

Introduction

Little is known about the early natural history of clots in the pulmonary circulation in patients with pulmonary embolism (PE). In the available studies, perfusion scintigraphy (Q-scan) has been the cornerstone to measure the degree of thromboembolic resolution, and complete normalization of perfusion was found in approximately 40% of patients after 6 months of treatment (1). However, incidental reports suggest discrepancies between clot resolution assessed by Q-scan compared to resolution by computed tomography angiography (CT-scan) (2). Clearly, these imaging techniques are not identical; Q-scan provides indirect information on the degree of vascular obstruction and CT-scanning involves direct visualization, perhaps offering more specific evidence to support the presence or absence of intravascular thromboemboli.

Furthermore, it may be clinically relevant to identify the speed of clot resolution during anticoagulant treatment. As in patients with a suspected recurrent deep venous thrombosis (DVT), it is often unclear whether thrombi reflect a recurrence or an old thrombus. Consequently, knowledge about the time to clot resolution might be helpful in the diagnostic work-up of patients with suspected recurrent PE.

In the Einstein PE study, the efficacy of initial treatment with rivaroxaban 15 mg twice daily without concurrent heparinization was assessed by repeating radiologic imaging after these 3 weeks of treatment (3).

In the present study, we analyzed and compared the resolution of pulmonary thromboembolic obstruction after 3 weeks of anticoagulant treatment in patients with acute PE measured by either Q- or CT-scan.

METHODS

Patients

The Einstein PE study was a randomized, open-label, non-inferiority study including patients with acute PE (3). Patients were randomized to treatment with either rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once a day) or vitamin K antagonists (VKA), with a target international normalized ratio (INR) between 2.0 and 3.0. In the VKA arm, enoxaparin (1.0 mg per kilogram of body weight twice daily) was given until the INR was above the lower target range on two consecutive occasions, with a minimum of five days of enoxaparin administration (3). PE was confirmed by either CT-scan or high-probability ventilation-perfusion scintigraphy (VQ-scan).

Patients with impaired renal function (creatinine clearance < 30 ml/min) and patients below 18 years were not eligible (3).The institutional review board of the participating hospitals approved the study protocol and written informed consent was obtained from all included patients. A follow-up scan was performed in the first 400 patients after 3 weeks of anticoagulant therapy, in order to ensure the safety of the administered dose of rivaroxaban in the acute phase of anticoagulant treatment, since the dose selection was based on studies in patients with symptomatic DVT (4;5).Patients underwent the same type of scan during follow-up as for the confirmation of the initial diagnosis. The type of scan that was used for diagnosis was based on availability in the study center, some centers performed only CT-scan and others Q-scan.

Imaging protocols to confirm the diagnosis of PE

Standard contrast enhanced CT-scans were performed using a multi-detector row CT-scanner according to state-of-the-art protocols for the diagnosis and evaluation of PE (6) and ventilation/perfusion (V/Q) scintigraphy was performed following the guidelines of the Society of Nuclear Medicine (SNM 2004) (7). The CT- and V/Q- scans were used to confirm the diagnosis of PE. For the the current analysis, only Q-scans were analyzed and the ventilations scans were ignored.

The following standard protocol for CT- and Q-scan was proposed to all participating centers and the adjudication committee assessed the quality of the scans.

CT-scans

Patients were scanned during a single breath-hold, in the caudocranial direction, from the upper level of the diaphragm to a level slightly above the aortic arch (pitch of 1, 120 kV, 150-200 mAs). One hundred milliliters of contrast was administered intravenously. An imaging delay of 20 seconds was used and overlapping images were reconstructed every 3 mm. PE was confirmed by the presence of a constant intraluminal defect in segmental or more proximal branches of a pulmonary artery.

Ventilation-perfusion scintigraphy

Images were obtained in the upright position immediately after the administration of 75-150 MBq of technetium-99m macroaggregated albumin particles after several deep breaths. Ventilation scintigraphy was also performed in the upright position immediately after inhalation of technetium-99m aerosols or xenon-133 or krypton-81m gases. Perfusion and ventilation planar images were acquired from multiple projections,

including anterior, posterior, both posterior oblique and if possible both lateral and even both anterior oblique projections; at least four and up to eight imaging projections were acquired (500 kilocounts per view). PE was confirmed by either ≥ 2 large mismatched (V:Q) segmental defects (PIOPED II criteria).

Assessment of pulmonary vascular obstruction

CT- and Q- scans were analyzed by two trained, who were unaware of timing of the scan (i.e. baseline or after three weeks), treatment allocation and clinical information. In case of disagreement, a consensus reading was carried out.

The percentage of vascular obstruction (PVO) was calculated, as described by Meyer et al (8) and Wartski et al (9) for both CT-scans (PVO-CT) and Q-scans (PVO-Q). For each lobe, the vascular obstruction was first assigned a semi-quantitative obstruction score from 0 (no obstruction) to 1 (no perfusion) (0, 0.25, 0.5, 0.75 and 1), estimated visually based on the comparison of film density with an apparently normal perfused area (Q-scan) or based on the localization of obstruction in the vascular tree for that lobe (CT-scan). The overall PVO (%) was the sum of the 6 separate lobar scores (x 100%), with the right lung contributing for 55% and the left lung for 45%. Clot resolution was assessed by calculating the relative and absolute change of PVO after 3 weeks. Clot resolution of 100% was considered as complete clot resolution.

Statistical analysis

PVO rates were calculated at baseline and after 3 weeks. The percentage of resolution was assessed by calculation of the mean relative change after 3 weeks relative to baseline. Clinical characteristics of the patients were compared using a chi-squared test or Fisher's exact test for quantitative variables, and a Student t-test or Mann-Whitney test for normally and not-normally distributed continuous variables, respectively. Assessment of the improvement in PVO after 3 weeks was performed with multivariate analysis for the following baseline characteristics: type of anticoagulant, pulmonary disease, known thrombophilia, recent surgery or trauma, immobility, use of estrogen, previous venous thromboembolism, malignancy, age, gender and body mass index. P-value for entry in the model was set at < 0.15. All analyses were performed using SPSS software, version 19.0 (SPSS Inc, Chicago, Ill). Statistical difference was set at $p<0.05$.

RESULTS

In total, 400 patients with CT- or Q-scan confirmed PE were eligible for the current analysis. In 33 patients, the repeat scan was not performed, because withdrawal of informed consent or death of the patients. Furthermore, 3 patients experienced recurrent symptomatic PE and did not undergo the follow-up scan after 3 weeks. The repeat scan differed from the scan at baseline in 14 patients; all these 50 patients were excluded. In 350 patients, baseline and follow-up scan were performed, of which the repeat scan was not evaluable in three patients. Of the remaining 347 patients, a CT-scan was performed in 264 patients (76%) and a Q-scan in 83 patients (24%). The clinical characteristics of the two study groups are described in Table 1. The time between the baseline and follow-up examination was similar for patients examined with CT- or Q-scan: 22 ± 4.3 days (mean ± standard deviation (SD)) for CT-scan, versus 22 ± 4.6 days with Q-scan. In patients who received VKA, the time in therapeutic range (INR 2.0-3.0) between CT- and Q-scan was similar (Table 1). Of the patients who underwent CT-scanning, 129 (49%) patients were treated with enoxaparin/VKA and 135 (51%) with rivaroxaban. In the patients in whom a Q-scan was performed, these rates were 38 (46%) and 45 (54%), respectively, (p = 0.6).

Percentage of vascular obstruction

At baseline, the mean PVO-CT and PVO-Q were both 21% (SD 13%) (p = 0.9). After 3 weeks of anticoagulant treatment, PVO-CT decreased to 6.5% (SD 8.7%) and the PVO-Q to 8.0% (SD 9.0%) (p=0.11), (Figure 1). The differences in the mean PVO (PVO-CT and PVO-Q combined) at baseline and after 3 weeks between the VKA and rivaroxaban group did not differ (p=0.3 and p=0.7 respectively).

At baseline, mean PVO-CT was 20% (SD 11%) in patients with VKA and 22% (SD 14%) in patients with rivaroxaban (p=0.57). The mean PVO-Q was 21% (SD 14%) for both patients with VKA and rivaroxaban (p=0.9) (Table 2). After 3 weeks of anticoagulant treatment, mean PVO-CT was 6% (SD 7%) in the VKA group and 7% (SD 10%) in the rivaroxaban group (p=0.32), whereas mean PVO-Q was 9% (SD 9%) and 7% (SD 9%), respectively (p=0.64).

The mean *absolute* decrease of PVO was also not different: 14% (SD 10%) and 13% (SD 11%) for PVO-CT and PVO-Q, respectively (p=0.25) (Table 2). However, the mean *relative* decrease of PVO after 3 weeks of anticoagulant treatment was significantly greater with CT-scan compared to Q-scan: 71% (SD 33%) and 62% (SD 36%) for PVO-

CT and PVO-Q, respectively (p=0.02) (Table 2). There were no significant differences in relative or absolute decrease of PVO between rivaroxaban and enoxaparin/VKA (p=0.4 and p=0.6, respectively) (Table 2.).

Table 1. Clinical characteristics of the 2 study groups at baseline*.

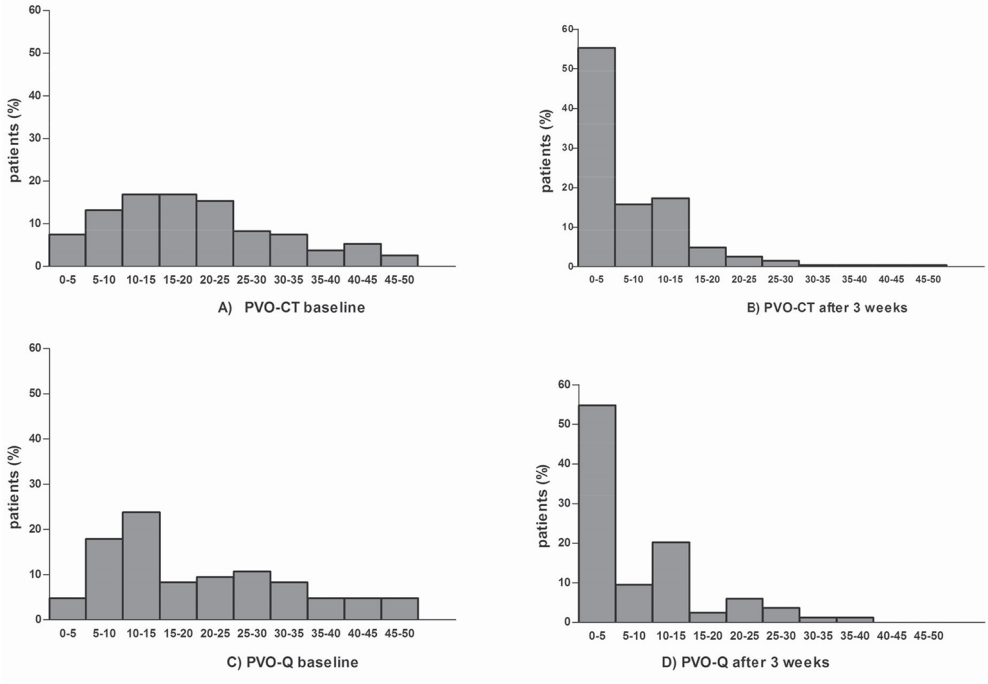
Characteristic	CT-scan	Q-scan
Number of patients, n	**264**	**83**
Male n (%)	135 (51)	52 (62)
Age, years, mean (SD)	57 (17)	59 (16)
Time (in days from randomization) to therapeutic INR, mean (SD)	7 (4.7)	7 (5.3)
Enoxaparin/VKA, n (%)	129 (49)	38 (46)
Rivaroxaban, n (%)	135 (51)	45 (54)
Pulmonary disease	63 (24)	10 (12)
Known thrombophilic condition, n (%)	18 (7)	7 (8)
Idiopathic PE, n (%) #	124 (47)	50 (60)
One or more risk factors for PE n (%)	140 (53)	33 (40)
Recent surgery or trauma, n (%) **	50 (19)	8 (10)
Immobilization, n (%) **	37 (14)	8 (10)
Use of estrogen containing drugs, n (%) **	24 (9)	10 (12)
Active cancer, n (%) **	24 (9)	6 (7)
Previous episode of VTE, n (%) **	55 (21)	19 (23)

CT computed tomography, N number, INR international normalized ratio, PE pulmonary embolism, SD standard deviation, VKA vitamin K antagonists, VTE venous thromboembolism.

* No significant difference in baseline characteristics between two study groups
# No risk factor
** Some patients had more than one risk factor

The correlation between the relative decrease in PVO and PVO at baseline (PVO-CT and PVO-Q combined) was modest, (spearman r=-0.2, $p < 0.001$), whereas a strong correlation was found between PVO at baseline and PVO after three weeks (spearman r=0.52, $p<0.0001$). Table 3 details the obstruction measured at baseline and after three weeks, categorized by extend of the baseline obstruction, (in quartiles) and shows that the higher the percentage of obstruction, the more residual thrombosis is observed.

Figure 1. Percentage of vascular obstruction (PVO) at baseline and after 3 weeks of anticoagulant treatment (enoxaparin/VKA or rivaroxaban) on computed tomography pulmonary angiography (PVO-CT) or perfusion scintigraphy (PVO-Q).



PVO-CT baseline; B) PVO-CT after 3 weeks; C) PVO-Q baseline; D) PVO-Q after 3 weeks.

Normalization of pulmonary artery obstruction

Three weeks of anticoagulant treatment resulted in complete resolution in 41% and partial resolution in 47% of the total study population, whereas in 12% no relevant change was observed. Other than the 3 patients with symptomatic worsening and confirmed recurrent PE, who were left out in this analysis, we found no patients with worsening of the obstruction after 3 weeks.

In patients examined with CT-scan, the complete resolution rate was 44% (116/264, 95% CI 38-50%) compared to 31% of patients evaluated with Q-scan (26/83; 95% CI 22-42%), p=0.04. No (relevant) change was observed in 10% of patients with CT-scan (27/264; 95% CI 7-14%), compared to 19% of patients examined with Q-scan (16/83; 95% CI 12-29%) (p=0.03; table 4).

Table 2. Mean percentage of vascular obstruction (PVO) at baseline and after 3 weeks, mean absolute and relative decrease of PVO of the total number of computed tomography scans (CT-scans) and perfusion scans (Q-scans) and of the enoxaparin and vitamin K antagonist (VKA) and the rivaroxaban group, divided per scan.

	total CT-scans	**total Q-scans**	**p-value**	**enoxaparin/ VKA CT-scan**	**rivaroxa-ban CT-scan**	**enoxaparin/ VKA Q-scan**	**rivaroxa-ban Q-scan**	**p-value**
Number of patients	**264**	**83**		129	135	38	45	
Baseline Mean PVO % (SD)	**21 (13)**	**21 (13)**	**0.9**	20 (11)	21 (14)	22 (14)	21 (14)	0.3
3 Weeks Mean PVO % (SD)	**6.5 (9)**	**8.0 (9)**	**0.1**	6 (7)	9 (9)	7 (10)	7 (9)	0.7
mean absolute decrease of PVO % (SD)	**14 (10)**	**13 (11)**	**0.3**	14 (10)	12 (10)	14 (10)	13 (12)	0.4
mean relative decrease of PVO % (SD)	**71 (33)**	**62 (36)**	**0.02**	73 (32)	59 (37)	70 (34)	65 (35)	0.6

SD standard deviation

Table 3. Percentage of obstruction (PVO) measured at baseline and after three weeks, categorized by extend of the baseline obstruction, in quartiles.

Baseline PVO	Number of patients	Median PVO at baseline, (IQR)	Median PVO at 3 weeks, (IQR)
CT-scan quartiles	**264**		
0-11	67	6.3 (5.0-9.5)	0.0 (0.0-5.0)
12-19	77	14.3 (11.8-17.5)	0.0 (0.0-6.3)
20-28	59	23.5 (21.8-25.0)	5.6 (0.0-11.9)
28-75	61	36.3 (30.6-42.3)	11.3 (6.3-14.9)
Q-scan quartiles	**83**		
0-11	24	8.0 (6.3-10.0)	0.0 (0.0-5.0)
12-16	19	12.0 (11.3-14.3)	5.0 (0.0-12.5)
16-30	20	24.5 (20.6-26.0)	7.0 (5.0-11.3)
30-65	20	38.3 (34.0-44.3)	12.8 (3.0-23.3)

In patients with complete resolution, the PVO rates at baseline were similar between CT-scan (PVO-CT 17%, SD 11%) and Q-scan (PVO-Q 15%, SD 10%) (p=0.5). Also, patients with complete resolution had a similar mean PVO at baseline compared with patients with no relevant change on the follow-up scan: mean PVO (PVO-CT and PVO-Q combined) at baseline was 20% (SD 10) in patients with complete resolution and 21% (SD 11%) for patients with no relevant change after 3 weeks, respectively (p=0.49).

The results were also comparable between patients treated with rivaroxaban or VKA in patients who had complete resolution (p=0.5) or those with no relevant change (p = 0.6).

Age was significantly correlated to PVO-Q after 3 weeks (r=0.4, $p < 0.001$), but had no influence on the PVO-CT (r=0.05, p=0.5). Adjustment by multivariate analysis for all baseline characteristics did not change the improvement of the scan after 3 weeks, nor the differences observed for the 2 different scan types (data not shown).

Table 4. Clot resolution after 3 weeks of anticoagulation for pulmonary embolism, evaluated with computed tomography scan (CT-scan) and perfusion scintigraphy (Q-scan) and in the enoxaparin and vitamin K Antagonists (Enox/VKA) and the rivaroxaban (Riva) group, divided per scan.

	total	**total CT-scan**	**total Q-scan**	**p-value**	**Enox/VKA CT-scan**	**Riva CT-scan**	**Enox/VKA Q-scan**	**Riva Q-scan**	**p-value**
Number of patients	347	264	**83**		129	135	38	45	0.6
Complete resolution, n	**142**	**116**	**26**	**0.04**	57	59	11	15	
(%, 95% CI)	**(41, 36-46)**	**(44, 38-50)**	**(31, 22-42)**		(44, 36-53)	(44, 36-52)	(29, 17-45)	(33, 21-48)	0.5
Partial resolution, n	**162**	**121**	**41**	**0.5**	58	61	19	22	0.8
(%, 95% CI)	**(47, 42-52)**	**(45, 40-51)**	**(49, 38-59)**		(45, 37-54)	(45, 37-54)	(50, 35-65)	(49, 35-63)	
No relevant change, n	**43**	**27**	**16**	**0.03**	12	15	8	8	0.6
(%, 95% CI)	**(12, 9-16)**	**(10, 7-14)**	**(19, 12-29)**		(9, 5-16)	(11, 7-18)	(21, 11-36)	(18, 9-31)	

CI confidence interval

Discussion

In this analysis, 3 weeks of anticoagulant treatment resulted in complete clot resolution in 41% of the patients with acute PE, in partial clot resolution in 47%, whereas no relevant change was observed in only 12%. Worsening of the vascular obstruction was not observed. In patients evaluated with CT-scan, the mean relative decrease in vascular obstruction after 3 weeks of anticoagulation was greater (71%) compared to patients evaluated with Q-scan (62%), (p=0.02). Furthermore, the normalization of the perfusion defects on the CT-scan occurred in significantly more patients compared to Q-scan (44% versus 31%). No difference in clot resolution was found between enoxaparin/VKA and rivaroxaban.

The differences in imaging techniques are the most likely explanation: CT-scan allows a direct visualization of the emboli, offering more specific information on the clot location and size, whereas Q-scan gives an indication of vascular obstruction that is derived from perfusion defects. It is known that small perfusion defects seen on Q-scan, may occur with increasing age, probably due to the presence of pulmonary co-morbidities (10-11). Furthermore, residual perfusion defects may persist even after complete resolution of the thromboemboli.

The normalization of vascular obstruction in this study (44% and 31% on the CT- and Q-scan, respectively) can only partly be compared to earlier studies, since, to our knowledge, vascular obstruction has not been measured after 3 weeks of therapy. After six weeks of anticoagulant treatment in 90 patients with PE, 32% of patients had normal pulmonary circulation with (4 slice) CT-scan (12), while this was 34% in 157 patients with Q-scan after 3 months (9). In addition, after 9 months, 68/80 (85%) patients had complete clot resolution on CT-scan and 67/93 (72%) patients on Q-scan. However, in order to minimize radiation exposure, no parallel Q-scans or CT-scans were assessed at baseline and after 9 months for direct comparison of the two imaging techniques (13). There is only one study that directly compared CT- and Q-scan, in 25 patients with acute PE 6 months after diagnosis; 32% of the patients had complete clot resolution with CT-scan and 44% with Q-scan (2). Although this difference was not significant due to the small sample size, this is in contrast with our results.

There are two important potential clinical consequences of our findings. First, the high frequency of clot resolution after acute PE may facilitate a correct diagnosis of recurrent PE, which is relevant considering the fact that many patients with recurrent PE will be treated with an indefinite duration of anticoagulant therapy. Furthermore, if

the need for a repeat CT-scan at the end of anticoagulant treatment as baseline for future evaluation in case of suspected recurrences can be questioned, especially in the patients with low percentage of obstruction at baseline. In these patients, the risk from radiation exposure can be avoided. Second, residual thrombosis of the pulmonary vasculature could lead to pulmonary hypertension. It has been generally accepted that after six months of treatment, over 50% of patients have residual thrombosis despite adequate anticoagulant therapy (1). However, the studies on which this percentage is based showed a large heterogeneity in duration of anticoagulation, type of patients, severity and location of vascular obstruction and imaging techniques. The studies had a small sample size, (2;12) used Q-scan (10) or included patients with massive PE only (14). If significant normalization is observed with CT-scan in nearly half of the PE patients after 3 weeks of anticoagulation, a larger proportion of patients will probably have complete normalization after 6 months, certainly higher proportions than is presently assumed.

Our study is the first to prospectively assess CT- and Q-scans in a large group of 347 consecutive patients and all scans were analyzed by the same independent adjudication committee. The limitations of our study merit some considerations. First, selection of the type of scan was based on the local protocol of the study centers, hence patients were not randomized to undergo either CT- or Q-scanning and only 24% of the studied patients underwent a Q-scan. However, because the type of scan was based on local practice, patients were distributed randomly. Furthermore, the degree of vascular obstruction assessed at baseline was similar between the 2 types of scans. Second, although the baseline characteristics between the 2 scan groups were not significantly different, they were not identical either and because detailed information on the presence of co-existing cardiopulmonary disease was not collected, we cannot rule out small differences between the 2 groups. Nevertheless, the number of patients with pulmonary disease was twice as high in the group who underwent a CT-scan, indicating that pre existing pulmonary disease could not explain the lower reperfusion rate of the Q-scans compared to the resolution rate of the CT-scans. Additionally, multivariate analysis revealed that pulmonary diseases, history of PE and malignancy were no significant factors for the observed differences. Also, because this analysis was part of a large study in patients with acute PE treated with either rivaroxaban or enoxaparin/VKA (3) there might have been an inclusion bias, since patients with much co-morbidity were likely to be not included. Lastly, we compared two imaging modalities which are not identical. Q-scan provides an estimation of the perfusion of pulmonary segments, whereas CT-scan visualizes clots in the pulmonary vasculature directly. To be able to compare the

two modalities, we assumed clot resolution was a derivative of improvement of vascular obstruction and vice versa, even though it is plausible that the time course of clot dissolution and restoration of perfusion may differ.

In conclusion, in patients with acute PE, 3 weeks of anticoagulant treatment leads to complete clot resolution in 44% with CT-scan and over 30% with Q-scan. This implies that clot resolution occurs early after the initiation of anticoagulant treatment and apparently more rapidly when assessed with CT-scan.

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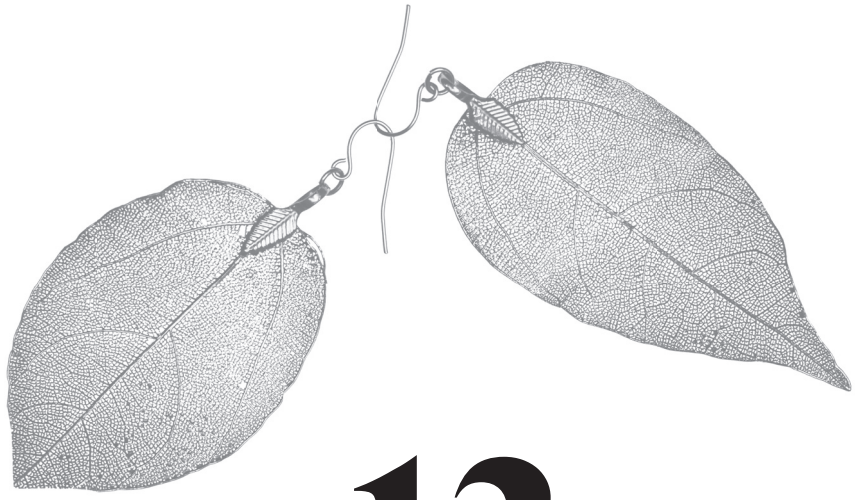

CHAPTER 12

Assessment of clot resolution following treatment of acute pulmonary embolism and its prognostic implications for recurrent venous thromboembolism

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Abstract

***Background**:* In patients with acute pulmonary embolism (PE), systematic assessment of residual thrombotic obstruction after long-term anticoagulation has been understudied. Nowadays physicians often order repeat CT-scans after six months of anticoagulant treatment without solid evidence for clinical relevance, because assessment of the presence of residual thrombotic obstruction is of clinical importance for these diagnostic baseline CT-scans, in case of clinically suspected recurrent PE or as a tool for risk stratification for recurrent venous thromboembolism (VTE). Information regarding residual thrombosis may be of clinical importance for assessing the need for repeat diagnostic baseline scans.

Methods: In this prospective, multi-center cohort study, consecutive patients with acute PE underwent baseline CT pulmonary angiography (CTPA) following 6 months of anticoagulant treatment. Two independent, expert thoracic radiologists systematically and independently assessed all CTPAs for the presence of residual thrombosis. The degree of pulmonary obstruction was calculated using the obstruction index of Qanadli. A two-year follow-up was performed to assess the correlation between residual thrombotic obstruction and recurrent VTE. Ethical approval and informed consent was obtained.

Results: A total of 141 patients were included. At time of diagnosis, the mean obstruction index was 30% (standard deviation (SD) 20). After six months of treatment, 95% of the patients had complete resolution of PE. Seven patients (5%; 95% CI 2-10%) had residual thrombosis in at least a segmental pulmonary artery, accounting for a mean obstruction index of 8% (SD 5). In another 14 patients (10%; 95% CI 6-16%), non-occlusive post-thrombotic webs or strictures were found. During follow-up, 13 (9.2%) patients experienced recurrent VTE. None of the patients with residual PE developed recurrent VTE.

Conclusion: This study reveals that the incidence of residual thrombotic obstruction following treatment for acute PE is considerably lower than currently assumed. These findings, combined with the absence of a correlation between residual thrombotic obstruction and the occurrence of recurrent VTE, do not support the use of baseline CTPA imaging in patients treated for acute PE.

Introduction

Acute pulmonary embolism (PE) is a potentially fatal disease with a high tendency to recur, with an incidence of 10-20% of patients in the first two years after cessation of anticoagulant therapy (1;2). The optimal duration of anticoagulant therapy is therefore a topic of ongoing debate. For the long-term management of acute PE, information on the resolution of PE has become of recent interest. Assessment of the presence of residual thrombotic obstruction appears to have two important clinical implications. First, baseline imaging may aid in the differentiation between residual and recurrent emboli in the diagnostic work-up of patients with suspected recurrent PE. This is of importance given the therapeutic consequences of prolonged or even lifelong anticoagulant treatment (3). Second, patients with residual thrombotic occlusion may be at increased risk of recurrent VTE or chronic thromboembolic pulmonary hypertension (4).

However, to date, little is known on the natural resolution of PE following anticoagulant treatment. Although a recent systematic review suggested that more than 50% of all patients with PE have incomplete PE resolution 6 months after diagnosis(5), the studies on which this pooled percentage was based were small and differed largely with respect to the duration of treatment, type of imaging test (i.e. CT-pulmonary angiography (CTPA) or VQ-scanning), and timing of the follow-up scan (6-8). Since CTPA, allowing direct thrombus visualization, has emerged as the first-line imaging test for the detection of acute PE, and considering the potential clinical implications of residual thrombus mentioned above, it would be important to study the natural history of PE and assess the degree of residual thrombotic obstruction with CT-scanning. However, prospective studies on the assessment of residual thrombotic obstruction with CTPA are scarce.

Therefore, this study investigated the course of clot resolution as assessed with CTPA, in patients treated with anticoagulants for six months for an episode of acute PE. Furthermore, this study investigated whether residual thrombotic obstruction is predictive for the development of recurrent VTE.

Methods

Participants

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

Procedure

Patients underwent a baseline CTPA 6 months after the diagnosis of PE. Subsequently, a half yearly follow-up during two years was performed by telephone or clinical visits at 12, 18 and 24 months to document the occurrence of recurrent PE, DVT as well as the occurrence of CTEPH. Demographic data and clinical information of the patients were collected on a case record form.

Patients were instructed to contact the study center or treating physician in case of any complaints suggestive of recurrent PE or DVT. In case of a clinically suspected recurrent PE or a suspected (recurrent) DVT objective imaging tests were performed, including CTPA or compression ultrasound, respectively. In case of death during follow-up, autopsy or an independent medical report was required to determine the cause of death. Deaths were classified as due to PE in case of confirmation by autopsy, in case of an objective positive test for PE prior to death or if PE could not be confidently excluded as the cause of death.

Patients with otherwise unexplained persistent dyspnea on exertion or at rest during follow-up, as assessed with a standardized questionnaire, were considered to have a suspicion of CTEPH. These patients underwent trans-thoracic echocardiography. If supportive findings were present, patients underwent further diagnostic workup consisting of ventilation–perfusion (V-Q) lung scanning and pulmonary angiography, with direct measurement of the pulmonary-artery pressure. CTEPH was considered

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

Imaging protocols

MDCT data acquisition and reconstructions

Standard contrast enhanced MDCT was performed using a 16-slice or 64-slice MDCT scanner with acquisition of 0.5 or 1 mm sections (depending on the weight of the subject) of the entire chest for diagnosing or excluding PE. The rotation time was 0.4 s and the pitch factor 1.4; the tube current was 250-300 mA and the tube voltage 100 kV. Acquisitions were performed during a single breath-hold, lasting 10-12 seconds or less, depending on the type of scanner. 80-100 ml of contrast agent was injected in the antecubital vein with an injection rate of 4.0 ml/sec. The acquisition of the static pulmonary angiography scan was started after automated threshold enhancement detection in the pulmonary trunk. A threshold difference of 100 Hounsfield units was selected for starting the acquisition. The effective radiation dose varied between 2.8-3.9 mSv.

Diagnosis of PE and obstruction index on CTPA

Images at baseline and 6 months after the diagnosis of PE were stored on CD-Rom or comparable storage. Diagnostic and follow-up CT-scans were analyzed by two expert thoracic radiologists of different academic medical centers (LJMK and LFMB), who were unaware of clinical information, initial report of the scan and timing of the scan (i.e. diagnostic or follow-up CTPA). In case of disagreement, a consensus reading was carried out to come to an agreement. Since the inter-observer agreement of the Qanadli score for the diagnosis of PE has previously reported to be excellent (r=0.944) (9), we performed an interim analysis on the interclass coefficient (ICC) of the scans at baseline. If the ICC after one-third of the scans was > 90%, we discontinued the consensus. However, as we are the first to use the Qanadli index to assess the degree of residual thrombotic obstruction all follow-up CT images were reviewed by the two trained, independent radiologists to assess its inter-observer variability, as expressed by the Kappa coefficient for the presence and the ICC for the degree of residual thrombotic obstruction.

PE at baseline and residual thrombotic occlusion were classified at two levels of thrombus occlusion, i.e. central or peripheral (including lobar, segmental and

subsegmental vessels) using the scoring system of Qanadli et al (9). In summary, this index is defined as the number of segmental artery branches that are blocked, corrected by a factor of 1 for partial blockage, or a factor of 2 for complete obstructive PE. Using this scoring system, 40 is the highest possible score (thrombus completely obstructing the pulmonary trunk), corresponding with a 100% obstruction index.

Right ventricular dysfunction

In all patients, parallel to the diagnosis of PE, right ventricular function was assessed at time of diagnosis and after 6 months treatment by determining right ventricular to left ventricular (RV/LV) diameter ratio on CTPA. Right ventricular dysfunction was considered present when the RV/LV ratio was larger than 1.0 (10).

Statistical analysis

Dependent on normal or skewed distribution, quantitative baseline data were presented as mean and standard deviation (SD) or medians and interquartile ranges (IQR), and qualitative data as frequencies.

The proportion of patients with residual thrombosis was calculated, with 95% confidence intervals (CI). To assess the inter-observer agreement, the interclass correlation coefficient (ICC) was calculated for the degree of thrombotic obstruction and the multi-reader kappa (κ) coefficient for the presence of residual PE at follow-up. Logistic regression analysis was used to assess the association between baseline characteristics and the presence of residual obstruction. In addition, we assessed whether residual thrombotic obstruction correlated with persistent right ventricular dysfunction.

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

Results

A total of 148 patients with PE were included. Six patients were excluded from analysis because either the diagnostic scan or the follow-up scan was considered non-interpretable for the definite presence of PE. One other patient was excluded because during follow-up the filling defects were considered to represent infiltration of angiosarcoma in the pulmonary artery. The baseline characteristics of the remaining 141 participants are depicted in Table 1. Mean age was 60 years and 37% of the participants were female. In 13% of the patients, PE was located centrally, and approximately one-third had a history of VTE.

Table 1. Baseline characteristics of patients with pulmonary embolism (PE).

Characteristics	Value N=141
Female, n (%)	66 (46.8)
Age in years, mean (SD)	56 (15)
BMI, mean (SD)	28 (5.6)
COPD, n (%)	7 (5.0)
CHF, n (%)	1 (0.7)
History of DVT or PE, n (%)	25 (18)
History of DVT	11 (7.8)
History of PE	11 (7.8)
History of DVT + PE	3 (2.1)
Active malignancy, n (%)	19 (11)
Known thrombophilia, n (%)	12 (8.5)
Centrally located PE, n (%)	23 (16)
Estrogen containing drugs, n (%)	13 (9.2)
Current smoker, n (%)	26 (18)
Duration anticoagulant therapy	
6 months, n (%)	89 (63)
> 6 months, n (%)	38 (30)
unknown, n (%)	14 (10)
Time span in months between initial CT for acute PE and control CTPA, mean (SD)	5.8 (2.1)

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

Assessment of the CTPAs

Based on the first 56 CTPAs that were evaluated, the ICC for the degree of thrombotic obstruction at baseline was 0.96. Based on this observation, it was decided that a double reading was not required for the remainder of the baseline CTPAs. For the follow-up scans, the ICC was 0.24. The interobserver reliability for the dichotomous categories of whether residual thrombosis was present or not, was moderate (κ=0.58). After consensus reading, the mean obstruction index at baseline was 30.3% (SD 20.0). After six months, this decreased to 1% (SD 3.7).

After six months of treatment, consensus reading showed complete resolution PE to have occurred in 95% of the patients. Seven patients (5%; 95% CI 2-10%) had residual arterial filling defects in at least a segmental pulmonary artery, accounting for a mean obstruction index of 8% (SD 5). In another 14 patients (10%; 95% CI 6-16%), non-occlusive post-thrombotic webs (n=5, 3.5%) or strictures (n=9, 6.3%) were identified.

The degree of thrombotic obstruction at baseline was associated with the degree of thrombotic obstruction index at follow-up (Spearman r=0.19, p=0.002). No correlation was found between the obstruction index at baseline or follow-up and age, gender, malignancy, BMI, history of VTE, COPD, smoking habits or centrally located PE.

The mean RV/LV diameter ratio at baseline and after six months of anticoagulant treatment was 1.0 (SD 0.30) and 0.9 (SD 0.14), respectively (p=0.22). The interobserver reliability of the RV/LV diameter ratio was both good (ICC=0.86 and ICC=0.75, respectively) (Table 2). An association was found between RV/LV diameter ratio at baseline and the initial thrombotic obstruction index (Pearson r=0.81, $p < 0.02$). There was, however, no correlation between the RV/LV ratio and the thrombotic obstruction after six months (Spearman r=-0.04, p<0.61).

At baseline, 48 patients presented with right ventricular dysfunction (RV/LV >1.0). After six months of anticoagulant therapy, this number had decreased to 24 patients ($p < 0.0001$). Residual thrombotic obstruction did not correlate with RV dysfunction at follow-up.

Clinical outcome during follow-up

During two years of follow-up, 23 (16%, 95% CI 11-23) patients presented with suspected recurrent PE. Of those, PE was ruled out in 15 (11%, 95% CI 6.6-17) patients, either with the use of a D-dimer testing or with CTPA. In the remaining 8 (5.7%, 95% CI 2.9-11) patients, CTPA confirmed recurrent PE. An additional 5 (3.5%, 95% CI 1.6-8.0) patients were diagnosed with DVT during follow-up. Thus, a total of 13 (9.2%, 95% CI

5.5-15) patients developed recurrent VTE during follow-up, accounting for a cumulative risk of 13.2%. In 7 (5.0%, 95% CI 2.5-9.9) patients, additional testing was performed for the suspicion of CTEPH. In all 7 patients, the presence of CTEPH was considered unlikely based on either echocardiography or VQ-scanning. A total of 6 (4.2%, 95% CI 2.0-8.9) patients died during follow-up, the cumulative risk for mortality was 6%. In all six patients, death was caused by a malignancy, none was suspected for recurrent PE.

Neither recurrent VTE nor death was correlated with the obstruction index at baseline or after six months. None of the patients with residual PE developed recurrent VTE. The hazard ratio (HR) for recurrent VTE was not significantly different for patients with residual thrombosis versus patients without residual thrombosis (HR: 0.45 95% CI 0.01-14.5), p=0.7. Adjustment for age, gender, and malignant disease did not materially influence the HR.

Table 2. Interobserver reliability of the obstruction index, measured by the Qanadli score (9) at baseline and after six months of anticoagulant therapy, the presence of residual thrombosis in the pulmonary arteries, and the right ventricular to left ventricular (RV/LV) diameter ratio.

	Observer 1	Observer 2	Interobserver reliability (95% CI)	Consensus Quanadli
Obstruction index (SD) by Qanadli baseline	30 (20)	32 (20)	0.96 (0.92-0.97)	
Obstruction index (SD) by Qanadli after six months	1.1 (3.7)	0.9 (2.8)	0.24 (0.08-0.40)	1.1 (3.7)
Number of patients with residual thrombotic obstruction, n (%)	8 (6)	18 (13)	$\kappa = 0.58$	7 (5)
RV/LV baseline, mean (SD)	1.0 (0.30)	0.99 (0.28)	0.86 (0.75-0.92)	
RV/LV baseline, mean (SD)	0.90 (0.14)	0.87 (0.21)	0.75 (0.57-0.86)	

CI confidence interval, N number, SD standard deviation.

Discussion

The present study, which systematically investigated the natural course of clot resolution and its impact on the outcome of patients with PE, demonstrates that the proportion of patients with residual thrombotic obstruction after six months of anticoagulant treatment is 5%, substantially lower than currently assumed. Second, the presence of residual thrombotic obstruction did not appear to correlate with the occurrence of recurrent VTE in patients with PE.

The rate of residual thrombotic obstruction that we found (5%) is in contrast with previous studies; a systematic review reported residual PE to be present in more than 50% of the patients six months after PE diagnosis (5). An explanation for our low incidence of residual PE may arise from the type of imaging test used. Up to date, most studies used V/Q-scanning to assess the presence of residual perfusion defects (11-13). CTPA principally differs from V/Q-scanning in detecting PE in that it allows direct embolus visualization, whereas V/Q-scans provide an indirect indication for the presence of emboli derived from perfusion defects. Residual perfusion defects detected on V/Q-scans may not always reflect the actual presence of residual thrombus, but may be caused by other pulmonary comorbidities (14). Also, residual perfusion defects may persist even after complete resolution of the emboli. In a retrospective study in which comparable patients with PE underwent either CTPA or V/Q-scanning after at least 3 months of anticoagulation, the proportion of residual thrombotic obstruction was almost two-fold higher in patients who underwent V/Q-scanning (28% vs. 15%) (15). A recently published safety analysis from the EINSTEIN PE study (16), where 347 patients with acute PE, confirmed by CTPA (n=264) or perfusion scintigraphy (n=83) underwent a repeat scan after three weeks of anticoagulant treatment (17), also pointed towards a higher rate of clot resolution assessed with CT-scan (44%) compared to perfusion scintigraphy (31%) (17). Still, our proportion of residual thrombotic obstruction is also lower compared to previous studies that did use CTPA to assess the presence of residual thrombotic obstruction. However, these studies were designed retrospectively and conducted CTPA after a limited duration of follow-up (18), included a limited sample of patients (8), or only included patients with central PE (7).

To determine the relevance of baseline CTPA imaging for clinical practice, its benefits should be weighted against its high costs and potential harms, including radiation exposure with its associated risk of cancer (19). The most important reason to perform baseline imaging following treatment for acute PE would be to aid in the differentiation between new and residual PE, in case a patient presents with suspected recurrent PE. Indeed, a recent study by the REVERSE investigators demonstrated that baseline imaging performed after treatment for either DVT or PE, was associated with an increased diagnostic certainty in patients investigated for suspected recurrent VTE (20). However, the number of patients with suspected recurrent PE included in this analysis was low (n=38), and in these patients the proportion of diagnostic non-classifiable patients did not differ significantly between patients with and without baseline imaging. Second, V/Q scanning was used as baseline-imaging test. Although it

should be stated that the golden standard for the assessment of residual PE is unknown, CTPA has currently largely replaced V/Q scanning in the diagnostic work-up of patients with suspected (recurrent) PE. The most important advantage of CTPA over V/Q scanning is the low number of inconclusive test results (0.0-3.0% vs. 28-40%) (21). The implementation of CTPA as first-line imaging test for suspected PE makes information on the level of clot resolution using this imaging test relevant, to assess its incremental value in managing patients with suspected recurrent PE. The high rate of complete clot resolution that we found suggests that the correct diagnosis recurrent PE with the use of CTPA is less complicated than currently anticipated, which does not support the routine use of baseline CTPA imaging.

A second rationale to routinely investigate the presence of residual PE would be the potential prognostic value. In patients with DVT, it has been demonstrated that assessment of residual thrombotic obstruction may aid in the differentiation of patients at risk for recurrent venous thrombosis (22). Considering that DVT and PE represent two expressions of a similar clinical pathological process, a similar prothrombotic tendency might be expected in PE patients with residual PE. In the present study, however, no correlation was found for the presence of residual thrombotic obstruction and the occurrence of recurrent VTE. It should be noted that given the low number of recurrent events during follow-up and the small proportion of residual PE, this study may have been underpowered to detect this correlation. However, the fact that residual PE was present in only 7 patients and none of these patients developed recurrent VTE, does not indicate that implementing baseline CTPA on a large scale may be useful to identify a subgroup of patients at high risk of recurrences. The absence of patients who developed CTEPH during follow-up, does not allow us to draw conclusions on the potential relation between residual PE and CTEPH.

The findings of this study are strengthened by its multi-center and prospective design. Furthermore, a pre-specified protocol was used to systematically identify residual thrombotic obstruction after a consistent duration of follow-up.

A limitation of this study includes the fact that we studied a relative healthy population of PE patients. Compared to previous studies on this topic, our patients are relatively young with low prevalence of comorbidities. This may be explained by the fact the fact patients were only eligible for this study if they survived the first 6 months following PE and were healthy enough to undergo baseline CTPA. This is a potential source of selection bias that may limit the extrapolation of our findings. Also, the incidences of recurrent VTE (13%) and mortality (6%) during follow-up were lower

than reported in previous studies assessing the outcome of PE patients (23). The relative large number of patients continuing anticoagulant therapy six months after diagnosis might have contributed to the observed low incidence of recurrent VTE. Although being the largest study in assessing residual thrombotic obstruction with CTPA up to date, the moderate sample size and limited event rate during follow-up do not allow us to draw definite conclusions on the prognostic value of residual thrombotic obstruction.

In conclusion, this study demonstrates that complete thrombus clot resolution assessed with CTPA following six months of treatment for acute PE, occurs in 95% of the patients. Baseline CTPA imaging may therefore be of limited value to improve the diagnostic work-up of patients with suspected recurrent PE. Together with the absence of a predictive value for recurrent VTE and the costs and potential harms associated with CTPA, our data do not support implementation of baseline CTPA imaging in clinical practice following treatment of acute PE.

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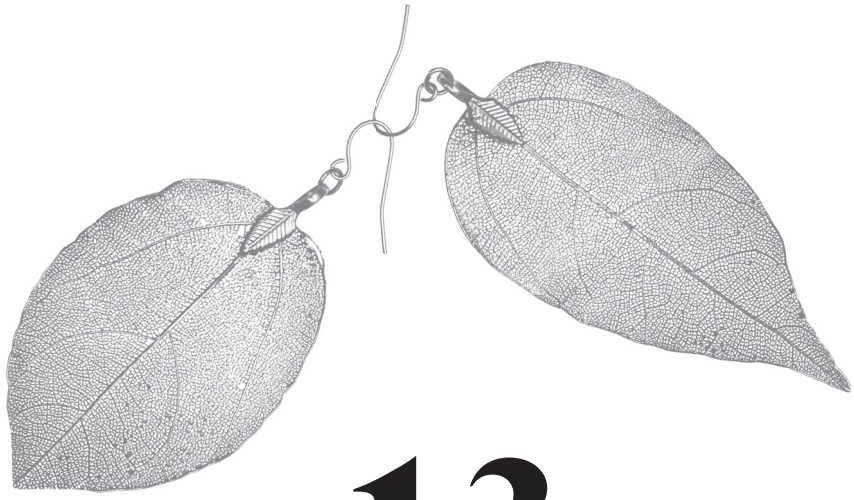

CHAPTER 13

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

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Abstract

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

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

Results*:* A delayed presentation (presentation > 7 days) was present in 754 (19%) of the patients. The failure rate of an unlikely clinical probability and normal D-dimer test was 0.5% (95% CI 0.01-2.7%) for patients with and 0.5% (95% CI 0.2-1.2%) for those without diagnostic delay. D-dimer testing yielded a sensitivity of 99% (95% CI 96-99%) and 98% (95% CI 97-99%) in these groups respectively. PE patients with diagnostic delay more frequently had centrally located PE (41% vs 26%, $p < 0.001$). The cumulative rates of recurrent VTE (4.6% vs 2.7%, $p=0.14$) and mortality (7.6% vs 6.6%, $p=0.31$) were not different for patients with and without delayed presentation.

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

Introduction

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

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

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

Methods

Study population

We analysed the combined data of two large prospective outcome trials that studied the diagnostic management of patients with suspected PE. The methods of both studies have been described in detail elsewhere (6;7). In short, the first study was a prospective management study including 3306 consecutive hemodynamically stable patients in 12

medical centers, evaluating a diagnostic algorithm consisting of the Wells rule, D-dimer testing, and computerized tomography pulmonary angiogram (CTPA) (7). The second study included 807 consecutive in- and outpatients in 7 hospitals to evaluate 4 different CDRs in the diagnostic management of suspected PE (6). For the purpose of the present analysis, we only evaluated the data on the performance of the Wells rule, which was uniformly calculated in all 807 patients in the original study. Both studies were approved by the ethical review boards of all participating hospitals and informed consent was obtained from all included patients.

Diagnostic work-up and management

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

Outcome

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

Statistical analysis

The cohort was stratified in two groups: 1) those without a delayed presentation, defined as presentation within 7 days from the onset symptoms, and 2) those with diagnostic delay, defined as presentation > 7 days from the onset of symptoms (10;11). Differences in patient characteristics between these strata were tested for statistical significance with the use of the Chi-square-test or the Fisher's exact test for categorical data and the student-t test or Mann Whitney test for continuous variables. P-values < 0.05 were considered to indicate statistically significance. Univariate and multivariate regression analyses were performed to identify factors associated with a delayed presentation. Any variable achieving a P-value of less than 0.05 was included in an unconditional multivariate regression model.

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

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

Results

Patient characteristics

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

Table 1. Baseline characteristics.

	Complaints ≤ 7 days (n=3290)	**Complaints > 7 days (n=754)**	**P-value**
Age (mean ± SD)	52 ± 18	56 ± 18	< 0.001
Male (n, %)	1375 (41.9)	315 (42.0)	0.943
Inpatients (n, %)	622 (18.9)	132 (17.5)	0.372
Duration of complaints, days (median, IQR)	1 (1-3)	14 (14-30)	NA
VTE Risk factors:			
Immobilization or surgery (n, %)	691 (21.0)	111 (14.7)	0.001
Paralysis, pareses or recent leg plaster (n, %)	83 (2.5)	6 (0.8)	0.004
Previous VTE (n, %)	396 (12.0)	108 (14.3)	0.086
Active Malignancy (n, %)	397 (12.1)	84 (11.1)	0.479
Estrogen use, women (n, %)	453 (13.8)	76 (10.1)	0.007
Comorbidities:			
COPD (n, %)	303 (9.2)	105 (13.9)	< 0.001
Heart failure (n, %)	216 (6.6)	66 (8.8)	0.035
D-dimer[a] (all patients; median, IQR)	750 (321-1873)	900 (400-2285)	0.007
D-dimer[a] (if confirmed PE; median, IQR)	2651 (1460-000)	3339 (1802-183)	0.059

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

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

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

Performance of the diagnostic algorithm

The proportion of patients in whom PE was excluded based on a Wells score ≤ 4 combined with a normal D-dimer test result (≤ 500 ng/mL) was similar in patients with and without delayed presentation (31% vs 28%, p=0.13). The duration of symptoms was not found to correlate with a false negative D-dimer test result: OR: 1.00 per day of delay (95% CI 0.978-1.03; p=0.91). The flow of the patients from the original studies, to their inclusion in the present analysis, is depicted in Figure 1.

Of the 1184 patients with an unlikely Wells score and a normal D-dimer test result, the failure rate was 0.5% (95% CI 0.2%-1.2%) in the group without a delayed presentation versus 0.5% (95% CI 0.01%-2.7%) in the group with delayed presentation (p = 0.98). Similar failure rates were observed when extending the definition of delay in presentation to 10 days (failure rate 0.5%; 95% CI 0.01-2.9%) or 14 days (failure rate 0.58%; 95% CI 0.01-3.3%).

In 3538 of 4044 patients a D-dimer test was performed. The AUC of the D-dimer in the group with delay in presentation was 0.86 (95% CI 0.83-0.89), this was not different from the AUC in the subgroup without diagnostic delay (0.85, 95% CI 0.83-0.86; p=0.52) (Figure 2).

The sensitivity of the D-dimer test in patients in the group without delay was 99% (95% CI 96-99%) at a specificity of 38% (95% CI 34-42%), whereas the sensitivity of the D-dimer in the group without delays in diagnosis was 98% (95% CI 97-99%) at a specificity of 44% (95% CI 42-47). When assessing a 10-day or 14-day cut-off for delayed presentation, similar D-dimer test characteristics were observed (Table 2). The sensitivity and specificity of a low clinical probability combined with delay.

Figure 1. Flowchart of the patients included in the analysis.

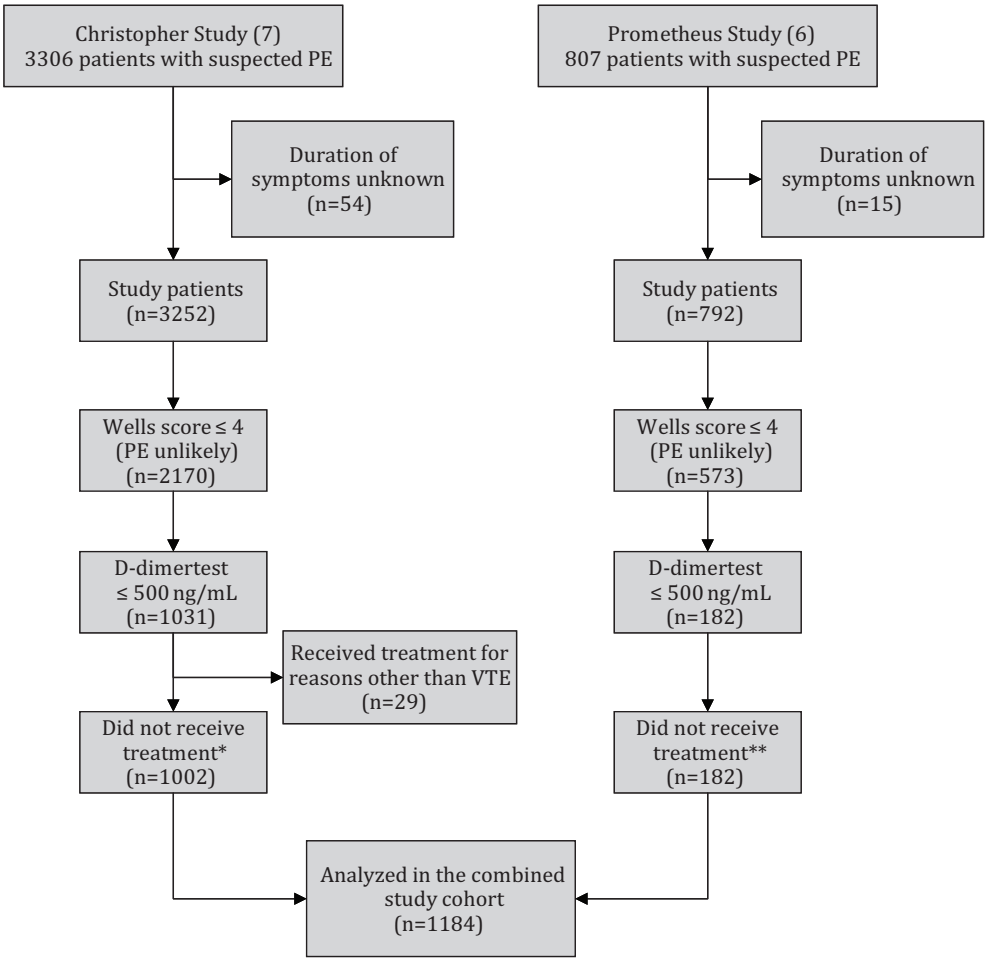
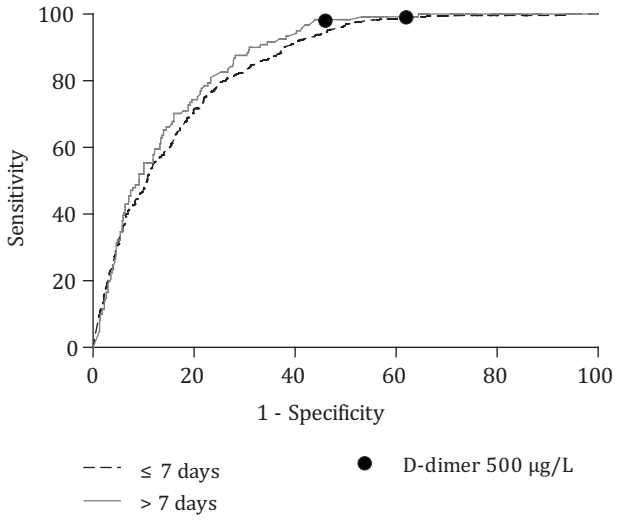


Figure legend: PE, pulmonary embolism; VTE, venous thromboembolism
Treatment refers to treatment with anticoagulant drugs
* In 25 patients, CT was performed although not indicated
** In 18 patients, CT was performed although not indicated

Figure 2. Receiver operating characteristic curves illustrating the diagnostic performance of the D-dimer of patients with ≤ 7 days and with > 7 days complaints. The areas under the curve were 0.85 (95% confidence interval (CI) 0.83-0.86) and 0.86 (95% CI 0.83-0.89) respectively.



Clinical outcome of patients who survived acute PE

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

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

Table 2. Diagnostic test characteristics.

	Complaints ≤ 7 days % (95% CI)	Complaints > 7 days % (95% CI)	Complaints < 10 days % (95% CI)	Complaints ≥ 10 days % (95% CI)	Complaints < 14 days % (95% CI)	Complaints ≥ 14 days % (95% CI)
Clinical probability						
Unlikely (wells score ≤ 4)	67 (65-69)	71 (68-74)	67 (66-69)	71 (67-74)	67 (65-69)	72 (69-76)
Likely (wells score > 4)	33 (31-35)	29 (26-32)	33 (31-34)	29 (26-33)	33 (31-35)	28 (24-32)
Test characteristics D-dimer						
Sensitivity	98 (97-99)	99 (96-99)	98 (97-99)	99 (95-100)	98 (97-99)	99 (94-100)
Specificity	44 (42-47)	38 (34-42)	44 (42-46)	39 (35-43)	44 (42-46)	41 (36-46)
Negative predictive value	99 (98-100)	100 (97-100)	99 (98-100)	100 (97-100)	99 (98-100)	100 (97-100)
Positive predictive value	29 (27-31)	27 (23-31)	29 (27-31)	27 (23-31)	28 (27-31)	27 (23-32)
Failure rate[a]	0.51 (0.17-1.2)	0.49 (0.01-2.7)	0.50 (0.16-1.2)	0.52 (0.01-2.9)	0.49 (0.16-.1)	0.60 (0.01-3.3)

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

Discussion

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

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

Since it has been proposed that the age of a clot, as reflected by the duration of symptoms, could inversely affect the performance of D-dimer testing, it has been doubted whether this test is still valid in patients with a delayed presentation (13). In a case-control study including 47 VTE patients with a false negative D-dimer result and 100 controls with a true-positive test result, the presence of symptoms more than 10 days was found to be a predictor for a false-negative D-dimer (OR: 3.2; 95% CI 1.4-7.4) (5). In a small series of 29 VTE patients, D-dimer testing yielded a false-negative result in two patients, both with symptoms for at least 30 days (14). Notably, both cases were classified as having a likely clinical probability.

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

used, which are known to be of superior sensitivity compared to semi-quantitative latex agglutination and whole-blood agglutination assays (15).

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

This study also addressed the outcome of PE patients who were diagnosed after a delay. An important and novel finding is that diagnostic delay was associated with a more prevalent central PE location. Theoretically this appears plausible, given that the presence of PE in the absence of anticoagulant therapy allows the clot to extend. This observation may have prognostic implications for PE patients with a delayed presentation, given that central emboli have been associated with a worse clinical outcome. Notably, Vedovati *et al.* reported a negative association between a central pulmonary embolism and adverse clinical outcome, only in hemodynamically stable patients (16). Furthermore, we found a higher proportion of patients with unprovoked PE among those diagnosed after delay, and unprovoked PE is known to be associated with a two-fold risk of recurrent VTE on the long-term, compared to those with provoked PE (17). Yet, in the present study, no significant differences in short-term clinical outcome were seen between PE patients with and without delay in presentation, although a trend towards a higher recurrent VTE risk was noted for those with diagnostic delay. We admit that this observation harbors the risk of underestimation due, to the low number of observed recurrent events. A previous study by Jimenéz et al. was also unable to detect an association between a delay in diagnosis and an increased risk of death or VTE recurrence among patients who survived an episode of PE (11).

The conclusions of this study are strengthened by its large sample of patients, and its multicenter design, which enhance the extrapolation of our findings. Limitations include the fact that these analyses were performed in a post-hoc fashion. Still, all patients were managed according to a consistent diagnostic protocol and all data were collected prospectively. Second, the variable duration of symptoms may be prone to recall bias. For those who present after a time delay, it may be difficult to recall the

exact day of onset of symptoms. By stratifying patients in those presenting within one week and those after one week, we believe that this recall bias is minimized. Third, the sample of patients with PE may have been too small and had a too limited follow-up, to draw definite conclusions on the impact of a delayed presentation on their clinical outcome. Furthermore, the fact that patients had to be hemodynamically stable to enter the original studies, forms a potential source of referral bias. It cannot be excluded that delay in presentaion has an impact on the hemodynamic outcome, and our results can thus only be extrapolated to hemodynamically stable patients who survived acute PE. Future studies, also including hemodynamically compromised patients, are needed to clarify this issue. Lastly, the D-dimer test characteristics do not reflect our entire study population since D-dimer test results were missing in 13% of the patients.

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

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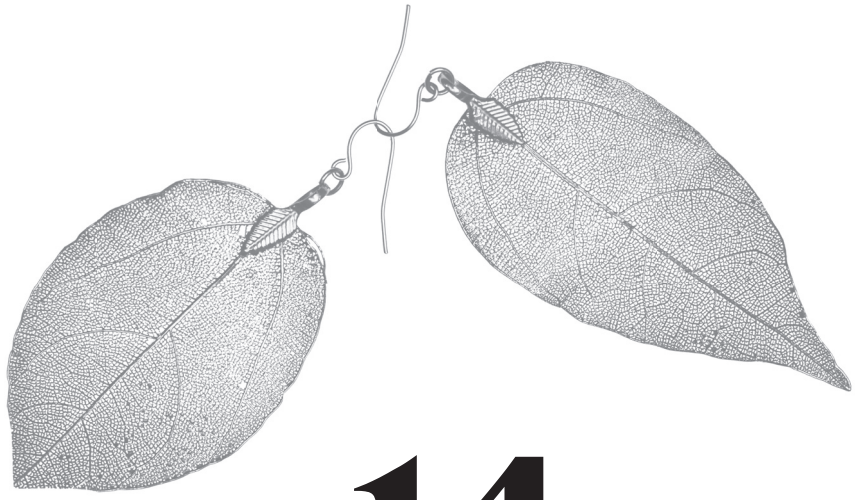

CHAPTER 14

Risk profile and clinical outcome of symptomatic isolated subsegmental acute pulmonary embolism

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Abstract

Aims: Improved imaging techniques have led to increased detection of subsegmental pulmonary embolism (SSPE). However, its clinical significance is often doubted by clinicians and remains to be determined. This study aimed to investigate whether SSPE forms a distinct subset of thromboembolic disease compared to more proximally located pulmonary embolism (PE).

Methods: We analyzed the combined data of two prospective outcome studies evaluating 3728 consecutive patients with clinically suspected PE. SSPE patients were contrasted to patients with more proximal PE and to patients in who suspected PE was ruled out, as regards the prevalence of thromboembolic risk factors and the 3-month risks of recurrent venous thromboembolism (VTE), bleeding complications, and mortality.

Results*:* PE was confirmed in 748 patients, of whom 116 (16%) had SSPE; in 2980 patients PE was ruled out. No differences were seen in the prevalence of VTE risk factors, the 3-month cumulative risk of recurrent VTE (3.6% vs 2.5%; p=0.42) and mortality (10.7% vs 6.5%; p=0.17) between patients with SSPE and those with segmental or more proximal PE. When compared to patients without PE, age > 60 years, recent surgery, estrogen use, and male gender were found to be independent predictors for SSPE, and patients with SSPE were at increased risk of VTE during follow-up (HR: 3.8; 95% CI 1.3-11.1).

Conclusion: In contrast to common belief that SSPE represents a clinically less severe subset of PE, this study indicates that patients with SSPE mimic those with more proximally located PE as regards their risk profile and clinical outcome.

Introduction

The introduction of multi-detector computed tomographic pulmonary angiography (CTPA) has considerably advanced the radiological visualization of pulmonary embolism (PE) and its diagnostic accuracy has been demonstrated to be robust enough to serve as single imaging test in the diagnostic work-up of patients with suspected PE (1). Compared to previously used imaging techniques to detect PE, multi-detector CTPA allows better visualization of peripheral pulmonary arteries (2). As a consequence of the widespread use of these scanners as first-line imaging tools to establish or rule out acute PE, small peripheral emboli limited to the subsegmental pulmonary arteries are increasingly being detected. The proportion of this so called isolated subsegmental pulmonary embolism (SSPE) detected on CTPA varies between 4% and 27% (3-5). With this increasing incidence of SSPE diagnoses that would probably have gone undetected and thus left untreated with former imaging techniques, physicians started to question the clinical relevance of these findings (6). The prognostic implications of SSPE are however uncertain, since in few studies the clinical outcome of these patients has been investigated. It remains therefore unclear whether a diagnosis of SSPE deserves the same therapeutic approach as PE located in segmental or more proximal pulmonary arteries (7). Recently, some evidence suggested that patients with SSPE may have a favourable clinical outcome, even without prescribing anticoagulant therapy (8;9).

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

Methods

Study-population

We used the combined data of two prospective outcome studies in which consecutive patients with clinically suspected PE had been included. The first study was a large, prospective management study including 3306 consecutive patients (10), with an aim to evaluate a diagnostic algorithm consisting of the Wells rule (11), D-dimer testing,

and CTPA. Exclusion criteria for this study were: treatment with therapeutic doses of unfractionated or low-molecular-weight heparin (LMHW) for > 24 h; life expectancy < 3 months; pregnancy; geographic inaccessibility for follow-up; age < 18 years; allergy to IV contrast agents; or hemodynamic instability (defined as a systolic BP < 90 mm Hg or clinical signs and symptoms of shock). The institutional review boards of all participating hospitals approved the study protocol, and informed consent was obtained from all participants.

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

The second cohort included 463 consecutive patients with suspected PE, with an aim to identify predictors for the outcome of patients with PE (13). All patients provided written informed consent. Exclusion criteria for this study were: impossibility for follow-up, age < 18 years, pregnancy, allergy to IV contrast agents or haemodynamic instability at initial presentation. All patients with a likely clinical probability by the Wells rule (> 4 points total) and/or an abnormal D-dimer test (> 500 ng/mL) underwent multi-detector row CTPA during breath-hold inspiration. The presence of PE was defined as at least one filling defect in the pulmonary artery tree. The method of Qanadli et al. (14) was used to quantify the degree of pulmonary arterial obstruction, and the largest pulmonary artery involved was recorded. All patients in whom PE was confirmed were treated similarly to patients with PE in the first cohort.

Risk factors

We investigated the influence of the following thromboembolic risk factors that were recorded in both studies at baseline: age; sex; hospitalization status; immobilization for at least 3 days within the past four weeks; paralysis, pareses or leg plaster within the past month; major surgery within the past month; a history of VTE; estrogen use; heart

failure (defined as New York Heart Association functional class II-IV for which specific therapy was administered); chronic obstructive pulmonary disease (COPD); and active malignancy, defined as any malignancy with ongoing treatment or treatment within the past 6 months, or malignancies in palliative stages.

Outcome

For this comparative analysis, the cohort was stratified into three groups: 1) patients with isolated SSPE, 2) patients with segmental or more proximal PE and 3) patients in whom clinically suspected PE was ruled out. These 3 groups were compared for the incidence of symptomatic (recurrent) VTE, the incidence of major bleeding complications, and the incidence of all-cause mortality during 3 months of follow-up. VTE during follow-up was defined as an objective diagnosis of recurrent PE or deep vein thrombosis (DVT), or death in which PE could not be ruled out as a contributing cause. The objective criterion for the diagnosis of recurrent PE was a new intraluminal filling defect on CTPA or pulmonary angiography; a new high probability perfusion defect on ventilation-perfusion scan; a new non-diagnostic lung scan accompanied by documentation of DVT by ultrasonography or venography; or confirmation of a new PE at autopsy. A diagnosis of (recurrent) DVT had to be confirmed by compression ultrasonography or contrast venography (15). Major bleeding was defined as fatal bleeding; symptomatic bleeding in a critical area or organ; clinically overt bleeding causing a fall in hemoglobin level of at least 20 g L^{-1} (1,24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells (16). An independent adjudication committee reviewed and classified all suspected outcome events. Mortality was classified as caused by PE in case of confirmation at autopsy, in case of an objective test demonstrating PE prior to death, or if PE could not be confidently ruled out as the cause of death.

Statistical analysis

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

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

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

Results

Patient characteristics

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

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

Thromboembolic risk factors

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

4.20), estrogen use (OR 2.5; 1.34-4.81) and male gender (OR 2.1; 1.38-3.32) remained significantly associated with SSPE (Table 2).

Table 1. Baseline Characteristics.

	SSPE (n=116)	Proximal PE* (n=632)	PE ruled out (n=2955)	P value SSPE vs proximal PE	P value SSPE vs PE ruled out
Age, mean (SD)	56 ± 17	57 ± 18	52 ± 18	0.46	0.02
Age > 60, n (%)	50 (43.1)	301 (47.6)	995 (33.7)	0.37	0.04
Male, n (%)	64 (55.2)	309 (48.9)	1201 (40.1)	0.23	0.002
Outpatients, n (%)	87 (75)	496 (78.5)	2411 (81.6)	0.41	0.07
Immobilization, n (%)	20 (17.2)	108 (17.1)	269 (9.0)	0.97	0.003
Paralysis, pareses or recent leg plaster, n (%)	5 (4.3)	37 (5.9)	61 (2.1)	0.51	0.10
Previous VTE, n (%)	17 (14.7)	128 (20.3)	389 (13.0)	0.16	0.64
Recent surgery, n (%)	15 (12.9)	72 (11.4)	155 (5.2)	0.64	<0.001
Active malignancy, n (%)	21 (18.1)	113 (17.9)	341 (11.4)	0.95	0.03
Estrogen use, n (%)	15 (30.0)	93 (29.2)	359 (12.0)	0.91	<0.001
Duration of complaints, days, median (range)	2 (0 - 90)	3 (0 - 90)	2 (0 – 120)	NA	NA
Suspected DVT, n (%)	10 (8.6)	81 (12.8)	86 (2.9)	0.08	0.001
Heart rate > 100 beats per minute, n (%)	28 (24.1)	209 (33.1)	607 (20.3)	0.005	0.61
Hemoptysis, n (%)	10 (8.6)	41 (6.5)	119 (4.0)	0.65	0.03
Wells score (11):					
– Unlikely (>4), n (%)	58 (50)	244 (38.6)	2169 (73.4)	0.02	<0.001
– Likely (≤ 4), n (%)	58 (50)	388 (61.4)	800 (26.9)		
COPD, n (%)	11 (9.5)	55 (8.7)	334 (11.2)	0.78	0.56
Heart failure, n (%)	10 (8.6)	30 (4.7)	232 (7.7)	0.09	0.75

COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; N, number; PE, pulmonary embolism; SSPE, subsegmental pulmonary embolism; SD, standard deviation; VTE, venous thrombo-embolism.
*Defined as pulmonary embolism localized in a segmental or central pulmonary artery.

Table 2. Risk Factors for SSPE on multivariate analysis.

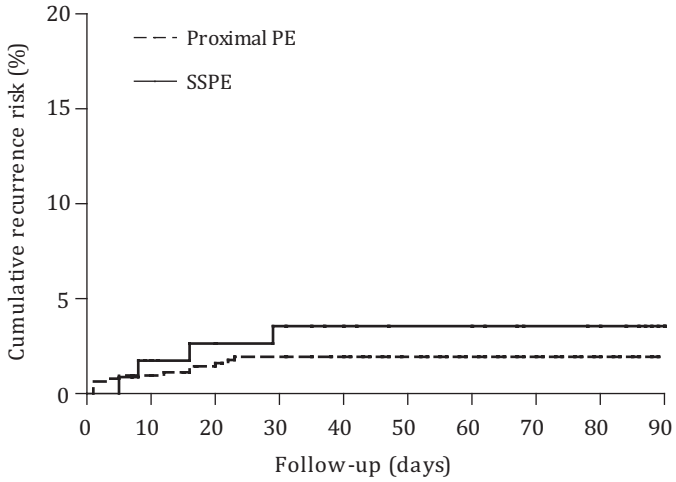
	SSPE vs PE excluded OR (95% CI)	SSPE vs proximal PE OR (95% CI)
Age > 60 years	1.6 (1.1-2.4)*	0.9 (0.6-1.4)
Male sex	2.1 (1.4-3.2)*	0.8 (0.5-1.2)
Immobilization	1.6 (0.9-2.7)	0.9 (0.5 -1.6)
Previous VTE	1.4 (0.8-2.4)	0.7 (0.4-1.3)
Recent Surgery	2.3 (1.2-4.2)*	1.1 (0.6-2.0)
Active Malignancy	1.5 (0.9-2.4)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

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

Risk of VTE during follow-up

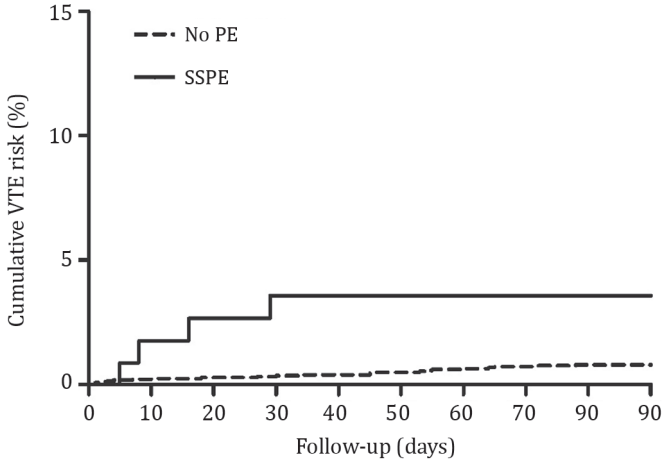
Follow-up was completed in 747 (99.9%) of the patients diagnosed with PE at baseline, and in 2974 (99.8%) of the patients in whom PE was ruled out. During 3 months of follow-up, symptomatic recurrent VTE occurred in 4 patients with SSPE (3 patients developed PE, of which 1 case was fatal, and one patient DVT) and in 14 patients with segmental or more proximal PE (10 patients developed PE and 4 patients DVT; in 9 patients, PE was adjudicated either as a direct cause of death or PE could not confidently ruled out as cause of death). The respective cumulative risks for recurrent VTE were 3.6% for subsegmental PE and 2.5% for more proximal PE, respectively (Figure 1; p=0.42 from the log-rank test). The HR for recurrent VTE was not significantly different for SSPE patients versus patients with more proximal PE (HR: 1.6; 95% CI 0.5-4.8). Adjustment for age, gender, malignant disease and history of VTE did not materially influence this HR.

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



In the group of patients in whom PE was ruled out at baseline, 25 patients (0.8%) developed VTE during follow-up (10 developed DVT, 7 developed PE, and in 8 patients PE was adjudicated either as a direct cause of death or PE could not confidently ruled out as cause of death). The cumulative risk for VTE in this group was 1.1% (Figure 2). The unadjusted HR for the risk of VTE during follow-up for patients with SSPE versus patients with no PE was 4.3 (95% CI 1.5-12.3). After adjustment for age, gender, malignant disease and history of VTE, the HR remained statistically significant: 3.8 (95% CI 1.3-11.1). Malignant disease was independently associated with the occurrence of VTE during follow-up (HR: 3.7; 95% CI 1.6-8.4).

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



Bleeding complications in patients with PE

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

Risk of mortality

Twelve (10.3%) patients diagnosed with SSPE and 40 (6.3%) patients with segmental or central PE died during follow-up. The respective cumulative mortality risks were 10.7% and 6.5% (adjusted HR: 1.5, 95% CI 0.8-2.8; p=0.17 from the log-rank test). In the patients in whom PE was excluded, 156 (5.2%) patients died during follow-up. Their cumulative mortality risk (5.4%) was significantly lower compared to patients with SSPE (p=0.01 from the log-rank test). Multivariate analysis identified malignancy (HR 5.6; 95% CI 4.2-7.6), male gender (HR 1.5; 95% CI 1.1-2.1), age (HR 1.04 per year; 95% CI 1.03-1.05), COPD (HR 1.5; 95% CI 1.1-2.2) and heart failure (HR 1.9; 95%: 1.3-2.7) as independent predictors for mortality. After adjustment for these covariates,

the HR for mortality was 1.4 (95% CI 0.8-2.6) for patients with SSPE compared to those in whom PE was ruled out.

Discussion

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

These findings challenge the hypothesis that a diagnosis of SSPE might be clinically insignificant. Evidence for this latter hypothesis was derived from a recent systematic review assessing the rates of SSPE diagnoses on multi-detector and single-detector CTPA examinations (8). Although the proportion of detected SSPE increased from 4.7% to 9.4% for single- compared to multi-detector CTPA, the rate of recurrent VTE in patients in whom PE was ruled out and who were thus left untreated, did not differ between the groups (0.9 versus 1.1%). Based on these results, the authors concluded that the additional SSPE cases detected by multi-detector CTPA may be clinically irrelevant. This however should be regarded as indirect evidence given that the outcome of patients with SSPE was not directly assessed. More indirect evidence supporting the concept that the increased proportion of SSPE detected by CTPA might be clinically insignificant comes from a large population based study (17). Based on discharge level data, Wiener et al. noticed an increased incidence of PE diagnosis following the introduction of CTPA, whilst the mortality risk remained unchanged and the case-fatality rate decreased. The authors referred to these findings as 'evidence of overdiagnosis', defined as the detection of an abnormality, specifically small pulmonary emboli, that will never cause symptoms or death. It should be noted, however, that all patients included in our study had clinical symptoms, which led to the suspicion of PE. Again this study does not provide us with direct evidence that the additional PE cases detected by CTPA are harmless. Furthermore, the study does not inform us

on the risk of recurrent VTE. Although the decreasing case-fatality rate does suggest that isolated, small pulmonary emboli are less likely to be a direct cause of death, its presence may still reflect a patients' prothrombotic state and therefore be associated with an increased risk of thrombus extension or VTE recurrence in the future.

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

Supporting evidence for our findings comes from the recently published Einstein PE study, in which the efficacy and safety of the novel oral anticoagulant rivaroxaban was compared to VKA for the treatment of PE (18). From that study, separate analyses were performed with respect to the anatomic location of PE. In both treatment arms, similar rates of recurrent VTE were observed for patients with anatomically limited PE (defined as ≤ 25% of vasculature of a single lobe) versus those with extensive PE (defined as multiple lobes and > 25% of entire pulmonary vasculature); respectively 1.6% versus 1.7% in the rivaroxaban group and 1.3% versus 1.4% in the standard-treatment group. Although the definition used for anatomically limited PE may also include segmental PE, one would have expected a lower rate of recurrent VTE in these patients in case SSPE would have had no clinical significance. In line with our findings, these data suggest that the risk of recurrent VTE is not influenced by the anatomic location of PE. It seems more likely that persistent risk factors for recurrent VTE are better risk predictors than the location of the PE. A recent population-based study demonstrated that active malignancy is by far the strongest predictor for recurrent VTE (19). Indeed, in the present study, active malignancy was independently associated with the occurrence of VTE during follow-up.

A potential limitation of our study is that an independent radiologist did not confirm the diagnosis of SSPE in the majority of cases. It has recently been demonstrated that significant differences in the interpretation of SSPE among radiologists could occur (20). Although all CTPAs were assessed according to a pre-specified protocol, it cannot be ruled out that some of our patients were misclassified as having SSPE, this however reflects the diagnostic process of SSPE in daily clinical practice. Second, our definition used for SSPE included both single and multiple SSPE. We were therefore unable to investigate whether the number of emboli and amount of branches affected,

influences the prognosis of SSPE patients. Third, the absolute incidences of recurrent VTE, bleeding complications and mortality were small. Although we did not detect a difference in outcome between SSPE patients and those with proximal PE, our study might be underpowered to detect small differences. Our findings should thus be considered hypothesis generating and need to be confirmed in larger studies. Fourth, the presence of DVT at baseline was not systematically assessed; this has recently been identified as an independent predictor for mortality in patients with acute PE (21). However, the proportions of patients who had signs and symptoms suggestive of DVT did not differ significantly between patients with SSPE and those with more proximal PE. Finally, it should be noted that this study was not designed to answer questions on the benefit of anticoagulant treatment in patients with SSPE; all patients included in this analysis were treated. There is a need for prospective studies assessing the outcome and management of SSPE, before considering distinct management guidelines for this specific group of PE patients. Indeed, a prospective management study assessing the safety of withholding anticoagulation in patients with isolated symptomatic SSPE, without DVT on bilateral lower extremity compression ultrasonography, is currently being conducted (NCT01455818).

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

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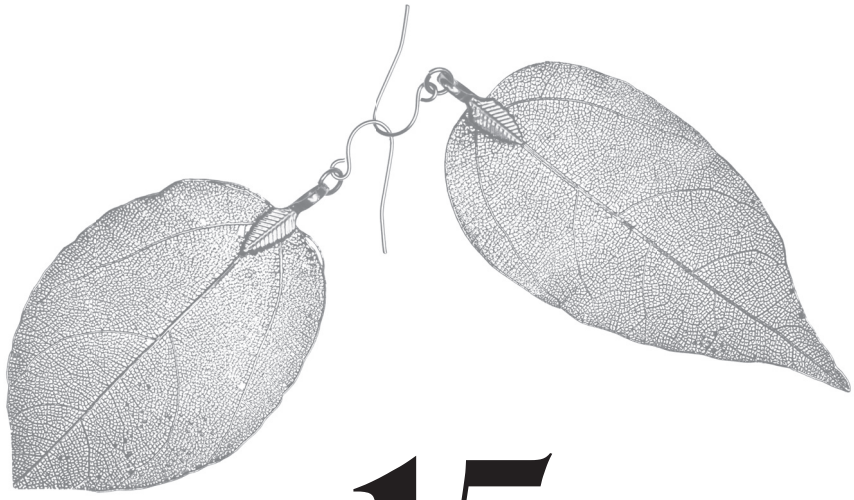

CHAPTER 15

Quality of life after pulmonary embolism as assessed with SF-36 and PEmb-QoL

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Abstract

Introduction: Although quality of life (QoL) is increasingly recognized as an important indicator of the course of a disease, it has rarely been addressed in studies evaluating the outcome of patients with pulmonary embolism (PE). The main objective of this study was to evaluate QoL in the long-term clinical course of patients with acute PE, using the Short Form-36 (SF-36) and the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaires, in comparison to general population norms, and to patients with other cardiopulmonary diseases.

Methods: SF-36 and PEmb-QoL were distributed among 150 consecutive out-patients with a history of objectively confirmed acute PE. SF-36 scores were compared to those of patients with chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF),a history of acute myocardial infarction (AMI) the previous year and a reference group of healthy Dutch individuals. PEmb-QoL, SF-36, and correlations between the PEmb-QoL and clinical patient characteristics were examined.

Results: A total of 109 patients with PE, of whom 9 had recurrent PE, completed the questionnaires, after a median of 25 months, range 5-46 months from time of diagnosis. QoL as assessed with SF-36 was superior in patients with PE compared to patients with COPD and CHF, comparable with patients with AMI the previous year, and worse compared to the general Dutch population. Age, obesity, cardiopulmonary comorbidity, centrally located PE did not correlate with QoL in patients with PE.

Conclusion: Our study demonstrates that this cohort of long-term survivors of acute PE had an impaired QoL compared to population norms. The QoL of PE patients appeared, however, to be comparable with patients with a history of AMI the previous year, and better than patients with COPD and CHF.

Introduction

Studies have demonstrated that quality of life (QoL), defined as patients' reported impact of disease and treatment on his/her physical, psychological and social functioning and wellbeing, is associated with clinical endpoints and is increasingly considered an important outcome measure in clinical research (1-3). QoL can be assessed by generic QoL instruments, e.g. the Short Form 36 (SF-36), scoring standardized responses to standardized questions. These generic instruments are designed to sample the complete spectrum of function, disability, and distress that is relevant to QoL. In doing so, generic instruments are applicable to a wide variety of populations, irrespective of the illness or condition of the patients, and allow comparison between different patient groups. Qol can also be assessed by disease-specific questionnaires, which assess disease specific elements of quality of life and have been shown to be sensitive in detecting and quantifying changes in QoL that might be relevant to patients with a specific disease (2-5). Although it is known that both the acute event itself as well as the long-term clinical course of acute pulmonary embolism (PE) is frequently complicated by serious adverse events, such as recurrent venous thromboembolism (VTE) or chronic thromboembolic pulmonary hypertension (CTEPH) (6), there is a lack of knowledge on how this translates into QoL, as perceived by PE patients.

Recently, a disease-specific instrument for assessing QoL after PE, called the Pulmonary Embolism Quality of Life (PEmb-QoL), has been developed and validated. The PEmb-Qol assesses pulmonary signs and symptoms in addition to limitations in daily activities, emotional and social complaints and anxiety (7;8). Given that recent data indicates that PE is frequently associated with serious long-term clinical consequences, it would be important to know to what extent the QoL of patients after acute PE compares to the QoL of patients with *chronic* (cardio-) pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) and to patients with *acute* cardiopulmonary disease such as a history of acute myocardial infarction (AMI) the previous year (9). Yet, such a comparison has not been performed. The primary objective of this study was to compare QoL as expressed by SF-36 scores in patients with acute PE with general population norms, and to patients with COPD, CHF and in the first year after AMI. The secondary objectives were to evaluate QoL in the short-term and long-term clinical course of patients with acute PE, as expressed the PEmb-QoL, and to investigate whether patients' characteristics impacted their QoL.

Methods

Participant, procedure and description of the questionnaires

Dutch PEmb-QoL and SF-36 questionnaires were distributed by post between August 2011 and January 2012, among a consecutive sample of 150 patients with first or recurrent PE between October 2008 and December 2011 in the Academic Medical Center, Amsterdam, Maastricht University Medical Center, and Leiden University Medical Center, the Netherlands. All patients with objectively proven PE by a CT-scan or high probability ventilation perfusion scintigraphy, who were hemodynamically stable and aged above 18 years, were eligible. The only exclusion criterion was impossibility to follow-up. All surviving patients had been contacted by telephone every 6 months from the time of diagnosis of PE to assess the PE recurrence and CTEPH rate, as part of an ongoing observational, prospective follow-up study, which aims to evaluate the natural clinical course of patients with PE.

Patients were treated with vitamin k antagonists, with a target International Normalized Ratio (INR) between 2.0 and 3.0, for at least 6 months (10). Low molecular weight heparin (LMWH) was given until the INR was above the lower target range on 2 consecutive occasions, with a minimum of 5 days. Patients with active malignant disease were treated with LMWH during the first 6 months of anticoagulant treatment (11). Demographic data and additional relevant information were collected on a Case Record Form.

The SF-36 and PEmb-QoL and questionnaire were applied in Dutch and results of the questionnaires were entered manually into a database. Patients filled out the questionnaires at home and returned them by regular mail.

The SF-36 (generic questionnaire) (12) contains eight scales: physical functioning, social functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain and general health, scoring 0-100, with higher values indicating a better health status (12).

The PEmb-QoL (disease-specific instrument assessing QoL after PE) (8) includes six scales: frequency of complaints, activity of daily life (ADL) limitations, work-related problems, social limitations, intensity of complaints, and emotional complaints. Higher scores indicate worse outcome.

In case of missing data, we excluded that specific scale in total from further analyses. The residual scales, however, were interpreted.

General population and disease comparison groups

The SF-36 has been administered to a representative sample of the general Dutch population to validate the Dutch version of the SF-36 in the Netherlands (13). We compare QoL reflected in SF-36 scores in patients with PE with general population norms, and with QoL of patients with COPD, CHF and AMI within one year prior to enrolment (9;14).

For the disease comparison groups, published data of SF-36 outcomes of patients with advanced chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease stage III or IV) (14), severe chronic heart failure (CHF) (New York Heart Association class III or IV) (14), and with a history of AMI < 12 months prior to inclusion were used (9]. Patients with COPD and CHF were included in 6 hospitals in the Netherlands in 2008 and 2009 (14) and data of patients with AMI the previous year were assessed from the Medical Outcomes Study (MOS), a survey of 22,462 patients, between the ages of 18 and 97, seen in the practices of 523 physicians in the USA (9).

Diagnosis of thrombus localization and thrombus load on CT-scan

PE was classified in two levels of thrombus occlusion, i.e. central (including central, interlobar vessels) or peripheral (including lobar, segmental and subsegmental vessels) using a scoring system according to Qanadli et al (15). Briefly, this index is defined as the number of segmental artery branches that are blocked, corrected by a factor of one for partial blockage, or a factor of 2 for complete obstructive clots. Using this scoring system, 40 is the highest possible score (thrombus completely obstructing the pulmonary trunk), corresponding with a 100% obstruction index.

Outcome measures

The primary outcome measure of this analysis was SF-36 scores of the patients with PE were compared to Dutch population norms and with patients with other cardiopulmonary diseases: COPD, CHF and the first year after AMI. For this analysis, we excluded patients in our cohort with a history of COPD, CHF and a history of AMI one year prior to exclusion in order to compare these chronic cardio-pulmonary diseases with patients with PE only. Our secondary outcome was QoL, as measured by the PEmb-QoL, after both intermediate and long-term follow-up in patients with a history of acute PE. We arbitrarily denoted follow-up as intermediate if the time frame between the diagnosis of PE and filling out of the questionnaire was shorter than 15 months (which was the 25th

percentile in this cohort), and long-term when the time frame was longer. We analyzed the responses to the questionnaires first in the total cohort and second in two groups of participants, divided by the 25th quartile of the timespan between diagnosis of PE and filling out the questionnaire. In addition, we investigated the impact of the following a priori defined clinical determinants on the QoL in our patient population: age, body mass index (BMI), active malignancy, COPD, CHF, history of venous thromboembolism, smoking habits, time frame between diagnosis and inclusion, Qanadli score and centrally located PE. Active malignancy was defined as cancer with ongoing treatment, treatment within the last 6 months, or in a palliative stage.

Statistical analyses

Normally distributed variables are presented as mean and standard deviation (SD), non-normally distributed variables are expressed as medians with ranges.

The scores for the SF-36 dimensions in our patient sample were compared to the published means and SDs for each scale among the general population and the comparison disease subjects, using the standard deviate (z-score). To adjust for age differences between patients and control subjects, the population norms were weighed with the age distribution of our sample.

Because the time frame between PE and measuring QoL ranged between 5 and 46 months, partial bivariate correlations -controlling for the time between PE and filling out questionnaires- were calculated between factors potentially influencing the QoL such as BMI, COPD, CHF, history of VTE, recurrent PE and malignancy and the different scales of the questionnaires For non-normally distributed data, we used a spearman correlation test.

P-values < 0.05 were considered statistically significant. The calculations of the scores of the PEmb-Qol and SF-36 and all analyses were conducted using statistical software SPSS, version 19.0; (SPSS Inc; Chicago, IL).

Results

Patients

The questionnaires were distributed among 150 patients with a history of acute PE, of whom 109 (73%) completed the questionnaire after a median of 25 months, range 5-46 months. A quarter of the patients filled out the questionnaire within the first 15 months after diagnosis of PE. The clinical characteristics at baseline of the participants are depicted in Table 1. In the time between PE and the questionnaire, 6 patients experienced a recurrent VTE, of which all cases were PE, and 1 patient developed CTEPH.

Table 1. Baseline characteristics of patients with clinically pulmonary embolism.

Characteristics	Value N=109
Female, n (%)	56 (51)
Age in years, mean (SD)	60 (15)
COPD, n (%)	8 (7)
CHF, n (%)	3 (3)
AMI one year prior to enrollment	0 (0)
History of PE, n (%)	9 (8)
History of DVT, n (%)	10 (9)
Active malignancy, n (%)	21 (19)
Current smoker, n (%)	18 (17)
Centrally located PE, n (%)	16 (15)
Anticoagulant therapy > 6 months, n (%)	28 (26)
Anticoagulant therapy at time of questionnaire completion, n (%)	17 (16)
Qanadli score (0-40), median (range)	7 (0-29)
Time span in months between PE and study inclusions, median (IQR)	25 (15-31)

CHF congestive heart failure, COPD chronic obstructive pulmonary disease, DVT deep venous thrombosis; IQR interquartile range, N number, SD standard deviation, PE pulmonary embolism, VTE venous thromboembolism

SF-36

The number of patients was, per complete SF-36 scale: 105 for physical functioning, 102 for social functioning, 102 for physical role functioning, 100 for emotional role functioning, 105 for mental health, 103 for vitality, 102 for bodily pain and 99 for general health.

The results of physical role functioning, emotional role functioning, mental health, bodily pain, and general health did not differ between the intermediate and the long-term follow-up (data not shown). The results of the scales physical functioning, social functioning, vitality, however, were significantly higher in the group of patients who completed the questionnaire at least 15 months after PE (66 versus 48, 81 versus 67 and 64 versus 54, respectively, $p < 0.05$)

Results of the SF-36 in PE patients compared to the general population and disease comparison groups

After leaving out the patients with COPD, CHF or AMI the previous year in our cohort, 98 patients with PE only remained for this analysis. We compared patients with PE to the general Dutch population subjects (n=140), which were population-based groups of non-institutionalized individuals with a mean age of 59 years of age in the Netherlands (15). Patients with PE had markedly lower scores than the general population on the scales social functioning and role emotional and general health ($p < 0.001$) and on the role physical and vitality scale ($p < 0.05$). On the scales physical functioning, mental health and pain no differences were observed (p=0.40, p=0.96 and p=0.12 respectively) (Table 2 and Figure 1).

Compared to the disease comparison groups, patients with PE were younger than patients with CHF (n=80), but age did not differ in patients with COPD (n=105) and AMI the previous year (n=107) (Table 2). Patients with severe COPD or CHF scored significantly lower compared to patients with PE on all scales. However, scores were not significantly higher or lower than patients with the first year after AMI on most scales; patients with PE scored significantly higher on the vitality scale (p=0.015) and the scale bodily pain (p= 0.018) only (Table 2 and Figure 1).

PEmb-QOL

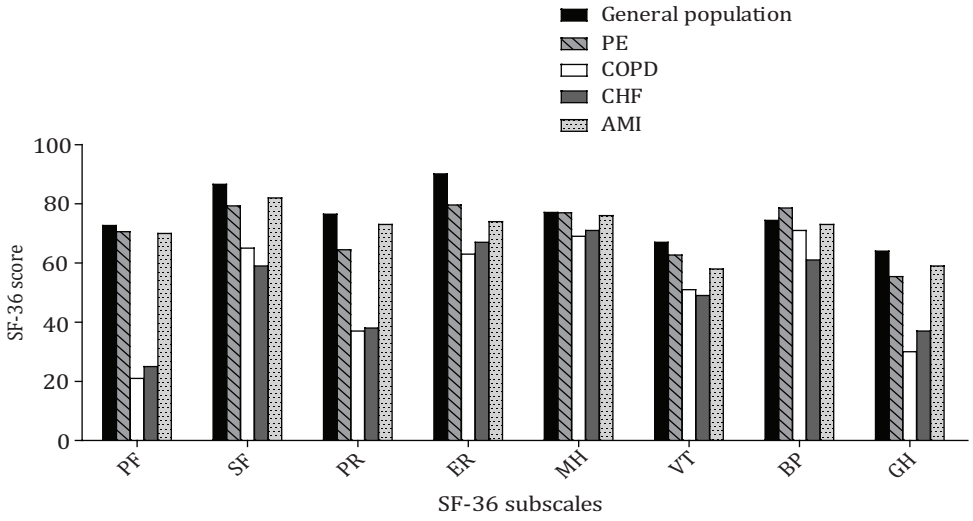
The numbers of patients per complete PEmb-QoL scales were: 102 for frequency of complaints, 103 for ADL limitations, 102 for work related problems, 108 for social limitations, 104 for intensity of complaints, 92 for emotional complaints. For all dimensions of the PEmb-QoL, a score of 1 point designates no complaints.

Table 2. Demographics and Mean Short Form 36 (SF-36) scores in patients with pulmonary embolism (PE) (leaving out the patients with PE and COPD or CHF), compared to the gender and age adjusted Dutch population norms, patients with severe to very severe Chronic Obstructive Pulmonary Disease (COPD),

	Total PE N=98	**Dutch population N=140**	**COPD N=105**	**Heart failure N=80**	**AMI N=107**
Female n (%)	50 (51)	91 (65)	40 (38)	26 (32.5)	33 (31)
Age mean (SD)	60.4 (15.0)	59 (range 55-64)	66.3 (9.2)	76.2 (8.3)	59.2 (11.4)
Care	secondary	N.A.	secondary	secondary	primary
Physical functioning	70.6	72.7	21.0	24.7	69.7
Mean (SD)	(32.4)	(24.4)	(21.1)	(23.0)	(26.1)
p-value*		0.40	<0.00001	<0.00001	0.78
Social functioning	79.3	86.6	65.0	58.6	81.6
Mean (SD)	(25.8)	(21.4)	(26.1)	(31.6)	(21.1)
p-value*		0.0008	<0.00001	<0.00001	0.39
Role physical	64.5	76.5	37.1	37.8	72.8
Mean (SD)	(45.1)	(38.1)	(42.8)	(43.0)	((25.2)
p-value*		0.002	<0.00001	<0.00001	0.36
Role emotional	79.6	90.1	62.9	67.1	73.5
Mean (SD)	(38.6)	(24.5)	(44.9)	(42.9)	(38.0)
p-value*		<0.00001	<0.00001	0.004	0.10
Mental	77 .0	77.1	68.6	71.3	75.8
Mean (SD)	(17.5)	(18.7)	(19.9)	(21.2)	(15.7)
p-value*		0.96	<0.00001	0.003	0.48
Vitality	62.7	67.0	51.1	48.7	57.7
Mean (SD)	(21.3)	(21.3)	(18.9)	(19.8)	(19.0)
p-value*		0.046	<0.00001	<0.00001	0.015
Pain	78.6	74.7	70.9	61.1	72.8
Mean (SD)	(25.5)	(25.0)	(29.5)	(31.4)	(25.2)
p-value*		0.084	0.002	<0.00001	0.018
General health	55.4	64.4	29.7	37.2	59.2
Mean (SD)	(26.8)	(22.2)	(19.1)	(17.3)	(19.3)
p-value*		<0.00001	<0.00001	<0.00001	0.14

Congestive Heart Failure (CHF), and myocardial infarction (AMI). SD standard deviation
*2-sided p-value for Z score, patients with PE versus general population, and patients with COPD, CHF and AMI versus patients with PE.

Figure 1. Mean SF-36 scores of patients with a history of acute Pulmonary Embolism, compared to a Dutch general population and disease comparison groups: COPD chronic obstructive pulmonary disease, CHF congestive heart failure, and AMI acute myocardial infarction.



Legend: PF = Physical functioning; SF = Social functioning; PR = Physical role functioning; ER = Emotional role functioning; MH = Mental health; VT = Vitality; BP = Bodily pain; GH = General Health

The total score per patient had a median of 7.1 (IQR 6.1-10.8). The median scores of the 6 dimensions of the PEmb-QoL were 1.7 (interquartile range (IQR) 1.0-2.1; max 5 points) for frequency of complaints, 1.5 (IQR 1.0-1.9; max 3 points) for limitations in ADL, 1.3 (IQR 1.0-1.5; max 2 points) for work-related problems, 1.5 (IQR 1.0-2.0; max 5 points) for social limitations, 2.0 (IQR 1.0-3.0; max 6 points) for intensity of complaints and 1.7 (IQR 1.0-3.0 max 6 points) for emotional complaints.

The scores of the patients who completed the questionnaires within 15 months after diagnosis of PE did not differ from the results of the patients who filled out the questionnaires longer than 15 months after diagnosis of PE (data not shown), except for the scales emotional complaints: 2.1 (IQR 1.2-3.2) versus 1.6 (IQR 1.0-1.9) respectively, p=0.028 and limitations in ADL 1.7 (IQR 1.1-2.2) versus 1.5 (IQR 1.0-1.7) respectively, p=0.03.

Associations between clinical characteristics and the PEmb-QoL

The total PEmb-QoL score did not correlate with age, BMI, COPD, CHF, history of VTE, recurrent PE, malignancy, smoking habits (partial correlations as we adjusted for time between PE and filling out the questionnaires). PEmb-QoL was neither related to localization of PE, thrombus load expressed as Qanadli score, nor the time span between PE and inclusion.

Of the 6 PEmb-QoL dimensions, modest correlations were found between COPD and intensity of complaints (r=0.23, p=0.02) and social limitations (r=0.28, p=0.025), CHF and social limitations (r=0.28, p=0.003), malignancy and emotional complaints (r=0.24, p=0.023), time span between PE and inclusion and emotional complaints (r=-0.2, p=0.04), and ADL limitations (r=-0.20, p=0.008).

Discussion

This study demonstrates that the QoL status, as assessed with SF-36, of patients who experienced PE is comparable to patients with a history of AMI the previous year and significantly better compared to patients with COPD and CHF. Second, the QoL in patients with PE as assessed with the disease-specific pemb-QoL questionnaire, was not influenced by severity of PE, as expressed in thrombus location and thrombus load.

Until now, only few studies addressed the QoL of patients with acute PE. Klok and colleagues (3) assessed the SF-36 in 392 patients with a history of PE and compared their SF-36 scores to Dutch population norms. Consistent with our findings, demonstrating that patients with a recent history of acute PE have an impaired QoL, they found significant differences on all scales, indicating a decreased QoL in PE patients. The time interval between PE and study inclusion was inversely related to QoL, and significant determinants of poor QoL were prior PE, age, obesity, active malignancy, and cardiopulmonary comorbid conditions (3). In the current study, we found only a modest correlation between COPD, CHF, malignancy and time span between PE and inclusion, and no correlation was found for all other clinical characteristics. An explanation for these differences could be that the current study represents a healthier population as reflected by the lower rates of cardiopulmonary comorbidity (8% versus 48%). Also, the current analysis had a smaller time-window between the PE episode and QoL-measurement, which has been demonstrated to be inversely related with QoL (17).

The PEmb-QoL has been validated in 2010 in 90 patients with a history of PE (7). The median time between PE and inclusion in that study was 3 years and 2 months,

(range 10 months -approximately 8 years). The median PEmb-QoL scores were all slightly lower in the previous cohort, indicating a better QoL, possibly due to the larger time gap between PE and inclusion.

As recent data reveal that a large proportion of patients with acute PE experience an adverse clinical course (6), it could be debated whether PE should be considered an acute or a chronic disease. We therefore investigated to what extent the QoL of patients with acute PE compares to the QoL reported by patients with chronic cardiopulmonary diseases, including COPD and CHF, using the generic SF-36 questionnaire. Notably, the QoL of patients with acute PE was significantly better on all SF-36 subscales. Furthermore, no clear differences were seen when we compared the QoL status of our patients to that of patients with a history of AMI the previous year. Thus, the QoL in patients with acute PE resembles more as an acute, than a chronic cardiopulmonary disease. These findings may be supported by the fact that for some scales in both questionnaires, we observed that the longer the period between the diagnosis and the QoL measurement, the better the QoL outcome.

To our knowledge, this is the first study that investigated the correlation between thrombus-load, as expressed by the Qanadli score and the location of the thrombus (i.e., central or lobar, segmental and subsegmental), and the QoL, as assessed with the PEmb-QoL questionnaire, in patients with PE. More centrally located PE or a higher thrombus load did not appear to affect QoL on the long-term. Although thrombus load has clearly been established as an important predictor for the short term clinical outcome (18), its implications for the long term clinical course, including the risk of developing CTEPH, have yet to be established.

The conclusions of this study are strengthened by the high response rate of 73%. A limitation includes the fact relatively low sample size, as a consequence, this study might have been underpowered to detect significant correlations between baseline characteristics and QoL. Additionally, our patient sample represents a relative healthy population, which is likely inherent to the fact that the patients had to survive the first months following PE to enter the study. In our view, however, this does represent the population of PE patient in whom assessing the QoL after PE is relevant. Furthermore, we measured both questionnaires once, which might give a bias as symptoms might change over time. Besides, for 84% of our population the question “Would you have been worried if you had to stop taking anticoagulant medication?” was not relevant. This question was then interpreted as “were you worried when you had to stop taking anticoagulants”. Last, we have assessed statistical differences in QoL scores between

different groups. However, a clinically meaningful difference is defined for SF-36, not yet for PEmb-QoL. Consequently, it is unknown whether such differences are meaningful to the patients even if $p < 0.05$.

In summary, QoL in our cohort of Dutch patients with a history of acute PE is impaired compared to the general population, irrespective of clinical characteristics such as age, comorbidity, or severity of PE. The presented population of patients with a history of acute PE report better QoL scores compared to patients with COPD and CHF, whereas the QoL of PE patient was comparable to patients with AMI.

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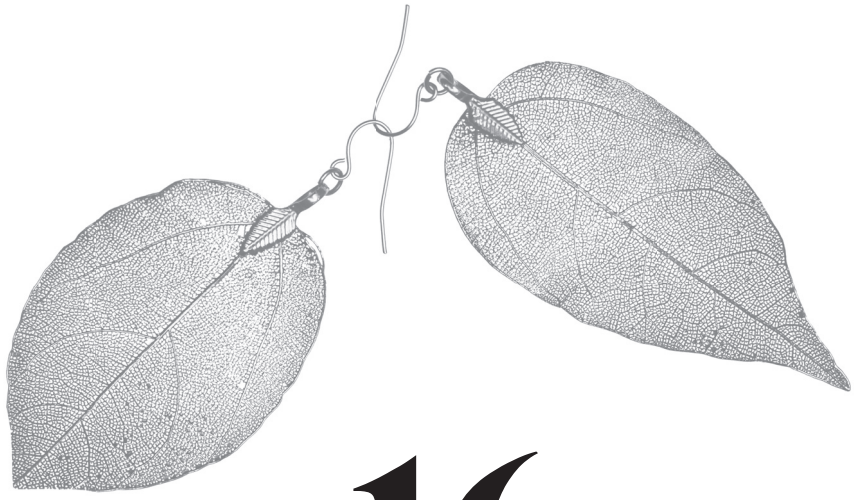

CHAPTER 16

Summary and perspectives

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Summary

This thesis focuses on the diagnosis, treatment and prognosis of pulmonary embolism (PE). In the first part, studies are described in which we further aimed to optimize the diagnostic workup of patients with suspected PE. The second part of the thesis focuses on the treatment and prognosis of patients with established PE.

In **chapter 2**, the safety and clinical utility of a new cut-off level for the D-dimer in patients above 50 years (age x 10 µg/L) was evaluated, combined with the original Wells score and the Revised Geneva score, and also with the recently introduced simplified version of the Wells score and revised Geneva score (RGS). The simplified Wells and simplified RGS are composed of the same clinical variables as the original version, but in the simplified rules, all items carry the same weight instead of different weights. In this retrospective validation study the diagnostic yield for excluding PE with the age-adjusted cut-off appeared to be highest in combination with the original Wells rule, i.e. 14.5% compared to 13.5% with the simplified Wells and 13.8% with both original and simplified RGS, although the differences were not statistically significant. The failure rates were similar for all clinical decision rules (2 patients, approximately 2.5%, 95% CI 0-8%).

In patients with a malignancy, the performance of these four clinical decision rules was compared in **chapter 3**. Direct comparison of four different clinical decision rules in patients with malignancy and suspected PE suggests that the simplified Wells score might have a higher sensitivity (94%, 95% CI 81-98) compared to the other three clinical decision rules (Wells score 65% (95% CI 48-95%), RGS 74% (95% CI 57-84%), simplified RGS 76% (95% CI 60-88%), respectively) ($p<0.05$). This did not translate in a higher number of patients in whom PE could be excluded without the need of computed tomography- (CT-scan), probably due to the low number of patients with a normal D-dimer result.

CT-scanning has become the standard test in the diagnostic work-up of patients with suspected PE. However, especially among young patients, concerns have been raised regarding the risk of cancer following radiation exposure with CTPA. Especially among young women, the lifetime attributable risk of cancer incidence is considerable, particularly the risk of breast cancer. Therefore, they may benefit from an alternative diagnostic modality, which is described in **chapter 4.** Perfusion scanning combined with chest X-ray result (X/Q) according to the PISAPED criteria seems an adequate alternative, but has never been validated. We therefore directly compared this strategy

with CT-scan in patients aged < 50 years with suspected PE. In patients younger than 50 years of age with a high risk of PE (likely Wells score or elevated D-dimer level), the accuracy of X/Q according to the PISAPED criteria was prospectively evaluated, in order to avoid CT-scanning and thereby the radiation exposure. In seven hospitals in the Netherlands and Belgium, 76 consecutive patients were included and X/Q-scans were analyzed by two trained nuclear physicians. The prevalence of PE in the patients was 33%. The interobserver agreement was high (κ=0.89). After consensus reading, 21 patients (28%) were categorized as 'PE present', 54 (71%) as 'PE absent', and two (2.6%) as 'non-diagnostic'. In 17 patients (22%) there was a discrepancy between the CPTA and the X/Q. The PPV and NPV were 71.4 (95% CI 50-86) and 83.0 (95% CI 71-91), respectively. Consequently, the diagnostic accuracy of X/Q according to PISAPED criteria seems limited in our cohort.

It is well known that the diagnostic accuracy of a test can vary with the strength of clinical suspicion. In that case, previously reported accuracy estimates may not be generalizable to all subgroups. In **chapter 5,** we tested the accuracy of the D-dimer test in patients with suspected PE who scored zero, one or two items of the Wells score. We used data of 723 patients with suspected PE, of which 177 (24%) patients had zero items on the Wells score, 300 (41%) had one item positive, and 136 (19%) had two items positive, including the subjective item of "PE more likely than an alternative diagnosis". The estimated sensitivity for the D-dimer test at the 500 µg/L positivity threshold was similar in the three subgroups whereas the specificity differed significantly, at 0.49, 0.30 and 0.16 respectively. Hence, we conclude that the diagnostic accuracy of D-dimer testing varies significantly across subgroups defined by the Wells score. As a next step, we aimed to develop a new clinical decision rule in **chapter 6** that incorporates Wells items and a D-dimer test result. We used 723 patients for a derivation cohort and a separate validation dataset of 2784 patients with suspected PE. After building a logistic regression model with the D-dimer result and Wells items, three Wells items were identified as significantly adding information to D-dimer: two clinical items (haemoptysis and clinical signs of deep venous thrombosis) and the subjective item (PE more likely than an alternative diagnosis). Based on the most frequent combinations, we identified two groups: (1) none of these items positive (41%), and (2) the subjective item or one of the clinical items positive (59%). We investigated the accuracy of this new rule with different cut-off values of the D-dimer test. The safety of this new clinical decision rule needs to be evaluated in future management studies.

In **chapter 7**, we prospectively studied whether alternative diagnoses observed on CT-scan, ordered for PE, have either diagnostic or therapeutic consequences in 203 consecutive patients with suspected PE. A total of 39 patients (19%) were diagnosed with PE and 61 (30%) had no abnormality on CT-scan. Findings supporting an alternative diagnosis were detected in 88 (43%) patients. However, in only 18 patients, a new and conclusive alternative diagnosis for the complaints was made based on the outcome of the CT-scan. Overall, findings supporting alternative diagnoses had therapeutic consequences in 10 (5%) patients. Incidental findings (nodules/lymph nodes) requiring diagnostic procedures were present in 17 (8%) patients. Although in patients undergoing CT- scan for suspected PE, findings supporting alternative diagnoses were found in almost half of the patients, in only few patients this had therapeutic consequences. Besides, the proportion of incidental findings was in the same range. CT-scan should therefore only be used to find or exclude PE, but not to establish an alternative diagnosis.

We measured prothrombin fragment 1+2 (F1+2) levels in urine and plasma in patients with venous thromboembolism (VTE) and myocardial infarction (MI), and in healthy controls in **chapter 8.** In this pilot study we showed that in patients with acute VTE plasma levels of F1+2 are elevated, and that F1+2 levels in the urine are increased, but to a lesser extent than in plasma. F1+2 levels in both urine and plasma were similar between patients with acute MI and healthy controls. These results show that F1+2 levels of the VTE patients are marginally increased in the urine. This was, however, not significantly different compared to healthy controls.

Part II – Treatment and prognosis of pulmonary embolism

In the first chapters of the second part of the thesis, **chapter 9** and **chapter 10** review the current treatment regimens for PE and VTE, respectively, discussing the new anticoagulants, duration of treatment and treatment in special patient groups, such as patients with renal failure, obesity or thrombophilia.

Although these chapters describe that standard treatment with anticoagulant therapy is known to effectively treat PE, little is known about the rate of clot resolution. This is of importance, because nowadays repeat CT-scans are often ordered after six months of anticoagulant treatment without solid evidence for clinical relevance. In **chapter 11**, 374 consecutive patients with PE confirmed by CT-scan (n=264) or perfusion scintigraphy (n=83) underwent a repeat scan after three weeks of anticoagulant

treatment. Overall, complete clot resolution occurred in 41% of the patients, while in 12%, no resolution occurred. Clot resolution was higher with CT-scan (44%) compared to perfusion scintigraphy (31%).This implies that clot resolution occurs early after PE in the majority of patients and suggests that normalization measured with CT-scan may be greater compared to perfusion scintigraphy.

In **chapter 12,** we assessed residual pulmonary thrombosis on a repeat CT- scan after six months of anticoagulant treatment in 141 patients with PE. The scans were analyzed independently by two different radiologists, who calculated the obstruction index using the scoring system of Qanadli. We also evaluated the relation between the presence of residual thrombosis and recurrent VTE in a 2-year follow-up, in this prospective, multicenter study. After six months of treatment, seven patients (5%; 95% CI 2-10%) had residual thrombosis in at least a segmental pulmonary artery. In another 14 patients (10%; 95% CI 6-16%), non-occlusive post-thrombotic webs or strictures were found. During follow-up, 13 (9.2%) patients experienced recurrent VTE. None of the patients with residual PE developed recurrent VTE.

With the introduction of improved imaging techniques, more isolated subsegmental PE has been detected, whereas the clinical significance of subsegmental PE is unclear. **Chapter 13** investigated the clinical outcome during three months follow-up of patients with subsegmental PE compared to more proximal PE (segmental and central PE), and to patients in whom PE was excluded. Subsegmental PE was confirmed in 116 of 748 (16%) patients with PE and these patients had an increased risk of mortality compared to patients in whom PE was ruled out and a similar mortality risk as those with more proximally located PE.

The influence of the duration of complaints before CT-scanning on the D-dimer level and the prognosis of patients is described in **chapter 14**, which aimed to assess the impact of diagnostic delay on the safety of excluding PE with the use of a clinical decision rule and D-dimer testing. Diagnostic delay (complaints present for at least 7 days) was present in approximately 19% of the patients. D-dimer testing yielded a high sensitivity rate, and the failure rate of an unlikely clinical probability and normal D-dimer test was 0.5% in patients with and without diagnostic delay. Hence, delay in confirming PE was associated with a more central PE location, but does not appear to impact the risk of recurrent VTE or mortality.

In **chapter 15** the quality of life of 109 patients with PE was investigated by a generic and a disease-specific questionnaire (PEmb-QoL). Quality of life assessed with the generic questionnaire was higher in patients with PE compared to patients with COPD and congestive heart failure, comparable to patients with acute myocardial infarction, and worse compared to the general Dutch population.

Future perspectives

The cornerstones of the diagnostic management of patients with suspected PE are clinical decision rules, D-dimer assays and imaging tests. In the last decade several large management studies support a standardized strategy consisting of these three diagnostic modalities to optimize safety and cost-effectiveness. Still, challenges remain and need attention to further optimize the strategy. First, the diagnosis is established on CT-scan in only 20-30% of the patients with suspected PE. Despite the many advantages of CT-scan, the concomitant radiation and iodine contrast exposure are important limitations of this imaging modality. Therefore, further optimizing the diagnostic work-up of PE is still needed. Besides, because inappropriate use of an algorithm could increase recurrence of VTE, it is important that the available strategies are adhered to and that these are used only in patients with suspected PE. Besides, since the signs and symptoms of PE overlap with other potentially dangerous cardio-pulmonary diseases, it is of importance to assess a fast and simple diagnostic work-up, which all physicians can assess appropriately, in or out of office hours. The use of an alternative clinical decision rule which is easier to remember and to apply, could increase the implementation of clinical probability assessment in a clinical setting.

Second, future studies should further focus on optimization of the strategy for subgroups of patients in whom the clinical utility of current strategies is low, for instance, patients with suspected recurrent PE, inpatients, patients with malignancy, and older patients. Once the age-dependent D-dimer cut-off value is prospectively validated (data of the ADJUST study are expected soon), it can be applied in a clinical setting and would improve the clinical utility of the strategy for elderly patients. With regard to the treatment of PE, new oral anticoagulant drugs have the potential to simplify treatment. So far, the results from large clinical trials have shown efficacy and safety for the prophylaxis and treatment of VTE. These new anticoagulants are now available.

Although treatment with both the conventional and new anticoagulants is very effective in patients with confirmed PE, the rate of clot resolution is less well studied. Patients with residual thrombosis in the pulmonary arteries are at risk of developing recurrent PE or chronic thromboembolic pulmonary hypertension. We found that the amount of residual thrombosis in the pulmonary arteries is less than always assumed. Further large prospective studies, which focus on the association between residual thrombosis and recurrent venous thromboembolism or chronic thromboembolic pulmonary hypertension, as well as on the risk factors for developing these sequels of PE, are welcome.

Nederlandse samenvatting

Een longembolie is een acute en levensbedreigende aandoening, waarbij een trombus, oftewel een bloedprop of stolsel, een of meerdere longslagaders blokkeert. Longslagaders vervoeren zuurstofarm bloed van het hart naar de longen (waar het bloed van zuurstof kan worden voorzien) en vervullen daardoor een belangrijke rol in het zuurstoftransport van het lichaam. De stolsels in deze vaten zijn meestal afkomstig uit stolsels in de vaten van de onderbenen. Van een dergelijk stolsel kan een stukje afbreken (een zogenaamde embolus), dat vervolgens via het bloed meegevoerd kan worden naar de longen.Dit leidt tot verminderde bloedstroom door de longen en verhoogde druk van de rechter kamer van het hart, wat levensbedreigend kan zijn.

Longembolie is de derde meest voorkomende cardiovasculaire aandoening in de westerse samenleving, met een incidentie van 1 à 2 per 1000 patiënten, tot zelfs 8 per 1000 per jaar bij oudere patiënten. De symptomen van patiënten met verdenking op een acute longembolie zijn zeer verschillend en wisselen van slechts milde symptomen tot ernstige benauwdheid, pijn bij inspanning, flauwvallen, of zelfs (cardiogene) shock. Daarom is het van groot belang om de diagnose tijdig en juist te stellen, zodat de patiënt behandeld kan worden met antistollingsmedicatie, oftewel anticoagulantia. Een dergelijke behandeling is echter niet zonder risico's. Behandeling met anticoagulantia geeft namelijk een verhoogd risico op bloedingen. Bovendien heeft gemiddeld maar 1 op de 5 patiënten met de verdenking op een longembolie, deze aandoening ook echt. Dit geeft aan dat het een moeilijke diagnose is om te stellen en het is dus net zo belangrijk om de diagnose correct uit te sluiten bij patiënten die geen longembolie hebben. Onnodige behandeling met anticoagulantia wordt daarmee voorkomen.

Wanneer er bij een patiënt aan een longembolie wordt gedacht, zijn er diverse diagnostische strategieën mogelijk. Allereerst wordt er een klinische beslisregel gebruikt voor het inschatten van het risico op een longembolie. De meest gebruikte beslisregel (de Wells score) bestaat uit zeven gegevens van de anamnese (het gesprek met de patiënt) en lichamelijk onderzoek. Gegevens van de anamnese zijn het eerder doorgemaakt hebben van een trombosebeen of longembolie, het hebben van kanker, bloed op hoesten, of recent geïmmobiliseerd zijn, door bijvoorbeeld ziekte, operatie of lang reizen. Gegevens uit het lichamelijk onderzoek zijn een snelle hartslag of tekenen van een trombosebeen. Als laatste is er nog een subjectief punt, namelijk dat een arts zelf bepaalt of longembolie de meest waarschijnlijk diagnose is of niet. Indien de beslisregel

als hoog-risico wordt beoordeeld moet de patiënt direct een CT-scan ondergaan om een longembolie aan te tonen of uit te sluiten. Als de beslisregel wordt geïnterpreteerd als laag-risico wordt er eerst een bloedafname gedaan voor een D-dimeertest, een indirecte maat voor de stollingsactiviteit in het bloed. Indien de D-dimeer verhoogd is volgt er alsnog een CT-scan, als de D-dimeer normaal is, zijn longembolieën uitgesloten.

Een CT-scan heeft vergeleken met beeldvormende onderzoeken van vroeger veel voordelen; het gaat snel, het is gevoelig voor longembolieën en de scan is toegankelijker dan zijn eerdere soorten scans. Ondanks de voordelen van CT-scan, gaat de scan wel gepaard met blootstelling van de patiënt aan röntgenstraling en aan contrastmiddel, dat schadelijk kan zijn voor de nieren. Het is dus erg belangrijk te bepalen voor wie een CT-scan noodzakelijk is en wie deze bespaard kan blijven.

Dit proefschrift beschrijft verschillende aspecten van de diagnostiek en de behandeling van longembolie. In het eerste deel worden onderzoeken beschreven die als doel hadden de diagnostiek te verbeteren. Het tweede deel gaat over de behandeling en de prognose van patiënten bij wie de diagnose is vastgesteld.

Deel I – Diagnostiek van longembolie

Naarmate patiënten ouder worden, neemt de specificiteit van de D-dimeertest af. De D-dimeer is namelijk hoger bij oudere mensen dan bij jonge mensen, ongeacht de aanwezigheid van een stolsel. Dit betekent dat oudere mensen minder vaak een normale D-dimeer hebben, ook zonder dat er sprake is van een longembolie. Dientengevolge kan een longembolie bij minder oudere mensen worden uitgesloten, op basis van de beslisregel en de D-dimeer. Als bij patiënten >50 jaar met een laag-risico, de D-dimeerafkapwaarde wordt opgehoogd door middel van de volgende regel: leeftijd x 10 µg/L, blijkt dat het aantal patiënten bij wie longembolie kan worden uitgesloten fors toeneemt, zonder dat dit ten koste gaat van de veiligheid. Met andere woorden, er hoeven minder CT-scans gemaakt te worden om toch veilig een longembolie te kunnen uitsluiten. In **hoofdstuk 2** werd de veiligheid en klinische toepasbaarheid van vier verschillende beslisregels onderzocht, gecombineerd met de leeftijdsafhankelijke afkapwaarde van de D-dimeer in mensen ouder dan 50 jaar en een verdenking longembolie. Deze afkapwaarde kon veilig een groot aantal CT-scans besparen in combinatie met alle vier de beslisregels. **Hoofdstuk 3** beschrijft de prestaties van deze vier beslisregels vergeleken in patiënten met een maligniteit (iedere vorm van kanker) en een verdenking longembolie. De versimpelde versie van de Wells score presteerde iets beter dan de andere drie regels.

Dit resulteerde niet in het vaker juist uitsluiten van een longembolie zonder een CT-scan. Dit komt waarschijnlijk door het lage aantal patiënten met een normale D-dimeer, door de maligniteit.

De CT-scan is momenteel de standaard radiologische test in de diagnostiek van longembolie. Echter, het risico op kanker ten gevolge van blootstelling aan röntgenstraling is verhoogd bij een CT-scan, vooral het risico op borstkanker bij jonge vrouwen. Dit risico is afhankelijk van de leeftijd en de hoeveelheid borstweefsel. Gemiddeld is het risico voor het ontwikkelen van borstkanker door een CT-scan voor vrouwen van 20 jaar 1 op de 114. In **hoofdstuk 4** werd een alternatieve diagnostische strategie onderzocht bij vrouwen onder de 50 jaar in zeven ziekenhuizen in Nederland en België, met als doel het aantal CT-scans te verminderen. In deze prospectieve studie werd een combinatie van beslisregel, D-dimeertest, thoraxfoto en long perfusiescan, volgens de nieuwe 'PISAPED' criteria, onderzocht. Alle perfusiescans werden beoordeeld door twee getrainde en onafhankelijke nucleair geneeskundigen. De strategie bleek helaas niet betrouwbaar genoeg om de diagnose correct aan te tonen of uit te sluiten.

In **hoofdstuk 5,** wordt de nauwkeurigheid/veiligheid van de D-dimeertest beschreven in patiënten met nul, één of twee items die positief waren van de Wells score. De diagnostische betrouwbaarheid van de D-dimeertest in de patiënten met 0 items positief was significant hoger dan de betrouwbaarheid van de D-dimeer test in de groepen met één of twee items van de Wells score positief. In **hoofdstuk 6** werd een nieuwe beslisregel ontworpen met inbegrip van de D-dimeer uitslag. Gebaseerd op een logistisch regressiemodel en de meest frequente combinaties van de significante Wells items, werden er twee groepen gemaakt: (1) geen items positief (41%), en (2) het subjectieve item positief of aanwezigheid van bloed ophoesten of tekenen van een trombose been (59%). Voor deze twee groepen zijn verschillende afkapwaarden berekend. Hieruit kon worden geconcludeerd dat het combineren van de Wells score items met het D-dimeer resultaat kan resulteren in een simpele beslisregel.

In **hoofdstuk 7** werd bij 203 patiënten met een verdenking op een longembolie prospectief onderzocht of alternatieve diagnoses, die gediagnosticeerd werden op de CT-scan, diagnostische of therapeutische consequenties hadden. Alternatieve diagnoses werden gedetecteerd in 88 patiënten (43%). Echter, deze diagnose was bij de meesten al bekend en bovendien verklaarde deze slechts in een klein deel de klachten. Uiteindelijk had ongeveer 5% van de alternatieve diagnoses therapeutische consequenties voor de patiënten. Dus als CT-scan wordt gebruikt om een alternatieve diagnose te stellen, is het netto klinische voordeel beperkt.

Protrombine fragmenten 1 +2 (F1 +2) werden gemeten in de urine en bloed van patiënten met longembolie of een trombosebeen en patiënten met een hartinfarct. De F1+2 levels werden vergeleken met gezonde controle patiënten in **hoofdstuk 8**. In deze pilotstudie werd aangetoond dat bij patiënten met een longembolie of een trombosebeen, de spiegels van F1 +2 in het bloed verhoogd waren, en dat ook F1 +2 in de urine waren verhoogd vergeleken met de gezonde controles. Dit was echter niet significant verschillend in vergelijking met gezonde controles.

Deel II – Behandeling en prognose van longembolie

De eerste hoofdstukken van het tweede deel van het proefschrift, **hoofdstuk 9** en **hoofdstuk 10,** geven een overzicht van de huidige behandelingen voor longembolie en longembolie plus een trombosebeen, respectievelijk. De nieuwe anticoagulantia, duur van de behandeling en behandeling in speciale patiëntengroepen, zoals patiënten met een nierziekte, obesitas of trombofilie (erfelijk verhoogde stollingsneiging) worden besproken. Deze hoofdstukken beschrijven dat standaard behandeling met anticoagulantia effectief is om longembolie te behandelen. Er is echter weinig bekend over de mate van de resolutie van de stolsels in de longen. In **hoofdstuk 11**, ondergingen 374 patiënten met longembolie, bevestigd door een CT-scan (n=264) of een perfusie scan (n=83) een herhaalscan na drie weken van antistollingsbehandeling. In totaal trad de complete resolutie van stolsels op in 41% van de patiënten, terwijl in 12% helemaal geen resolutie had plaatsgevonden. Complete resolutie van de stolsels werd vaker gezien met de CT-scan (44%) dan met perfusie scan (31%). In **hoofdstuk 12** werd bij 148 patiënten met een longembolie het voorkomen van resterende stolsels (resttrombose) in de longen na zes maanden behandeling onderzocht. De CT-scans werden onafhankelijk geanalyseerd door twee radiologen. Na zes maanden had 5% van de patiënten nog resttrombose. Het hebben van resttrombose had geen relatie met een recidief longembolie of overlijden.

Door de verbeterde beeldvormende technieken, worden er vaker geïsoleerde subsegmentele longembolieën gedetecteerd, terwijl de klinische betekenis hiervan onduidelijk is. Subsegmentele longembolieën zijn stolsels in de kleinste vaten van de longen. **Hoofdstuk 13** onderzocht de klinische resultaten van drie maanden follow-up van patiënten met subsegmentele longembolie vergeleken met longembolieën in de grotere vaten (segmentele en centrale longembolie), en patiënten bij wie longembolie was uitgesloten. Deze studie liet zien dat patiënten met een subsegmentele longembolie

hetzelfde overlijdingsrisico hebben als patiënten met longembolieën in de grotere vaten en een verhoogd risico op overlijden in vergelijking met patiënten zonder longembolie.

De invloed van de duur van de klachten voor CT-scan op het D-dimeer niveau en de prognose van patiënten wordt beschreven in **hoofdstuk 14**. Er was sprake van diagnostische vertraging (presentatie op de eerste hulp na meer dan 7 dagen klachten) bij ongeveer 19% van de patiënten. Vertraging van het vaststellen van een longembolie was geassocieerd met een centrale locatie van de longembolie, maar lijkt het risico van recifdief longembolie of trombosebeen of sterfte niet te beïnvloeden.

In **hoofdstuk 15** werd de kwaliteit van leven van 109 patiënten met longembolie werd onderzocht middels twee verschillende vragenlijsten. De kwaliteit van leven was beter bij patiënten met longembolie in vergelijking met patiënten met COPD en hartfalen, vergelijkbaar met patiënten met een acuut hartinfarct, en slechter in vergelijking met de algemene Nederlandse bevolking.

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Curriculum Vitae

Op 23 december 1983 werd Josien van Es geboren als dochter van Ruud van Es en Betty Driehuis in Amsterdam waar zij opgroeide op de Prinsengracht. Na het voltooien van haar middelbare schooltijd op het Vossius Gymnasium, begon zij in 2002 met de studie geneeskunde aan de Universiteit van Amsterdam. Ze rondde de doctoraalfase af met een wetenschappelijke stage in Semarang, Indonesië en de co-schappen met een keuze coschap spoedeisende hulp en infectieziekten in Kansas City, USA. Na haar artsexamen in 2009 ging zij aan de slag als arts-assistent interne geneeskunde in het Tergooi ziekenhuis in Hilversum. In januari 2010 kreeg zij de kans promotieonderzoek te doen bij de bij de vasculaire geneeskunde in het Academisch Medisch Centrum en het Slotervaartziekenhuis. Naast haar onderzoek naar de diagnostiek en prognose van patiënten met longembolieën, wat heeft geleid tot dit proefschrift, werkte zij als stollingsconsulent binnen het Academisch Medisch Centrum. Zij is 1 maart jl. met veel plezier gestart met de opleiding longgeneeskunde en tuberculose in het Onze Lieve Vrouwe Gasthuis, te Amsterdam. Josien woont samen met haar vriend Maurits.

De paranimfen,

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List of publications and portfolio

1. **van Es J.,** den Exter P.L., Erkens P.M.G., van Roosmalen M.J.G., van den Hoven P., Hovens M.M.C., Kamphuisen P.W., Klok F.A., Huisman M.V. *Impact of delay in clinical presentation on the diagnostic management and prognosis of patients with suspected pulmonary embolism*. American Journal of Respiratory and Critical Care Medicine. 2013 March

2. **van Es J,** Douma RA, Kamphuisen PW, Gerdes VEA, Verhamme P, Wells PS, Bounameaux H, Lensing AWA, Büller HR. *Clot resolution after 3 weeks of anticoagulant treatment of pulmonary embolism: comparison of computed tomography and perfusion scintigraphy.* J Thromb Haemost. 2013 Apr;11(4):679-85.

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4. **van Es J**, Beenen L.F.M., Gerdes V.E.A., Middeldorp S., Douma R.A., Bossuyt P.M.M. *The accuracy of D-dimer testing in suspected pulmonary embolism varies with the Wells score.* J Thromb Haemost 2012 Dec: 2630-2.

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6. **van Es J**, Mos I.C.M., Douma R.A., Huisman M.V., Kamphuisen P.W. *Performance of four clinical decision rules in patients with malignancy and suspected pulmonary embolism*. J Thromb Haemost. 2012 Feb;10(2):312-4.

7. **van Es J**, Mos I, Douma R.A., Erkens P.G.M., Durian M, Nizet T, van Houten A, Hofstee H, Ten Cate H, Ullmann E, Buller H, Huisman M, Kamphuisen PW. *The combination of four different clinical decision rules and an age-adjusted D-dimer cut-off increases the number of patients in whom acute pulmonary embolism can safely be excluded.* Thromb Haemost. 2011 Nov 10;107(1).

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Portfolio

Courses

Biostatistics 2011
Good Clinical Practice 2010
Epidemiology 2010
English oral presentation 2010
Basiscursus Organisatie Klinisch wetenschappelijk onderzoek (BROK) 2010
AIO course arterial thrombosis 2010
AIO course bleedings 2011
AIO course venous thrombosis 2012

Selection of posters and oral presentations

Seminar Department Clinical Epidemiology, Biostatistics & Bioinformatics, 2012
Improving the accuracy of D-dimer testing in suspected pulmonary embolism

International Society for Thrombosis and Hemostasis (ISTH), Kyoto, Japan, 2011
Performance of four clinical decision rules in patients with malignancy and suspected pulmonary embolism.

The combination of four different clinical decision rules and an age-adjusted D-dimer cut-off increases the number of patients in whom acute pulmonary embolism can safely be excluded.

Urinary prothrombin fragment 1+2 in patients with venous thrombosis and myocardial infarction

Adviesraad "Orale anticoagulantia bij VTE", presentatie van de resultaten van de 'EINSTEIN DVT en Extensie'-studie, N Engl J Med 2010

Symposium Dutch Society for Thrombosis and Haemostasis (NVTH), Koudekerke, 2011
The combination of four different clinical decision rules and an age-adjusted D-dimer cut-off increases the number of patients in whom acute pulmonary embolism can safely be excluded.

Teaching

College veneuze stolling, 2011
Daily coach of 4th year students Reim Aarab, Niels Kappelhof, 2010-2013

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