Improving efficiency of the diagnostic management of pulmonary embolism

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IMPROVING EFFICIENCY OF THE DIAGNOSTIC MANAGEMENT OF PULMONARY EMBOLISM

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Chapter 1

General introduction and outline

Pulmonary embolism (PE) refers to a blood clot in the pulmonary artery or one of its branches, which is most commonly originating from deep venous thrombosis (DVT) of the legs or pelvis. Venous thrombo-embolism (VTE) encompasses both pulmonary embolism (PE) and deep venous thrombosis (DVT) (1). VTE is the third most frequent cardiovascular disease and it is a major cause of mortality, morbidity and chronic disease and disability. In Europe, it affects 430,000 patients each year and worldwide the overall annual incidence is 100-200 per 100,000 inhabitants (2, 3).

The diagnostic process of patients with suspected PE is challenging due to the non-specific symptoms and clinical presentation. Integrated diagnostic algorithms including validated clinical decision rules, high sensitive D-dimer tests and imaging tests such as computed tomography pulmonary angiography (CTPA) may guide the clinician, and close adherence to the diagnostic algorithm is of crucial importance for the clinical outcome of patients with suspected PE (1, 2). The focus of this thesis is the diagnostic management of patients with suspected PE.

The first part of this thesis focuses on the diagnostic management of pregnant patients with suspected PE. During pregnancy, women have a 4 to 5 fold increased risk for venous thrombo-embolism (VTE) compared age matched non-pregnant women, and PE contributes to an important degree to maternal mortality in Western Europe; an accurate diagnosis of PE during pregnancy is thus of crucial importance (4-6). There are different reasons why the diagnosis of PE is challenging during pregnancy. First, many of the common VTE-symptoms are also associated with normal pregnancy, such as oedema, tachycardia and dyspnea, which makes PE more difficult to diagnose. Moreover, clinical decision rules and D-dimer tests have not been validated in the pregnant population (7, 8). An overview of the current diagnostic strategies of suspected PE -and the limitations thereof - in the pregnant population is presented in chapter 2. Imaging is the gold standard to confirm or rule out PE in the pregnant population, although associated with radiation exposure to mother and foetus. Both ventilation-perfusion scan and CTPA may be used for this purpose. In chapter 3, a meta-analysis is provided to compare the risks and results of these imaging tests in the pregnant population. A new safe and simplified diagnostic algorithm for patients with suspected PE, the YEARS algorithm, was evaluated in pregnant patients. Results of this prospective multinational, multicenter diagnostic management study are described in chapter 4.

The second part of this thesis focuses on the diagnostic management of unselected patients with suspected PE. The results of a sex-specific prevalence and performance of three different diagnostic algorithms from seven prospective management studies are described in chapter 5. The aim of this study was to evaluate the efficiency and failure rate of three different diagnostic strategies in men versus women and to determine the sex-specific prevalence of PE.

Different strategies to reduce the number of required CTPA's and to improve the efficiency for excluding PE have been published in the last decade , i.e. YEARS, ADJUST and PERC. The first strategy is the YEARS diagnostic algorithm, which consists of simultaneous assessment of three clinical YEARS-items and a D-dimer test in all patients (9). Using the YEARS algorithm resulted in an improved efficiency with a reduction of 14% in the need to perform CTPA with a very low three month VTE failure rate. Another strategy is the age-adjusted D-dimer cut-off in patients of 50 years and older, defined as patients' age x 10 ng/ml as threshold (ADJUST) (10, 11). In chapter 6 the combination of this age-adjusted D-dimer threshold with the YEARS algorithm was evaluated to investigate if this combination could potentially further improve the efficiency in the diagnostic work-up of patients with suspected PE. A third strategy to improve the efficiency of the diagnostic management of patients with suspected PE is the use of the pulmonary embolism rule-out criteria (PERC) (12, 13). This rule involves eight clinical items, and when all the items are scored negative, PE is ruled out without further diagnostic tests. Chapter 7 evaluates the combination of this PERC rule and the YEARS algorithm.

Since the YEARS algorithm is easier to apply in daily clinical practise in comparison with the conventional algorithm, it may provide additional benefits over more improved efficacy, i.e. less CT scans with comparable safety. Chapter 8 provides an overview of the total time of an emergency department visit for patients with suspected PE and the associated costs when using the YEARS algorithm in comparison with the conventional algorithm. The aim of chapter 9 was to evaluate if chest X-ray results differ between patients with confirmed PE and with PE ruled out and to investigate whether chest X-ray provides incremental diagnostic value to the YEARS criteria when selecting patients with an indication for CT-scan. Lastly, since the introduction of multi-detector CT-scan, the sensitivity for visualizing smaller PE has noticeably advanced (14). These advances have led to a more frequent detection of filling defect in the smaller pulmonary arteries or subsegmental arteries. The prevalence of these small emboli – subsegmental PE – in patients with suspected PE using the YEARS algorithm was compared to the conventional algorithm in chapter 10.

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Chapter 2

Use of clinical prediction rules and D-dimer tests in the diagnostic management of pregnant patients with suspected acute pulmonary embolism

L.M. van der Pol, A.T.A. Mairuhu, C. Tromeur, F. Couturaud, M.V. Huisman, F.A. Klok

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ABSTRACT

Because pregnant women have an increased risk of venous thromboembolism (VTE) and at the same time normal pregnancy is associated with symptoms, mimicking those present in the setting of acute pulmonary embolism (PE), the latter diagnosis is frequently suspected in this patient category. Since imaging tests expose both mother and foetus to ionizing radiation, the ability to rule out PE based on non-radiological diagnostic tests is of paramount importance. However, clinical decision rules have only been scarcely evaluated in the pregnant population with suspected PE, while D-dimer levels lose diagnostic accuracy due to a physiological increase during normal pregnancy. Consequently, clinical guidelines provide contradicting and weak recommendations on this subject and the optimal diagnostic strategy remains highly debated. With this systematic review, we aimed to summarize current evidence on the safety and efficacy of clinical decision rules and biomarkers used in the diagnostic management of suspected acute PE in pregnant patients.

INTRODUCTION

Women are at an increased risk of venous thromboembolism (VTE) during pregnancy. Compared to age matched women who are not pregnant, the risk of VTE is increased 4- to 5-fold (1). The overall prevalence of thromboembolic events during pregnancy has been reported to be 1.72 per 1000 deliveries with acute pulmonary embolism (PE) causing 1.1 deaths per 100,000 deliveries, accounting for 14% of all maternal deaths in the Western World (2, 3). This higher thrombotic risk is attributed to a physiological pregnancy-induced hypercoagulable state as well as decreased venous outflow of the lower extremities due to mechanical venous obstruction by the uterus (4). This hypercoagulability of pregnancy may have evolved to protect women from haemorrhage at the time of miscarriage or childbirth, and consists of increased concentrations of factors VII, VIII and X as well as von Willebrand factor, fibrinogen and plasminogen activator inhibitor type 1, whereas protein S levels are decreased (5).

In addition to the higher risk of PE, many of the common VTE symptoms such as leg swelling, tachycardia, tachypnea and shortness of breath are also associated with normal pregnancy. Consequently, in clinical practice physicians tend to test for PE at low thresholds, which are demonstrated by the very low VTE incidences of 5.0% or less in most studies focussing on pregnant patients with suspected PE, compared to 20-25% in the non-pregnant population (6-10). Notably, despite the frequent occurrence of suspected PE in pregnant patients, large high quality studies evaluating the optimal diagnostic strategy for this patient category are unavailable. Moreover, the recommended diagnostic management of suspected PE consisting of sequential standardized clinical probability assessment, D-dimer measurement and computed tomography pulmonary angiography (CTPA), may not be applicable to pregnant patients for three main reasons (11, 12). First, studies that were used to derive clinical prediction rules have mostly excluded pregnant women. What's more, available prediction scores have hardly been prospectively validated in pregnancy or during the postpartum period. Second, D-dimer levels physiologically increase throughout pregnancy with a peak around delivery, making this test less useful to rule out VTE. Lastly, CTPA and ventilation perfusion lung scanning, which in the absence of other diagnostic tests, are the current cornerstone of the diagnostic management of suspected PE in pregnant patients, are associated with foetal and maternal radiation exposure. Recent studies suggest that diagnostic imaging test to rule out PE in pregnant and postpartum women are ordered with a very low threshold, such that the harms of investigation with diagnostic imaging may outweigh its benefits (13). The ability to safely rule out acute PE in pregnant patients without radiological tests is therefore of paramount importance.

Most literature that has been published on the optimal diagnostic management of pregnant patients with suspected PE targets the discussion whether CTPA or VQ scintigraphy should be preferred as imaging test. However, the greatest improvement lies in excluding PE without imaging tests, a subject that remains scarcely studied. The aim of this review was

therefore to generate a complete overview of all literature on excluding PE without radiological imaging in pregnant patients. To do so, we have evaluated current evidence on the safety and efficacy of clinical decision rules and biomarkers used in the diagnostic management of suspected acute PE in pregnant patients, by performing a systematic search for relevant articles and abstracts in MEDLINE (via PubMed), EMBASE, Web of Science, CINAHL, the Cochrane Database of Systematic Reviews, Academic Search Premier, Science Direct and the Clinical trials registry that were published in the last 10 years. The search string is detailed in **Appendix A**.

D-DIMER TESTS IN PREGNANT PATIENTS WITH SUSPECTED PE

Natural course of D-dimer levels during pregnancy and post-partum

In the 1990s several studies have shown that D-dimer levels rise steadily throughout pregnancy (14-16). In the past 10 years, five studies further contributed to this subject. The first one enrolled 50 healthy women who were seeking medical advice to become pregnant, in whom sequential D-dimer tests were performed during the course of their pregnancy (17). The mean age of these women was 31 years, 82% were Caucasian and 44% had never been pregnant before. Extensive exclusion criteria of the study were applied to rule out any alternative cause of increased D-dimer, such as renal disease or malignancy. Blood samples were drawn at preconception, during each trimester of pregnancy (at 12, 24 and 36 weeks), and four weeks postpartum. Successful pregnancy was achieved in 32 patients and complete data were available for 18 study subjects. D-dimer levels as measured with a quantitative latex immunoagglutination D-dimer assay (MDA immunoturbidimetric Assay; Organon Teknika) increased throughout the pregnancy with a mean of 0.43 mg/L at baseline, 0.58 mg/L in the first trimester, 0.83 mg/L in the second trimester, 1.2 mg/L in the third trimester and 0.61 mg/L in the postpartum period. This corresponds to 79%, 50%, 22%, 0% and 69% of women with a normal D-dimer respectively, using the established threshold of 0.5 mg/L (**Figure 1**).

A second study applied a comparable design: D-dimer levels were measured in all trimesters as well as postpartum in 89 healthy pregnant subjects using a quantitative latex immunoagglutination D-dimer assay (HemosIL D-dimer HS assay, Instrumentation Laboratory, Milan, Italy) (18). The included women were between 18-40 years old and had no history of VTE. Women with a prior history of diabetes, SLE, chronic hypertension, hepatic or renal disease were excluded from the study. As with the previous study, D-dimer levels increased in the course of pregnancy with a normalisation in the postpartum period. Using the reference value of 0.230 mg/l, 84%, 33%, 1% and 88% of patients would have had a normal D-dimer tests in the three trimesters and postpartum respectively.

The third study was a large cross sectional study including 1343 pregnant females in whom D-dimer levels were measured at one point during pregnancy or post-partum with the latex-

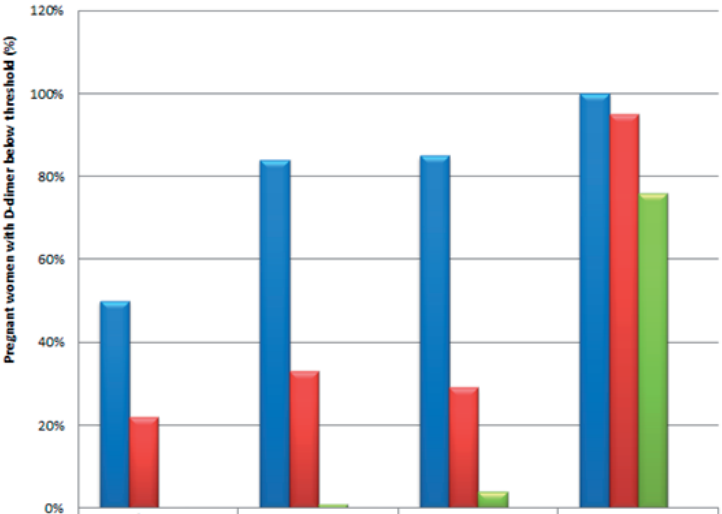
based immunoturbidimetry on the STA-R evolution coagulation analyser (Diagnostica Stago) (19). Again, the D-dimer levels increased significantly during the pregnancy trimesters. During the first trimester, 85% of pregnant women had a D-dimer below the threshold of 0.5 mg/l, which decreased to 29% and 4.1% in the second and third trimester respectively. The D-dimer levels returned to normal after 42 days postpartum. D-dimer concentrations of women who delivered by caesarean sections were significantly higher than those delivering vaginally on the 2nd and 3rd postpartum days, but this difference disappeared on day 42. Normalisation of D-dimer levels occurred on average 3 weeks postpartum in the fourth observational study (20).

The fifth study showed that the amount of D-dimer increase during pregnancy was more pronounced in twin pregnancies than in singleton pregnancies (21). This study evaluated 1106 patients with a singleton pregnancy and 25 patients with a twin pregnancy. In singleton pregnancies, the mean values of D-dimer in the first and third trimesters were 1.1 ± 1.0 and 2.2 ± 1.6 mg/l and for twin pregnancies, the mean values of D-dimer were 1.1 mg/l ± 0.7 and 3.7 mg/l ± 2.5 respectively. In this study, the increase of D-dimer in twin pregnancies was higher than for singleton pregnancies, although statistical substantiation was not provided. According to the reported information, this is the only study that evaluated twin pregnancies. The other selected studies in this described paragraph do not specify the pregnancy into a single- or twin pregnancy.

The final study is a cross-sectional study which determined D-dimer levels in 416 pregnant women at one random time point during their pregnancy, and in 32 age-matched healthy non-pregnant women (22). The reason for inclusion of the 32 non-pregnant controls is not entirely clear. The authors have described that these controls are added after recommendation of the "International Federation of Clinical Chemistry and Clinical and Laboratory Standards Institute". Exclusion criteria were designed to minimize any possible influence on D-dimer levels: any history of thromboembolic disease, auto-immune diseases and morbid obesity. D-dimer analysis was performed using the AMAX AUTO D-dimer kit, based on an immunoturbidimetric method. Median age of the study subjects was 27 years old.

As compared to non-pregnant women, D-dimer and fibrinogen levels were found to be elevated in each trimester.

In summary, the specificity of the D-dimer test decreases considerably during pregnancy (**Figure 1**). Notably most PE suspicions occur in the third trimester, in which the specificity of D-dimer test approximates 0% when applying diagnostic thresholds established in non-pregnant patients (6, 8).



	Kline [17]		Kovac [18]		Wang [19]		Ercan [22]	
1st trimester	n=32	50%	n=89	84%	n=203	85%	n=123	100%
2nd trimester	n=31	22%	n=89	33%	n=401	29%	n=164	95%
3rd trimester	n=23	0%	n=86	1%	n=739	4%	n=126	76%
Used D-dimer threshold	< 0.5 mg/l		< 0.23 mg/l		< 0.5 mg/l		< 0.5 mg/l	

Figure 1 Overview of pregnant women (%) with D-dimer levels below non pregnancy threshold (< 0.5mg/l) during pregnancy

Alternative D-dimer thresholds

There are six studies that evaluated alternative D-dimer thresholds in pregnant patients with suspected VTE (**Table 1**).

The above described study from Ercan and colleagues also calculates different D-dimer thresholds for each trimester (22). Reference intervals for normal D-dimer levels were determined as 0.11-0.40mg/l, 0.14-0.75 mg/L and 0.16-1.3 mg/l for the first, second and third trimester respectively (22). The second study was of the same design (19). This large cross sectional study included 1343 pregnant Chinese women. The adjusted thresholds for normal D-dimer level were determined at 0.66 mg/l, 2.29 mg/l and 3.12 mg/l during the first, second and third trimester (19).

Two above described studies and 2 additional small studies measured D-dimer levels during different time points of the pregnancy and used the range of identified D-dimer values to suggest new modified normal values (**Table 1**)(17-19, 22-24). All 6 studies used different methods of determining the alternative thresholds, i.e. based on the extreme values or on certain percentiles. Also, and importantly, the identification of a 'normal range' is in fact very different from identifying a safe exclusion threshold for PE. Together with the wide variety in suggested alternative thresholds, this indicates that the evidence for recommending a certain threshold depending on pregnancy duration is poor at best.

Table 1: Identified studies that evaluated adjusted thresholds for normal D-dimer levels in pregnant patients during the trimesters of pregnancy.

Study	D-dimer assay	Study design	Number of pregnant study participants	Suggested threshold for normal D-dimer (mg/l)		
				1st trimester	2nd trimester	3rd trimester
Kline, 2005 [16]	MDA immune-turbidometric assay (Organon Teknika)	D-dimer measured preconceptionally, each trimester and 4 weeks post-partum	50	0.76	1.09	1.48
Kovac, 2010 [17]	HemosIL D-dimer HS (IL)	D-dimer tested each trimester and 6-8 weeks post-partum	89	0.27	0.46	0.64
Wang, 2013 [18]	Latex-based immunoturbidimetry (Diagnostica Stago)	single D-dimer measurement at random moment during pregnancy	1343	0.66	2.29	3.12
Ercan, 2015 [21]	AMAX AUTO D-dimer Kit (Trinity Biotec Plc)	single D-dimer measurement at random moment during pregnancy	416	0.40	0.75	1.30
Parilla, 2016 [22]	Unknown	single D-dimer testing and diagnostic imaging (spiral CT or VQ scan)	45	0.95	1.29	1.70
Kappert, 2009 [37]	HemosIL D-Dimer HS 500 test	D-dimer tested in each trimester	50	*n.p.*	*n.p.*	*n.p.*
Morse, 2004 [23]	D-dimer assay (IL)	D-dimer tested each trimester	48	0.28	0.47	0.64

Note: np=not provided

Studies using D-dimer to rule out PE

Although many of the studies identified in our search described the D-dimer test results in incident cases of VTE in general and in acute PE specifically, we did not identify any study that ruled out PE based on a normal D-dimer level alone. In the studies discussed in this review, we could extract 45 patients with confirmed VTE with known D-dimer levels (6, 18, 23, 25-28). These levels exceeded the assay-specific predefined threshold of 0.5 mg/l in 44 patients, and were normal in one patient, for a sensitivity of 98% (95% confidence interval (CI) 88-99.9). Of note, we anticipate the issue of publication bias on this matter.

From this, it may be hypothesised that this 98% sensitivity could be sufficient to allow for a sufficiently high negative predictive value of a normal D-dimer to rule out acute PE, especially because of the known low disease frequency in cohorts of pregnant patients with suspected PE. The above described adjusted trimester-specific D-dimer thresholds may – if properly validated – increase the specificity and with that the usefulness of the test, although prospective data to confirm that hypothesis are lacking.

OTHER BIOMARKERS IN PREGNANT PATIENTS WITH SUSPECTED PE

A few alternative biomarkers to replace D-dimer tests or to be used in combination with D-dimer test have been suggested in recent years. In the above described study by Ercan and colleagues, fibrinogen levels were assessed along with D-dimer levels (22). Fibrinogen levels were higher in the pregnant patients then in the non-pregnant controls, but remained stable during the first 2 trimesters, after which a statistically significant but absolute small increase was shown. Because of the wide range in fibrinogen levels as well as the lack of both a standardized normal value and a relevant threshold for PE, fibrinogen seems not to have potential to replace D-dimer tests in the diagnostic work-up of suspected PE in pregnant patients.

In a case report, it was suggested to increase the specificity of D-dimer tests by combining that with N-terminal pro-B-type-natriuretic peptide (NT-proBNP) measurement (26). NT-proBNP is secreted by the cardiac ventricles in response to dilatation or increased intraventricular pressure. With that, NT-proBNP has been established as a prognostic serum marker for acute PE but not as a diagnostic test (29). Moreover, it has been shown that NT-proBNP levels increase during normal pregnancy as well, making it an unlikely useful diagnostic tool in the setting of suspected PE (30).

Lastly, the diagnostic accuracy of a protein C sensitivity test for PE in pregnant women was evaluated in a small Japanese study (25). This study was based on the observation that functional sensitivity to activated protein C (APC) decreases during pregnancy and especially during pregnancy-associated VTE. To test their hypothesis, the authors measured the normalized APC sensitivity ratio in 111 randomly selected healthy Japanese pregnant females and compared that with those in 200 non-pregnant females (selection criteria not provided) and 7 pregnant patients with established VTE using an endogenous thrombin potential-based assay. Indeed, the sensitivity to APC in patients with VTE was reduced in comparison to the control groups, although the measured values largely overlapped. A sensitive diagnostic threshold could not be extracted from the acquired data.

Because the biomarkers seem unsuitable for clinical practice and validation studies in larger patient numbers as well as prospective outcome trials for all three suggested biomarkers are lacking, it seems that no valuable options to replace the D-dimer test for this purpose are available in the near future.

CLINICAL DECISION RULES IN PREGNANT PATIENTS WITH SUSPECTED PE

Diagnostic accuracy of clinical decision rules

Current diagnostic workup of patients with suspected acute PE usually starts with the assessment of clinical pre-test probability using standardized and validated clinical prediction rule. The best validated, and therefore most widely used, clinical decision rules are the original and

simplified versions of the Wells rule and revised Geneva rule (9, 31-33). In our literature review, we identified three articles that evaluated the Wells rule in pregnant patients, of which two reported on the same patient cohort (6-8, 23). Other clinical prediction rules have not yet been tested in pregnant or postpartum women with suspected PE. Since there is great paucity of studies on clinical decision rules, detailed information on discriminatory factors is missing as well.

The first study was a retrospective evaluation of 81 pregnant and 22 post-partum patients who were referred for CTPA imaging because of clinically suspected PE (6, 7). The Wells score was calculated post-hoc from the medical charts. The majority of patients (60%) were in the third trimester of their pregnancy and 4.8% of patients were diagnosed with PE at baseline. Of the 14% of patients with a high clinical probability (Wells score of 6 or more points), 35% were diagnosed with PE, whereas PE was ruled out in all of the patients with a Wells score of less than 6 points, suggesting an maximal sensitivity of 100% and a specificity of 90% with this diagnostic threshold. Notably, follow-up data were not available.

The second study involved 183 pregnant patients with suspected PE, of whom 58% were in the third trimester (8). All were referred for ventilation perfusion scanning and the Wells score was calculated by two independent assessors retrospectively by examining medical records of the initial presentation. PE was confirmed in six patients (3.3%). A total of 107 patients (58%) had an unlikely pre-test probability (Wells score ≤4 points), of whom none were diagnosed with PE (0%). Of the patients with a likely clinical probability (Wells score >4 points), 7.9% were diagnosed with PE for a sensitivity of 100% and a specificity of 60%. As for the previous study, follow-up data were not available.

The third study prospectively evaluated whether trimester specific D-dimer level and an unlikely clinical probability by the Wells score would be a safe criterion to rule out PE (23). The trimester specific D-dimer thresholds applied were <0.95 mg/l, <1.29 mg/l and <1.70 mg/l in the first, second and third trimester respectively, derived from unclear historical data (34). The Wells score was calculated at baseline, after which all patients were subjected to diagnostic imaging (either CTPA or VQ-scan), independent of the D-dimer level or pre-test probability. The final diagnosis was based on the imaging test alone. A total of 45 women with suspected PE were included. The median age was 30 years and the majority of them were multiparous. In addition to these, 14 prior patients with an established PE diagnosis of whom D-dimer levels were available were included as well, resulting in a cohort of 59 pregnant patients in total. All women with proven PE had D-dimer level > 0.5mg/L and/or a likely clinical probability, compared with only 11 (26%) of the women in whom PE was ruled out. A total of 55 patients (55/59, 93%) had an unlikely clinical probability, of whom 31 also had a normal D-dimer test result (31/59, 53%). None of these latter patients was diagnosed with PE at baseline, for a sensitivity of 100% (95%CI 80-100). Notably, follow-up data were not available. Although these findings support the hypothesis that a normal D-dimer in combination with an unlikely clinical probability safely rules out acute PE, it needs to be stressed that this was not an outcome study and concerned a limited number of patients. Hence, this study should be regarded as hypothesis generating.

CURRENT STUDIES

Based on a search in international trial registries, two large prospective studies on the subject of optimizing the diagnostic management of suspected PE in pregnant patients are currently running. The Swiss "Ruling Out Pulmonary Embolism During Pregnancy: a Multicenter Outcome Study" evaluates the safety and efficacy of a diagnostic strategy of sequential clinical probability assessment, D-dimer measurement, lower limb compression ultrasonography and multi-slice computed tomography (NCT00771303). The study aims to include 300 pregnant patients with a clinical suspicion of acute PE. Major exclusion criteria include age less than 18 years, absence of informed consent, allergy to contrast medium, impaired renal function (creatinine clearance less than 30 ml/min as estimated by the Cockcroft-Gould formula) and geographic inaccessibility for follow-up. The results of this study are expected in 2016.

The Artemis study is a Dutch-French initiative, that prospectively evaluates the safety and efficacy of the YEARS diagnostic algorithm in pregnant patients (NTR 5913). The YEARS criteria form a simple algorithm consisting of the only three Wells items that significantly added incremental value to the D-dimer test – haemoptysis, signs of deep vein thrombosis and 'PE most likely diagnosis' - in combination with CTPA if necessary (35). In patients without any of the 3 Wells items and a D-dimer level <1.0 mg/l, PE is considered excluded without further testing. In patients with 1 or more of the items, a D-dimer level <0.5 mg/l is required to rule out PE. In all patients with either a D-dimer level of ≥1.0 mg/l or ≥0.5 mg/l in combination with at least one YEARS criterion, CTPA is indicated (**NTR 4193**). The derivation study of this algorithm suggested that this approach is safe -incidence of symptomatic VTE in untreated patients during three months follow-up was 1.9% (24/1295, 95%CI 1.2-2.7%) - and more efficient - absolute reduction in CT-scans of 11%- when compared to the current standard strategy. The sample size of this study is determined to be 445 patients. Major exclusion criteria are i) age <18 years, ii) treatment with therapeutic low molecular weight heparin, unfractionated heparin or other therapeutic anticoagulants, initiated 24 hours or more prior to eligibility assessment, iii) unable to give consent, iv) unable to complete follow-up or life-expectancy < 3 months and v) contraindication to CTPA because of iodine allergy. The study objectives include validation of the clinical utility and safety of the Years-diagnostic algorithm in pregnant patients and the assessment of the percentage of pregnant patients with suspected PE in whom a CTPA is required when adhering to the Years-diagnostic algorithm. The results of the Artemis study are expected in 2018.

WHAT DO THE GUIDELINES RECOMMEND?

Guidelines provide contradicting and low grade recommendations with regard to the role of D-dimer testing and clinical pre-test probability assessment in the diagnostic management of acute PE in pregnancy. Guidelines from the 2014 European Society of Cardiology and the 2016 German Society of Thrombosis and Haemostasis recommend measuring D-dimer levels, stating that normal D-dimer levels do exclude PE in pregnancy (Class IIb, level C recommendation) whereas guidelines from the American Thoracic Society/Society of Thoracic Radiology (2011) and the Royal college of Obstetricians and Gynaecologists (2015) recommend that D-dimer should not be used to exclude PE in pregnancy and physicians should refrain from clinical probability assessment (Class III/IV, level C recommendation) (13, 36, 37).

CONCLUSION

In the setting of suspected PE in pregnant women, a frequent situation, more than ever the diagnosis of PE should be ruled-in or ruled-out. However, the role of clinical probability assessment in the diagnostic management in pregnant patients is uncertain. There is great paucity of studies on clinical decision rules and detailed information on discriminatory factors is missing as well. D-dimer tests with the conventional threshold lack the specificity to be of incremental diagnostic value. Alternative thresholds have been suggested but lack adequate prospective validation in high quality studies with adequate sample sizes using standardized contemporary high-sensitive D-dimer assays. The issues are not only the accuracy of the diagnosis management, primary based on clinical probability and optimized threshold D-dimer, of suspected PE in pregnant women, but also to reduce recourse to irradiative tests. Discrepancies in leading international guidelines emphasize the great need for more studies on this subject, of which two are currently under way. For now, imaging tests remain the cornerstone of evidence based diagnostic management of suspected PE in pregnancy and we recommend not to make use of D-dimer tests or clinical decision rules in this patient category until this approach has been proven safe.

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Chapter 3

Computed tomography pulmonary angiography versus ventilation-perfusion lung scanning for diagnosing pulmonary embolism during pregnancy: a systematic review and meta-analysis

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ABSTRACT

Differences between computed tomography pulmonary angiography and ventilation-perfusion lung scanning in pregnant patients with suspected acute pulmonary embolism are not well-known, leading to ongoing debate on which test to choose. We searched in PubMed, EMBASE, Web of Science and the Cochrane Library databases and identified all relevant articles and abstracts published up to October 1, 2017. We assessed diagnostic efficiency, frequency of non-diagnostic results and maternal and fetal exposure to radiation exposure. We included 13 studies for the diagnostic efficiency analysis, 30 for the analysis of non-diagnostic results and 22 for the radiation exposure analysis. The pooled rate of false negative test results was 0% for both imaging strategies with overlapping confidence intervals. The pooled rates of non-diagnostic results with computed tomography pulmonary angiography and ventilation-perfusion lung scans were 12% (95% confidence interval: 8-17) and 14% (95% confidence interval: 10-18), respectively. Reported maternal and fetal radiation exposure doses were well below the safety threshold, but could not be compared between the two diagnostic methods given the lack of high quality data. Both imaging tests seem equally safe to rule out pulmonary embolism in pregnancy. We found no significant differences in efficiency and radiation exposures between computed tomography pulmonary angiography and ventilation-perfusion lung scanning although direct comparisons were not possible.

INTRODUCTION

Pulmonary embolism (PE) is a major complication of pregnancy and responsible for 2% to 14% of all maternal deaths worldwide (1,2). Although accurate diagnostic tests for PE are essential for this specific population, high quality diagnostic studies are unavailable (3). Clinical decision rules, which are the cornerstone of PE diagnostic management in the non-pregnant population, were not developed for, nor validated in pregnant patients (4). Furthermore, considering the physiological increase of D-dimer levels throughout pregnancy, the optimal D-dimer threshold to rule out PE is unknown (5). The application of D-dimer tests and clinical decision rules as the initial step of the diagnostic algorithm for suspected PE cannot, therefore, be recommended in pregnant patients (3).

Moreover, the optimal choice of imaging test to rule out or confirm acute PE in pregnant patients is highly debated. The two most used imaging tests for suspected acute PE in the non-pregnant population are computed tomography pulmonary angiography (CTPA) and ventilation-perfusion (V-Q) lung scanning, with CTPA being the imaging test of choice because of its high accuracy, wide availability, and ability to exclude other pathologies (6, 7). As is generally the case with V-Q lung scans, the risk of non-diagnostic tests with CTPA is relatively high, in part because of the hemodynamic changes that occur during pregnancy, such as hemodilution and increased heart rate, which make it necessary to have a CTPA protocol specifically designed for pregnant patients. Additionally, elevation of the diaphragm, due to the enlarged uterus, accentuates the interruption of contrast by non-opacified blood from the inferior vena cava and may lead to decreased contrast attenuation in areas of the pulmonary arteries (6). Moreover, both CTPA and V-Q lung scanning involve exposure of the fetus and patients' breasts to radiation. The lack of high quality management studies comparing both imaging tests fuels an ongoing debate in the literature on which of the two options should be preferred.

We set out to perform a systematic review and meta-analysis of published literature to compare the diagnostic efficiency of CTPA versus V-Q lung scans in pregnant patients with suspected acute PE. We also aimed to compare the rate of non-diagnostic scan results and radiation exposure for both the mother and fetus.

METHODS

Search strategy

For this meta-analysis, we conducted a search for all relevant full publications in PubMed, EMBASE, Web of Science and the Cochrane Library databases. We searched EMBASE, Web of Science and the Cochrane library databases for relevant meeting-abstracts as well. The complete search strategy is detailed in Online Supplementary Appendix A.

Selection of studies

Search results were combined and duplicates were removed. Studies were screened for relevance by two independent reviewers (CT and LvdP) following a specific three-step program and applying Covidence software (www.covidence.org). Disagreements were resolved by a third investigator (FK) by majority rule. The first and second steps consisted of title and abstract screening followed by full text screening for the remaining articles. The final selection of the studies to include in the meta-analysis was based on assessment of relevance and study quality. The assessment of relevance was based on the following criteria: (i) prospective patient inclusion, (ii) inclusion of consecutive patients, (iii) reported rate of non-diagnostic test results, and (iv) reported incidence of PE at baseline. The assessment of bias was evaluated in accordance with the PRISMA criteria (8): (i) pre-specified study protocol, (ii) clear description of inclusion and exclusion criteria, (iii) inclusion of consecutive patients, (iv) objective diagnosis of PE, (v) reported losses to follow-up, (vi) clear distinction between pregnant and post-partum patients, and (vii) assessment of the primary endpoints in all patients. Studies were included in the meta-analyses according to the definition of each endpoint.

The final step was data extraction. For each included study, we extracted the first author's name and year of publication, study design (prospective or retrospective), setting of the study (single- or multicenter), number of patients in the index cohort, the baseline incidence of PE, the duration of follow up, and the predefined study endpoints.

Study outcomes and definitions

We predefined three major study endpoints. The first was the diagnostic efficiency of both imaging tests as expressed by the number of false negative scans. This first outcome required a follow up of at least 3 months as well as reporting of the number of diagnosed PE events during this follow up. The second endpoint was the rate of non-diagnostic results with CTPA and V-Q lung scans. For CTPA, scan results were defined non-diagnostic when the radiologist was unable to confirm or exclude the diagnosis of PE, usually because of suboptimal contrast opacification and respiratory motion artifacts, or the need for an additional imaging test. For V-Q lung scanning, the definition of non-diagnostic results was based on the PIOPED criteria, i.e. intermediate and low probability scan results, since these require an additional diagnostic test to confirm or rule out PE with sufficient certainty. The third endpoint was fetal and maternal radiation exposure due to CTPA and V-Q lung scanning. The CTPA radiation exposure was collected for studies in real-life patients as well as with anthropometric phantom models simulating a gravid woman.

Statistical analysis

The baseline incidence of PE and rate of false negative scans were calculated with corresponding 95% confidence intervals (95% CI). The number of non-diagnostic results from all studies was collected and the rate of non-diagnostic results was calculated using the number of non-diagnostic tests divided by the number of patients in each study. We applied a random effects

model according to DerSimonian and Laird for the calculation of the pooled rates of the four study endpoints (9). We predefined that we would not undertake data pooling in case studies for any of the three endpoints because they were not comparable due to extensive differences in study design or imaging protocols, which do not allow for reliable statistics or data pooling. Heterogeneity across the various cohort studies was assessed by calculating the I^2 statistic. Heterogeneity was defined as low when I^2 was <25%, intermediate when I^2 was 25-75% and high when I^2 was >75% (10). All analyses were performed in Stata 14.0 (Stata Corp., College Station, TX, USA).

RESULTS

Study selection

The initial search identified 303 records in PubMed, 318 articles in EMBASE, 76 articles in Web of Science, and three articles in the Cochrane Library. After a first screening of titles and abstracts, 565 articles were excluded. A further 78 articles were excluded based on the predefined inclusion criteria (Figure 1): 20 studies did not report the study outcomes of interest, two articles concerned thyroid function after CTPA, five articles involved surveys about clinical practice, two articles were duplicates, four were guidelines, five were letters to the editor and

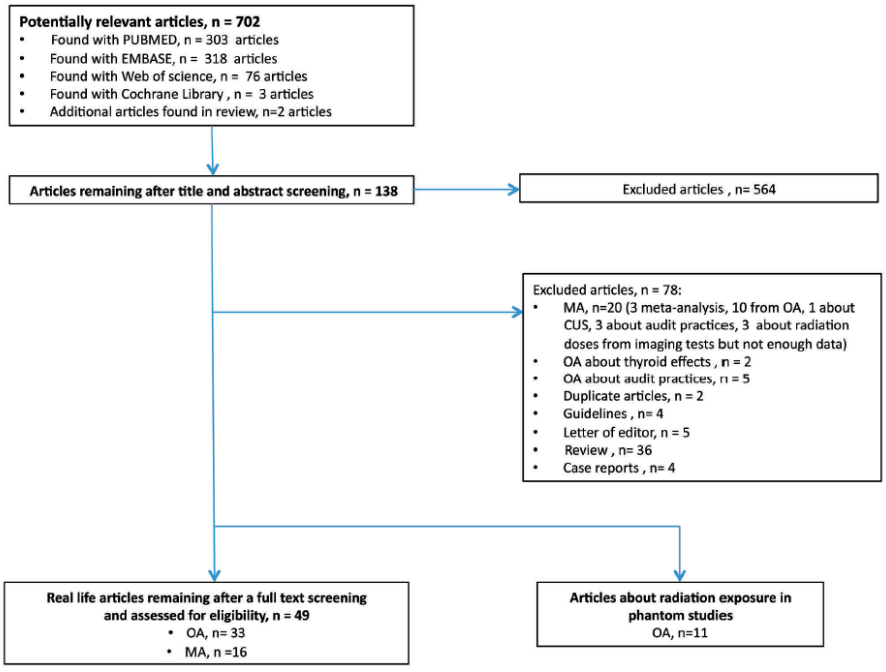

Figure 1. Flow chart of the systematic review. MA: meeting abstract; OA: original article; CUS: compression ultrasonography.

Table 1: Assessment of relevance and bias of the included studies

	Assessment of relevance						Assessment of bias					Study included		
Article	Sample size	Prospective study	Cohort of consecutive patients	Multicentre	Non diagnostic results reported	PE incidence reported	Follow up	Complete follow up <5%	Representative population	Quality of PE diagnosis (according to the guidelines)	Overall risk of bias Bias in a certain direction?	False negative tests	Non diagnostic imaging test	Radiation exposure
Andreou et al.2008	16	🔴	🟢	🔴	🔴	🟢	🔴	🔴	🟢	🟡	🔴	🔴	🔴	🔴
Bourjeily et al. 2012	343	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🔴
Browne et al.2014	70	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢
Jordan et al.2015	34	🔴	🟢	🔴	🟡	🟢	🔴	🔴	🟡	🟢	🔴	🔴	🔴	🟢
King-Im et al. 2008	40	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Moradi et al. 2015	27	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Shahir et al.2015	36	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Litmanovitch et al.2009	26	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢
Ridge et al.2011	45	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Abujudeh et al.2009	14	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🔴	🟢	🔴	🔴	🔴	🔴
Ridge et al.2009	50	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🔴	🟢	🔴
Moriarty et al. 2015	100	🔴	🟢	🔴	🔴	🟢	🟡	🔴	🟢	🟢	🔴	🔴	🔴	🔴
Balan et al.1997	82	🔴	🟢	🔴	🟢	🟢	🟡	🟢	🟢	🟢	🟡	🟢	🟢	🔴
Sellem et al.2013	116	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Chan et al. 2002	120	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🔴	🟡	🟢	🟢	🔴
Angulo et al.2004	30	🔴	🟢	🔴	🔴	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Cutts et al.2014	183	🔴	🟢	🟢	🟢	🟢	🟡	🔴	🔴	🟢	🔴	🟢	🟢	🔴
Bajc et al. 2015	127	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🔴	🟢	🔴
Richard et al.2015	77	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Cahill et al.2009	199	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟡	🟢	🔴	🔴	🔴	🔴
Scarsbook et al. 2007	105	🔴	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🔴
Scott et al.2011	375	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Shahir et al.2010	199	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴
Revel et al.2011	128	🔴	🟢	🔴	🟢	🟢	🟢	🔴	🟢	🟢	🟡	🟢	🟢	🟢
Abele et al. 2013	74	🔴	🟢	🟢	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴
Astani et al. 2014	53	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Sheen et al. 2017	322	🔴	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴
Yeo et al. 2017	7	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🔴

Table 1: Assessment of relevance and bias of the included studies (continued)

	Assessment of relevance						Assessment of bias					Study included		
Article	Sample size	Prospective study	Cohort of consecutive patients	Multicentre	Non diagnostic results reported	PE incidence reported	Follow up	Complete follow up <5%	Representative population	Quality of PE diagnosis (according to the guidelines)	Overall risk of bias Bias in a certain direction?	False negative tests	Non diagnostic imaging test	Radiation exposure
Halpenny et al. 2017	204	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Mitchell et al. 2017	99	🔴	🔴	🟢	🟡	🟡	🔴	🔴	🟢	🟢	🔴	🔴	🟢	🟢
Golfman et al. 2017	362	🔴	🟢	🔴	🟢	🟢	🟢	🟡	🟢	🟢	🟡	🟢	🟢	🔴
Armstrong et al. 2017	991	🔴	🟢	🟢	🟢	🟢	🔴	🔴	🟢	🟢	🟡	🔴	🟢	🟢
Hamilton et al. 2016 *	210	🔴		🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Ramsay et al.2015	127	🔴	🟢	🔴	🟢	🟢	🔴	🔴	🔴	🟢	🔴	🔴	🟢	🔴
Gruning et al.2016	168	🔴	🟢	🔴	🟡	🟡	🔴	🔴	🟢	🟢	🔴	🔴	🔴	🔴
Edwards et al. 2012 *	125	🔴	🟢	🔴	🟢	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Ma et al. 2014*	137	🔴	🟢	🔴	🟢	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Slim et al. 2012*	105	🔴	🟢	🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Bowlen et al. 2011*	82	🔴	🟢	🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Ezwawah et al. 2008*	21	🔴	🟢	🔴	🟡	🔴	🟢	🟡	🟡	🟡	🔴	🟢	🔴	🔴
Hufton et al. 2015*	55	🔴	🟢	🔴	🔴	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Hullah et al. 2011*	46	🔴	🟢	🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Ma et al. 2015*	324	🔴	🟢	🔴	🔴	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Butt et al. 2011*	105	🔴	🟢	🔴	🟡	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Vanes et al. 2014*	99	🔴	🟢	🔴	🔴	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴
Tomas et al.2013*	75	🔴	🟢	🔴	🟢	🟢	🟡	🟡	🟡	🟡	🔴	🔴	🟢	🔴
Nijkeuter et al. 2013*	149	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢	🟢	🔴
Potton et al. 2009*	34	🔴	🟢	🔴	🟢	🔴	🟡	🟡	🟡	🟡	🔴	🔴	🟢	🔴
Roseverne et al. 2011*	27	🔴	🟡	🔴	🔴	🔴	🟡	🟡	🟡	🟡	🔴	🔴	🔴	🔴

🟡 unknown or unclear
🔴 no
🟢 yes

Follow up
🟡 follow up not indicated/ follow up <3months
🔴 no follow up
🟢 follow up of at least 3 months with results

Representative population: patient selection
🟡 no distinction between post-partum and pregnant patient
🔴 not pregnant patient
🟢 pregnant patient with suspicion of PE clearly identified

Overall risk of bias
🟢 low risk
🟡 moderate risk
🔴 high risk

*Abstract

did not report the outcomes of interest, 37 were review articles and four were irrelevant case reports. Two additional relevant articles were identified after reviewing the references lists of the selected studies. A final 49 evidence-based studies were fully assessed for study quality (6, 7, 11-57) (Table 1): 13 were included in the analysis of false negative scans (7, 14-17, 20, 33, 35, 37, 45, 51, 53, 55) (Table 2), 30 were included in the analysis of non-diagnostic results (7, 14-17, 19-21, 23-29, 32-37, 45, 46, 49, 52-57) (Table 3), and 11 were included in the radiation exposure analysis (16, 18, 20, 21, 24, 28, 33, 34, 52, 54, 57) (Table 4). Finally, 11 studies involving anthropometric phantoms simulating pregnancy were also included (58-68) (Table 5).

First study endpoint: diagnostic accuracy

A total of 13 relevant studies were selected to study the rate of false negative CTPA and V-Q lung scan examinations (7, 14-17, 20, 33, 35, 37, 45, 51, 53, 55). These studies were published between 1997 (14) and 2017 (53, 55), and involved a total of 1270 patients investigated with V-Q lung scanning and 837 patients investigated with CTPA (Table 2). Data were extracted from ten full text articles (7, 14-17, 20, 33, 35, 37, 55) and three meeting abstracts (45, 51, 53). Only one of these 13 studies was a prospective study in 143 patients investigated with CTPA (45). The prevalence of PE ranged between 0% (20) and 22.2% (35), with the highest prevalences in the few smaller studies (median 4.1%). The duration of follow up varied from at least 3 months to 24 months (35). In two studies, the total duration of follow up was not reported (14, 17). None of the 1270 patients investigated with V-Q lung scanning was diagnosed with recurrent PE or deep vein thrombosis (DVT) during follow up, resulting in a pooled number of false negative scans of 0% (95% CI: 0-0.04; I^2=0.0). Three of 837 patients were diagnosed with non-fatal PE after a normal initial CTPA, for a pooled number of false negative scans of 0.0% (95% CI: 0.0-0.16; I^2=5.7) in the CTPA group (Figure 2). The risk of bias was high in two studies (17, 51), moderate in nine studies (7, 14-16, 20, 33, 35, 45, 53) and low in only two studies (37, 55) (Table 1).

Second study endpoint: non-diagnostic results

A total of 30 relevant studies were selected to evaluate the rate of non-diagnostic or inconclusive results of V-Q lung scans or CTPA (7, 14-17, 19-21, 23-29, 32-37, 45, 46, 49, 52-57). These studies involved a total of 2535 patients investigated with V-Q lung scanning and 1774 patients assessed by CTPA (Table 3). The rate of non-diagnostic results with V-Q lung scanning ranged from 1.3% (36) to 40% (14) whereas the rate of non-diagnostic results with CTPA ranged from 0% (19) to 57.1% (23, 56). The rate of additional imaging tests after a first non-diagnostic V-Q lung scan ranged from 14%[37] to 100% (23, 27) whereas it ranged from 0% (35) to 62% (15) after a first non-diagnostic CTPA. The pooled rates of non-diagnostic test results with V-Q lung scanning and with CTPA were 14% (95% CI: 10-18, I^2=90.30%) and 12% (95% CI: 6-17, I^2=93.86%), respectively. The 95% confidence intervals of the non-diagnostic rate values overlap (Figure 3). The risk of bias was high in 16 studies (17, 19, 21, 24-28, 32, 34, 36, 46, 49, 54, 56, 57), moderate in 12 studies(7, 14-16, 20, 23, 29, 33, 35, 45, 52, 53) and low in only two studies (37, 55) (Table 1).

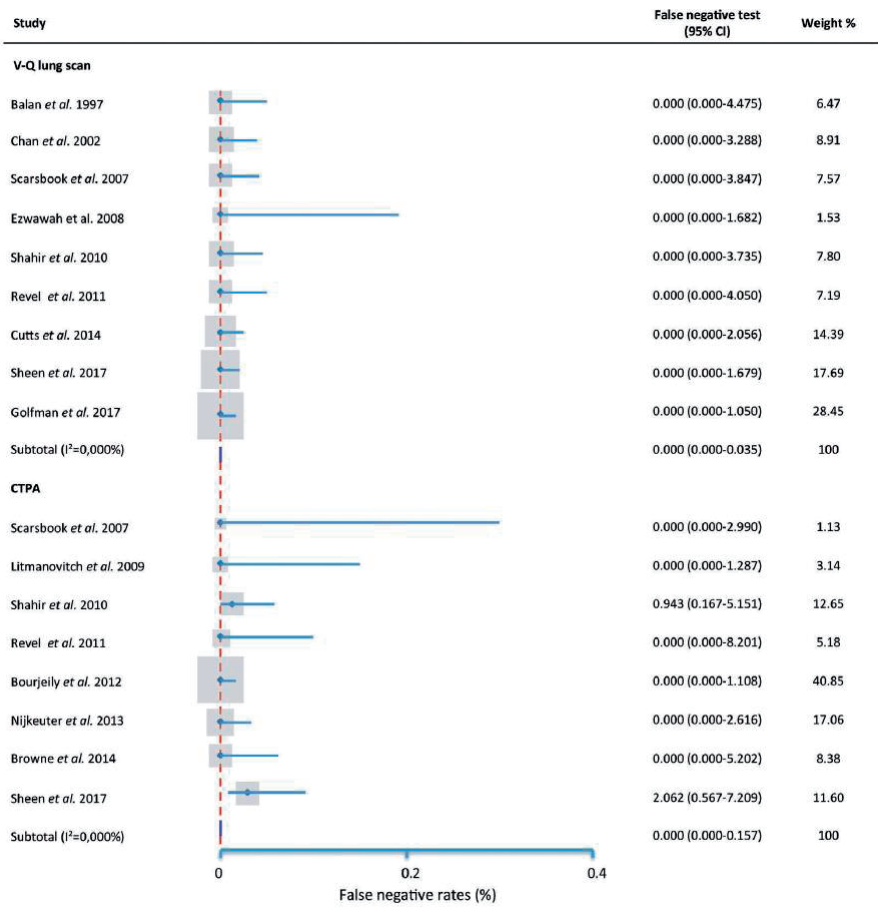

Figure 2. Meta-analysis of false negative tests after a first negative ventilation-perfusion lung scan and computed tomography pulmonary angiography in pregnant patients with suspected acute pulmonary embolism. A false negative test is defined by a first negative computed tomography pulmonary angiography (CTPA) or ventilation-perfusion (V-Q) lung scan in a woman who had a pulmonary embolism (PE) diagnosed during the 3 months of follow-up. Three patients had a PE during the follow up.[37,55] The type of imaging test performed to diagnose the PE was not provided.

Third study endpoint: radiation exposure

Eleven clinically based studies were selected to compare radiation exposure during CTPA and V-Q lung scanning (16, 18, 20, 21, 24, 28, 33, 34, 52, 54, 57). The mean maternal effective dose ranged from 0.9 to 5.85 milliSievert (mSv) with V-Q lung scanning and from 0.23 to 9.7 mSv with CTPA (Table 4). The fetal/uterus absorbed dose ranged from 0.2 to 0.7 milliGray (mGy) with V-Q lung scanning and from 0.002 to 0.51 mGy with CTPA (28). Direct comparisons between V-Q lung scanning and CTPA were not possible because of variations in the imaging protocols used and the methods of measuring or calculating radiation exposure. The dose-length product (DLP) was available in four studies (16, 20, 21, 57): it ranged from 69.34±10.95

Table 2: Analysis of rate of false negative test results after V-Q lung scan and CTPA

Study	Number of patients subjected to imaging test (n)	Baseline PE-prevalence	Number of true negative test (n)	Number of VTE during follow-up (n)	NPV (%), CI 95%	Duration of follow-up (months)
V-Q lung scan						
Balan et al. 1997	82	22% (18/82)	31	0	100, (88.97-100)	NP
Chan et al. 2002	113	7.1% (8/113)	83	0	100, (95.58-100)	6
Scarsbook et al. 2007*	96	1.0% (1/96)	89	0	100, (95.86-100)	24.5
Ezwawah et al. 2008	19	NP	19	0	100, (83.18-100)	3
Shahir et al. 2010**	99	1% (1/99)	77	0	100, (95.25-100)	3
Revel et al. 2011	91	11% (10/91)	64	0	100, (94.34-100)	3
Cutts et al. 2014	183	2.2% (4/183)	173	0	100, (97.83-100)	NP
Sheen et al. 2017	225	2.7% (6/225)	198	0	100 (98.10-100)	3
Golfam et al. 2017	362	4.7% (17/363)	316	0	100 (98.95-100)	3
CTPA						
Scarsbook et al. 2007	9	22.2% (2/9)	6	0	100, (60.97-100)	24.5
Litmanovitch et al. 2009	26	0% (0/26)	26	0	100, (87.13-100)	18
Shahir et al. 2010	106	3.7% (4/106)	95	1	98.96, (94.33-99.82)	3
Revel et al. 2011	43	16% (7/43)	28	0	100, (87.94-100)	3
Bourjeily et al. 2012	343	2.6% (9/343)	335	0	100, (98.86-100)	3 months or 6 weeks postpartum
Browne et al. 2014	70	1.4% (1/70)	69	0	100, (94.73-100)	6
Nijkeuter et al. 2013	143	4.2% (6/143)	129	0	100, (97.11-100)	3
Sheen et al. 2017	97	4.1% (4/97)	84	2	97.94, (99.43-92.79)	3

Abbreviations PE: pulmonary embolism; VTE: venous thromboembolism; NPV: Negative Predictive Value; CI: confidence intervals; NP: not provided; V-Q scan: ventilation perfusion scan; CTPA: computed tomography pulmonary angiography; *one PE was diagnosed after 3 months of follow-up. **very low PE probability V-Q lung scans are considered as normal V-Q lung scans

mGy/cm (57) to 397.54±100.4 mGy/cm (16). Because of the large differences in the applied, mostly unstandardized CTPA protocols among these studies, we refrained from data pooling.

A total of 11 relevant studies assessing CTPA radiation exposure in female phantoms showed that the mean maternal effective dose ranged from 2.5 mSv (58) to 4.9 mSv (59) (Table 5). The fetal/uterus absorbed dose ranged from 0.003 mGy (66) to 0.73 mGy (67). These results from the phantom studies should be interpreted with caution and may not be directly extrapolated to clinical practice because of the wide variations in scan techniques and methods of measuring and/or calculating the radiation exposure. No phantom studies with V-Q lung scanning were available.

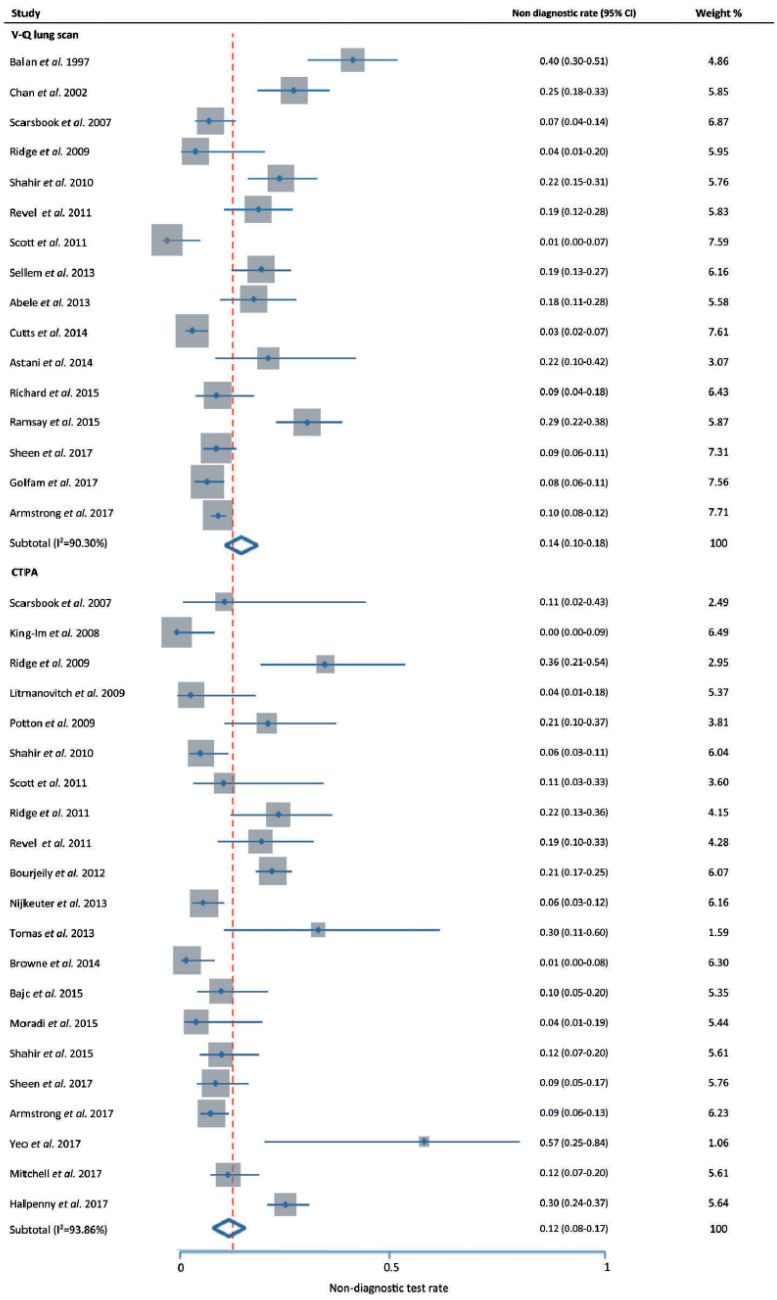

Figure 3. Meta-analysis of non-diagnostic results of ventilation-perfusion lung scanning and computed tomography pulmonary angiography in pregnant patients with suspected acute pulmonary embolism. The number and type of additional imaging tests are provided in Table 3. V-Q: ventilation-perfusion; CTPA: computed tomography pulmonary angiography

Table 3: Analysis of rate of non-diagnostic test results of V-Q lung scan and CTPA

Study	Number of patients subjected to imaging test (n)	Non diagnostic imaging test (n)	Non diagnostic imaging test (%)	Additional Imaging tests in case of first non-diagnostic tests N (%)	Additional imaging test	Additional imaging test confirming PE (n)	Additional imaging test excluding PE (n)	Non conclusive additional imaging test (n)	Anticoagulation despite non diagnostic results
V-Q lung scan*									
Balan et al. 1997	82	33	40	NP	NP	NP	NP	NP	12
Chan et al. 2002	113	28	24,8	NP	NP	NP	NP	NP	4
Scarsbook et al. 2007	96	7	7.3	2 (29)	CTPA	0	2	0	0
Ridge et al. 2009	25	1	4	1 (100)	CTPA	NP	NP	NP	NP
Shahir et al. 2010 **	99	22	21	3 (14)	CTPA	1	2	0	NP
Revel et al. 2011	91	17	18.7	NP	NP	NP	NP	NP	NP
Scott et al. 2011	73	1	1.3	NP	NP	NP	NP	NP	NP
Sellem et al. 2013	116	22	18.9	NP	NP	NP	NP	NP	NP
Abele et al. 2013‡	74	13	16.2	13 (100)	CTPA	1	9	3	NP
Astani et al. 2014 **	23	5	21.7	NA	NA	NA	NA	NA	NA
Cutts et al. 2014†	183	6	3.3	2 (33)	CTPA	0	0	2	2
Ramsay et al. 2015†	127	37	29.1	19 (51)	CTPA	1	8	10	4
Richard et al. 2015	77	7	9	1	CTPA	0	0	0	2
Sheen et al. 2017	225	21	9.3	9 (43)	CTPA	2	5	2	NP
Golfam et al. 2017	362	29	8	NP	NP	NP	NP	NP	NP
Armstrong et al. 2017	769	74	9.1	NP	NP	NP	NP	NP	NP
CTPA									
Scarsbook et al. 2007	9	1	11	0 (0)	NA	NA	NA	NA	NP
King-Im et al. 2008	40	0	0	NP	NP	NP	NP	NP	NP
Ridge et al. 2009	28	10	35.7	5 (50)	3 CTPA 2 V-Q lung scan	1 (V-Q lung scan)	1 (CTPA) 1 (V-Q lung scan)	2 (CTPA)	NP
Bourjeily et al. 2012	343	71	20.7	44 (62)	5 CUS+V-Q lung scan or CTPA 39 CUS alone	1 (CUS)	NP	NP	NP
Browne et al. 2014	70	1	1.4	NP	NP	NP	NP	NP	NP
Moradi et al. 2015	27	1	3.7	NP	NP	NP	NP	NP	NP
Shahir et al. 2015	95	11	11.5	NP	NP	NP	NP	NP	NP
Ridge et al. 2011	45	10	21.7	5 (50)	3 CTPA 2 V-Q lung scan	1 (V-Q lung scan)	1 (CTPA) 1(V-Q lung scan)	2 (CTPA)	NP
Bajc et al. 2015	61	6	9.8	1 (17)	CTPA	0	0	1	NP
Scott et al. 2011	18	2	11.1	NP	NP	NP	NP	NP	NP
Shahir et al. 2010	106	6	5.7	3 (50)	Q lung scan	0	3	0	0

Table 3: Analysis of rate of non-diagnostic test results of V-Q lung scan and CTPA (continued)

Study	Number of patients subjected to imaging test (n)	Non diagnostic imaging test (n)	Non diagnostic imaging test (%)	Additional Imaging tests in case of first non-diagnostic tests N (%)	Additional imaging test	Additional imaging test confirming PE (n)	Additional imaging test excluding PE (n)	Non conclusive additional imaging test (n)	Anticoagulation despite non diagnostic results
Revel et al. 2011	43	8	18.6	3 (37.5)	CTPA	0	2	1	NP
Nijkeuter et al. 2013	143	8	5.5	NP	NP	NP	NP	NP	1
Tomas et al. 2013	10	3	30	NP	NP	NP	NP	NP	NP
Litmanovitch et al. 2009	26	1	3.8	NP	NP	NP	NP	NP	NP
Potton et al. 2009	34	7	20	4 (57)	NP	NP	NP	NP	NP
Sheen et al. 2017	97	9	9.3	3 (33)	Q lung scan	0	2	1	NP
Armstrong et al. 2017	269	23	8.9	NP	NP	NP	NP	NP	NP
Yeo et al. 2017	7	4	57.1	NP	NP	NP	NP	NP	NP
Mitchell et al.2017	99	12	12	NP	NP	NP	NP	NP	NP
Halpenny et al. 2017	204	62	30.4	NP	NP	NP	NP	NP	NP

Abbreviatons CTPA: computed tomography pulmonary angiography; V-Q scan: ventilation perfusion scan; NP: not provided; NA: not applicable; PE: pulmonary embolism; CUS: compression ultrasonography; * Non diagnostic V-Q lung scans are defined by intermediate and low probability scan results. † 89 low probability V-Q scans are considered as normal V-Q lung scans ‡ non diagnostic V-Q scans are defined as abnormal perfusion scans ** very low PE probability V-Q lung scans are considered as normal V-Q lung scans

DISCUSSION

Our systematic review and meta-analysis provides an overview of all published literature on diagnostic accuracy, scan efficiency and radiation exposure dose of V-Q lung scans versus CTPA in pregnant patients with suspected acute PE. The negative predictive value and rates of non-diagnostic tests were comparable between V-Q lung scans and CTPA, although significant heterogeneity, overall high risk of bias and absence of direct comparisons prevent definite conclusions. Moreover and importantly, studies included in the meta-analysis are mostly outdated and none of the available studies evaluated state-of-the-art imaging techniques as currently used in clinical practice. Maternal and fetal radiation exposure with CTPA and V-Q lung scanning could not be compared because of lack of homogeneity in radiation calculation methods and large differences between the scan protocols used. However, all reported radiation measurements for both imaging techniques were clearly below the established harmful threshold of 100 mGy (69).

The pooled failure rate for both imaging modalities was negligible, suggesting that both CTPA and V-Q lung scanning can equally safely exclude PE during pregnancy. Our findings are concordant with those recently reported (70). Indeed, in the Cochrane review including 11

Table 4: Overview of studies on radiation exposure by CTPA or V-Q lung scan in real life patients

Radiation exposure : Real life studies														
			CTPA radiation exposure				V-Q lung scanning radiation exposure								
							Q lung scanning				V-Q lung scanning				Dose Length Product
Study	Number of imaging test		1st	2nd	3rd	Average	1st	2nd	3rd	Average	1st	2nd	3rd	Average	(DLP) mGy/cm
Browne et al. 2014	70 CTPA		7.15mSv*				NP								397.54±100.4
Jordan et al. 20151	34 CTPA		9.0 mSv	9.5 mSv	9.7 mSv	9.4 mSv	NP								NP
Moradi et al. 2015	27 CTPA		5.46mSv*				NP								303.55±98.74
Ridge et al. 20112	28 CTPA		4.8mSv**				NP								NP
	20 CTPA		5.6mSV**				NP								NP
Richard et al. 2015	77 V-Q lung scanning	Mean Maternal Effective dose mSv****	NP				2.18				5.82				NP
		Breast absorbed dose mGy					0.27				1.24				NP
		Fetal absorbed dose mGy					0.19	0.24	0.19	0.21	0.81	0.76	0.7	0.76	NP
Astani et al. 2014	23 V-Q lung scanning 30 CTPA	Maternal effective dose mSV****	21.07	21.26	20.74	21.02	1.04	1.00	1.07	1.04	1.22	1.32	1.34	1.29	NP
		Breast-absorbed dose mGy	43.36	43.14	46.55	44.35	0.28	0.27	0.29	0.28	0.35	0.37	0.39	0.37	NP
		Uterus/fetal-absorbed dose mGy	0.47	0.51	0.38	0.46	0.24	0.27	0.24	0.25	0.40	0.42	0.38	0.40	NP
Revel et al. 2011	94 V-Q lung scan 46 CTPA	Mean maternal effective radiation dose mSv	7.3mSv*				0.9mSv†								NP
Litmanovicth et al. 2009	26 CTPA	Mean maternal effective radiation dose mSv	1.79mSv				NP								105.65±39.77
Armstrong et al. 2017	769 V-Q lung scan 269 CTPA	Breast-absorbed dose mGy	2-14				0.28								NP
		Uterus/ Fetal-absorbed dose mGy	0.002-0.02				0.2								NP
Mitchell et al. 2017	84 CTPA 120 kV	Mean maternal effective dose mSv	0.23				NP								NP
		Breast-absorbed dose mGy	2.24												NP
	15 CTPA 80kV	Mean maternal effective dose mSv	0.04												NP
		Breast-absorbed dose mGy	0.25												NP
Halpenny et al. 2017	69A	Mean effective dose mSv	1.66				NP								118.48±20.05
	135B	Mean effective dose mSv	0.97				NP								69.34±10.95

Note: CTPA: computed tomography pulmonary angiography; V-Q scanning: ventilation-perfusion lung scanning; Q: perfusion; NP: not provided; *DLP :dose length product (image noise) ; mSv =DLP mGy/cm *0.018(standard conversion); ** The mean effective dose per patient; †88 MBq*11 * 10 - 3 ; each injected megabecquerel represents an effective dose of 11 *10 -3 mSv; 1 Average radiation exposure in milliSieverts (k=18 μSv/mGy cm), Radiation dose in pregnant patient; 2 Two different CTPA protocols are assessed; **** dose calculation method not provided

Table 5: Overview of studies on radiation exposure by CTPA or V-Q lung scan in phantom studies

Phantom studies with CTPA							
		Foetal/uterus absorbed dose (mGy)			**Maternal effective dose (mSv)**		
Study		**1st trimester**	**2nd trimester**	**3rd trimester**	**1st trimester**	**2nd trimester**	**3rd trimester**
Chatterson et al. 2014	100kVp	0.05	NP	0.13	2.5		
Chatterson et al. 2011	100kVp	0.11	0.3	0.5	4.9		
Doshi et al. 2008	100kVp	0.06*			NP		
	120kVp**	0.10-0.23*			NP		
Hurwitz et al. 2006	140kVp	0.024-0.07	NP	NP	NP		
Litmanovitch et al. 2011	100kVp	0.084*			NP		
	120kVp‡	0.023-0.140*			NP		
Winer-Muran et al. 2002 ***	120kVp	0.003-0.020	0.008-0.077	0.051-0.131	NP		
Perisinakis et al. 2014 ***	100kVp	NP	NP	NP	NP	NP	NP
	120kVp	NP	NP	NP	NP	NP	NP
Iball et al. 2008	NA	NA	NA	NA	NA	NA	NA
Kennedy et al.2007	NA	NA	NA	NA	NA	NA	NA
Motavalli et al. 2017***	80 kVp	< 0.01	<0.02	0.04	NP	NP	NP
	100kVp	0.02	0.08	0.18	NP	NP	NP
	120kVp	0.09	0.2	0.47	NP	NP	NP
Isodoro et al. 2017	100kVp	0.28	0.73	0.57	NP	NP	NP

Abbreviations: CTPA: computed tomography pulmonary angiography; kVp: kilovolt protocol; NP: not provided; NA: not applicable; *mean fetal absorbed dose;** two different CTPA protocols with 120kV are assessed; ‡ three different CTPA protocols with 120kV are assessed; *** Monte Carlo simulation

studies with 695 CTPA and 665 V-Q lung scan results, the median negative predictive value for both imaging techniques was 100% (70). The very high negative predictive values need to be interpreted on the background of the very low prevalence of PE, which varied between 1% and 7% in the studies evaluated, implying a very low post-test probability of PE even with less than optimal sensitivity of a diagnostic test (71). Only if current active trials confirm the safety of using the clinical decision rule and a D-dimer test to select patients with a higher pre-test probability of PE, could the diagnostic safety of CTPA and VQ-lung scanning be better tested and compared (3, 72). Notably, increasing the level of suspicion of PE with a specific strategy during pregnancy may lead to a lower negative predictive value of both CTPA and V-Q lung scanning.

It has been widely acknowledged that, in contrast to CTPA, the risk of a non-diagnostic test result with V-Q lung scanning is considerable. Importantly, we found that the pooled risks of a non-diagnostic test for both imaging tests in the setting of pregnant patients with suspected PE were comparable. These pooled risks need to be put in perspective. For CTPA, a non-conclusive result was defined as suboptimal contrast opacification and respiratory motion artifacts that did not allow for a certain inclusion or exclusion of PE. For V-Q lung scanning, we defined non-diagnostic or inconclusive results according to the PIOPED criteria as intermediate and low

probability scan results (73). We found considerably higher rates of non-diagnostic results with CTPA and V-Q lung scanning than those reported in a recent Cochrane review (70). Notably, the definition of non-diagnostic tests was not provided in the Cochrane review and, based on our results, was probably underestimated. Indeed, most of the retrospective studies included in the Cochrane review used intermediate probability V-Q lung scan results as the definition of non-diagnostic results and low probability scans as normal scans whereas we classified low and intermediate probability scan results as non-conclusive. Importantly, clinical probability assessed by clinical judgement or a validated prediction rule is essential for the correct interpretation of a V-Q lung scan: a non-diagnostic V-Q lung scan may exclude PE when combined with negative proximal compression ultrasound sonography in patients with a low clinical probability of PE (73). Compression ultrasound sonography may also be helpful when combined with an intermediate V-Q lung scan probability to confirm or rule out acute PE. Unfortunately, such information was not provided by the studies identified. Therefore, the rate of non-diagnostic V-Q lung scans in our analysis may be biased towards overestimation. Again, the lack of direct comparisons and studies evaluating state-of-the art imaging protocols does not allow for definite conclusions. Of note, we cannot rule out the potential bias that while standard V-Q scan reporting involves a statement on non-diagnostic results, this is not the case for CTPA.

It is generally known that CTPA results in relatively higher maternal radiation exposure but lower fetal absorbed doses than V-Q lung scanning. Importantly, most of the radiation exposures reported in the literature were not measured directly but were calculated and, therefore, fully dependent on the scan techniques used, which were largely outdated compared to the ones currently used. The higher breast radiation exposure with CTPA partly explains the recommendation of V-Q lung scans by international guidelines for pregnant patients with suspected PE. The Society of Thoracic Radiology clinical practice guidelines have presented comparable radiation exposure doses to our findings (74). However, since the studies in our review did not provide all imaging protocol details or full disclosure of the mathematical formulas used, the reported radiation doses in Table 5 are neither comparable between studies nor reproducible. Moreover, mathematical body phantoms (Monte Carlo simulation) of pregnant patients were used instead of realistic physical phantoms in three of the CTPA phantom studies (65, 66, 68). The presented radiation exposure doses in both phantom and human studies should therefore be interpreted with great caution. Moreover, the risk of early breast cancer seems similar after VQ lung scanning and CTPA (75).

STATE-OF-THE-ART IMAGING TECHNIQUES

For the diagnosis of acute PE, accuracy and pulmonary arterial opacification are significantly improved by optimizing the CTPA protocol for the pregnant patient. This optimization includes a high flow rate (6 instead of 4 mL/s), a high volume (an approximately 25%

increase) followed by saline flush, a high concentration of contrast medium (370 mg I/mL), and shallow held inspiration (to avoid the Valsalva maneuver) (24). In the Leiden University Medical Center, the contrast volume and speed are titrated according to the patient's weight. Advised measures to reduce radiation dose include using a 100 kV protocol (76) and reduced z-axis technique with limited scan volume from just above the aorta to the basal lung fields (excluding the upper and lower marginal zones) (77). For the diagnosis of acute PE with lung scintigraphy in pregnancy, a two-step protocol is suggested to minimize radiation. Initially, perfusion-only scintigraphy should be performed using a reduced dose of ^{99m}Tc-MAA (approximately a quarter of the usual dose administrated for a one-step V/Q scan). Because of the low frequency of co-morbid pulmonary disorders, PE can be excluded in most cases on the basis of a normal perfusion pattern. Ventilation images should only be performed in the case of abnormal perfusion images.

CONCLUSION

Based on the available data, direct comparisons of safety and efficiency between CTPA and V-Q lung scanning do not seem valid. The available studies are based mostly on techniques that are outdated with regard to the current and presently evolving techniques, for both CTPA and V-Q lung scanning. Our most important finding appears to be the very low rate of false negative test results for both imaging modalities, although the low disease prevalence among the studies prevents a solid evaluation of the sensitivity. Moreover, radiation doses associated with CTPA and V-Q lung scanning are well below the safety threshold. Depending on new developments and insights of pending studies, decisions regarding the imaging modality of choice should be based on local availability of techniques combined with use of optimal scan protocols tailored to the pregnant patient.

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Chapter 4

Diagnostic Management of Suspected Pulmonary Embolism During Pregnancy

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ABSTRACT

Background

Pulmonary embolism is one of the leading causes of maternal death in the Western world. Because of the low specificity and sensitivity of the d-dimer test, all pregnant women with suspected pulmonary embolism undergo computed tomographic (CT) pulmonary angiography or ventilation–perfusion scanning, both of which involve radiation exposure to the mother and fetus. Whether a pregnancy-adapted algorithm could be used to safely avoid diagnostic imaging in pregnant women with suspected pulmonary embolism is unknown.

Methods

In a prospective study involving pregnant women with suspected pulmonary embolism, we assessed three criteria from the YEARS algorithm (clinical signs of deep-vein thrombosis, hemoptysis, and pulmonary embolism as the most likely diagnosis) and measured the d-dimer level. Pulmonary embolism was ruled out if none of the three criteria were met and the d-dimer level was less than 1000 ng per milliliter or if one or more of the three criteria were met and the d-dimer level was less than 500 ng per milliliter. Adaptation of the YEARS algorithm for pregnant women involved compression ultrasonography for women with symptoms of deep-vein thrombosis; if the results were positive (i.e., a clot was present), CT pulmonary angiography was not performed. All patients in whom pulmonary embolism had not been ruled out underwent CT pulmonary angiography. The primary outcome was the incidence of venous thromboembolism at 3 months. The secondary outcome was the proportion of patients in whom CT pulmonary angiography was not indicated to safely rule out pulmonary embolism.

Results

A total of 510 women were screened, of whom 12 (2.4%) were excluded. Pulmonary embolism was diagnosed in 20 patients (4.0%) at baseline. During follow-up, popliteal deep-vein thrombosis was diagnosed in 1 patient (0.21%; 95% confidence interval [CI], 0.04 to 1.2); no patient had pulmonary embolism. CT pulmonary angiography was not indicated, and thus was avoided, in 195 patients (39%; 95% CI, 35 to 44). The efficiency of the algorithm was highest during the first trimester of pregnancy and lowest during the third trimester; CT pulmonary angiography was avoided in 65% of patients who began the study in the first trimester and in 32% who began the study in the third trimester.

Conclusion

Pulmonary embolism was safely ruled out by the pregnancy-adapted YEARS diagnostic algorithm across all trimesters of pregnancy. CT pulmonary angiography was avoided in 32 to 65% of patients. (Funded by Leiden University Medical Center and 17 other participating hospitals; Artemis Netherlands Trial Register number, NL5726.)

INTRODUCTION

Acute pulmonary embolism (PE) is one of the leading causes of maternal death in Western countries; the overall incidence is reported to be 1.72 cases per 1000 deliveries, and it accounts for approximately one death in every 100,000 deliveries (1-4). A wide overlap exists between the clinical symptoms of venous thromboembolism (VTE) and symptoms caused by physiological changes in pregnancy, such as tachycardia, swelling of the legs, and dyspnea. However, because of the well-known elevated risk of VTE with potentially fatal pulmonary embolism during pregnancy, the threshold to test for pulmonary embolism during pregnancy is low. This clinical dilemma is best indicated by published reports that show a prevalence of pulmonary embolism of 5% or less among pregnant women in whom pulmonary embolism is suspected, as compared with a rate of 15 to 20% among nonpregnant women (5, 6).

Studies that have validated the use of clinical decision rules or d-dimer tests to rule out pulmonary embolism without the use of imaging tests during pregnancy are scarce (7), and recent publications have called into question the safety of such practices (8, 9). A recent study showed that pulmonary embolism could be ruled out without computed tomographic (CT) pulmonary angiography in only 16% of pregnant women on the basis of a decision rule, d-dimer test, and compression ultrasonography of both legs (9). Therefore, the diagnostic workup of pregnant women with suspected pulmonary embolism relies mainly on imaging of the chest (i.e., CT pulmonary angiography or ventilation–perfusion scanning), with associated potential harm to the mother and fetus through exposure to intravenous contrast enhancement and ionizing radiation (10-12). Because of the lack of strong evidence for validated diagnostic algorithms, there is no consensus among international guidelines regarding the approach to take in the diagnosis of pulmonary embolism during pregnancy (12-14).

Recently, the YEARS study (Netherlands Trial Register number, NL4020) assessed the use of the diagnostic YEARS algorithm in men and women with clinically suspected pulmonary embolism. The study showed that the algorithm had a low incidence of failure, as evidenced by the incidence of VTE at 3 months of 0.61% (95% confidence interval [CI], 0.39 to 0.96), and that the use of CT pulmonary angiography was 14 percentage points lower when the YEARS algorithm was applied than when conventional algorithms were applied. These findings were observed in all age groups and across several relevant subgroups (15). We conducted a prospective study to evaluate the use of a pregnancy-adapted YEARS algorithm in the management of suspected pulmonary embolism in pregnant women (Figure 1).

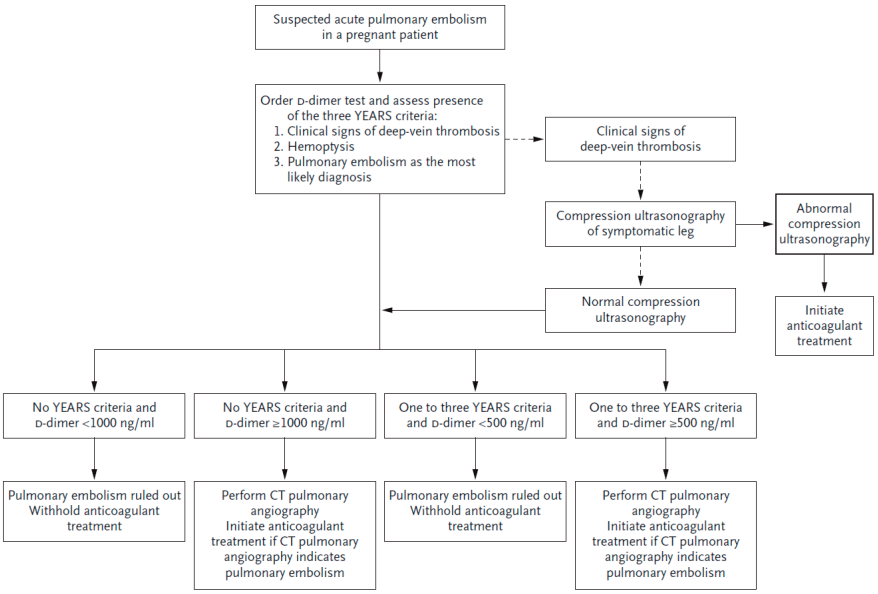

Figure 1: The pregnancy-adapted YEARS algorithm for pregnant patients with suspected acute pulmonary embolism
Abbreviations: DVT= deep vein thrombosis; CUS= compression ultrasonography; PE= pulmonary embolism; CTPA= computed tomography pulmonary angiography

METHODS

Study Design and Oversight

The Artemis study was a multicenter, international study that was conducted at 11 academic and 7 nonacademic teaching hospitals. From October 2013 through May 2018, we consecutively screened pregnant women who were 18 years of age or older and had been referred to the emergency department or the obstetrical ward because of suspected pulmonary embolism, which was defined by new onset or worsening of chest pain or dyspnea, with or without hemoptysis or tachycardia. Exclusion criteria were treatment with a full-dose therapeutic anticoagulant agent that had been initiated 24 hours or more before the eligibility assessment, unavailability of the patient for follow-up, allergy to iodinated contrast enhancement, or a life expectancy of 3 months or less. In the YEARS study, which was initiated in 2013, pregnancy was not an exclusion criterion. However, very few pregnant women participated in the study, and we decided to continue the study in pregnant women only. This extension study and its protocol, available with the full text of this article at NEJM.org, were approved by the institutional review board at the Leiden University Medical Center (for all participating hospitals in the Netherlands) and by the institutional review board at the Brest University Hospital Center, Brest (for all participating hospitals in France). The institutional review board in

Leiden waived the need for informed consent from study participants at the hospitals in the Netherlands and the institutional review board in Brest waived the need for informed consent from study participants at the hospitals in France, a decision that was endorsed by the local institutional review board at each participating site. In Ireland, the institutional review board at the Rotunda Hospital approved the study protocol, and the patients at the site provided written informed consent. The study was designed by the authors with no involvement of any commercial entity. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol. No one who is not an author contributed to the writing of the manuscript.

Procedures

The attending physician evaluated whether a clinical suspicion of pulmonary embolism was present on the basis of the patient's reported symptoms, including sudden onset of dyspnea or chest pain. If pulmonary embolism was suspected, management followed the prespecified pregnancy-adapted YEARS algorithm (Figure 1). Three criteria from the YEARS algorithm were assessed in all the patients: whether clinical signs of deep-vein thrombosis were present, whether hemoptysis (which was defined as the coughing up of small amounts of blood or a streak of blood) was reported, and whether pulmonary embolism was considered by the physician to be the most likely diagnosis. The third criterion (pulmonary embolism as the most likely diagnosis, above any alternative diagnosis) was evaluated on the basis of the patient's history and physical examination results, as was originally proposed by Wells et al. (16) These three criteria were chosen because they had been shown to be the most predictive for pulmonary embolism in an earlier post hoc analysis that was performed to construct the YEARS algorithm (17). The d-dimer level, which was assessed in parallel with the confirmation of suspicion of pulmonary embolism and the assessment of the YEARS criteria, was measured with the use of automated, well-validated, high-sensitivity, quantitative d-dimer assays (VIDAS d-Dimer Exclusion, bioMérieux; Tina-quant, Roche Diagnostica; STA-Liatest, Diagnostica Stago; Innovance, Siemens; or HemosIL, Instrumentation Laboratory). Because of the strict parallel timing of the assessment of YEARS criteria and the measurement of the d-dimer level, physicians may occasionally have been aware of the d-dimer result when they were assessing the YEARS criteria.

Patients who had clinical signs of deep-vein thrombosis underwent two-point compression ultrasonography of the deep veins of the symptomatic leg (at the popliteal and inguinal levels) to confirm or rule out proximal deep-vein thrombosis. In the case of confirmed deep-vein thrombosis, a diagnosis of pulmonary embolism was considered to be established, and no other diagnostic imaging test was performed. In the case of either absence of signs of deep-vein thrombosis or a normal compression ultrasonogram, the rest of the algorithm was followed. If a patient did not meet any of the three YEARS criteria and the d-dimer level was less than 1000 ng per milliliter or if a patient met one or more of the three YEARS criteria

and the d-dimer level was less than 500 ng per milliliter, a diagnosis of pulmonary embolism was considered to be ruled out, and anticoagulant treatment was withheld. All the remaining patients were referred for CT pulmonary angiography, which was considered to be the diagnostic standard, to confirm or rule out the diagnosis of acute pulmonary embolism.

Before the start of the study, local procedures for CT pulmonary angiography were adapted and standardized for pregnancy (e.g., a high flow rate of administration of contrast medium, a high concentration of contrast medium, a shallow breath hold [to avoid the Valsalva maneuver], and a reduced dose of radiation) (10). Patients in whom the diagnosis of pulmonary embolism was ruled out were followed for 3 months for the occurrence of symptomatic VTE.

Patients were instructed to return to the hospital before the 3-month appointment if symptoms of VTE occurred, at which time objective tests to diagnose or rule out the disease were performed. Patients who had confirmed pulmonary embolism, deep-vein thrombosis, or both were treated with therapeutic low-molecular-weight heparin in accordance with international guidelines (13).

Outcomes

The primary outcome was the cumulative incidence of symptomatic VTE, with confirmation by objective tests, during a 3-month follow-up period in the subgroup of patients in whom anticoagulant treatment was withheld on the basis of a negative result of the algorithm (i.e., a diagnosis of pulmonary embolism was ruled out). Pulmonary embolism was considered to be present if CT pulmonary angiography with contrast enhancement showed a new filling defect in a subsegmental or more proximal pulmonary artery (18). A death was classified as having been caused by pulmonary embolism if the presence of a pulmonary embolism was confirmed on autopsy or was shown by objective testing before death or if sudden death occurred for which no other cause could be identified. Proximal deep-vein thrombosis was considered to be present if compression ultrasonography showed noncompressibility of a proximal vein (i.e., the popliteal vein or a more proximal vein) (18). An independent committee assessed and adjudicated all suspected cases of VTE and deaths that occurred during follow-up.

The secondary outcome was the proportion of patients in whom CT pulmonary angiography was not indicated to safely rule out pulmonary embolism. The results of this analysis were compared with those of a hypothetical situation in which all the patients would have undergone CT pulmonary angiography or ventilation–perfusion scanning (12-14).

Statistical Analysis

Assuming a 1.0% incidence of recurrence of symptomatic VTE during the 3-month follow-up period and considering a maximum incidence of recurrence of 2.7% as the upper limit of a safe strategy, we estimated that a sample of 425 patients who did not have pulmonary embolism according to the algorithm and who completed follow-up would provide 80% power

to reject the null hypothesis that the incidence of recurrence of symptomatic VTE would be greater than 2.7%, at an overall one-sided alpha level of 0.05, using a binominal test (19). Assuming a 5% prevalence of pulmonary embolism at baseline, we determined that a total of 445 pregnant women with suspected pulmonary embolism should be included. Finally, anticipating a 5% incidence of loss to follow-up, we aimed to include 469 patients.

For the analysis of the primary outcome, which assessed the safety of the algorithm, we used a per-protocol approach. For the analysis of the secondary outcome, which assessed the efficiency of the algorithm, we used both an intention-to-diagnose approach and a per-protocol approach (15). The difference between the two approaches was the way in which we reported the proportion of patients in whom CT pulmonary angiography was performed but not indicated by the algorithm. Cases in which pulmonary embolism was diagnosed at presentation on the basis of CT pulmonary angiography that was not indicated were considered to be a failure of the diagnostic strategy. Prespecified subgroup analyses were planned to assess the pregnancy-adapted YEARS algorithm during each of the three trimesters. An analysis of the worst-case scenario was performed in which all patients who were lost to follow-up were considered to have had a diagnosis of VTE during follow-up. The primary and secondary outcomes are reported as percentages with corresponding exact 95% confidence intervals. Analyses were performed with the use of SPSS software, version 23.0.

RESULTS

Patients

A total of 510 consecutive pregnant women with clinically suspected pulmonary embolism were screened at the 18 participating hospitals; 12 of the women (2.4%) were excluded for various reasons (Figure 2). The baseline characteristics of the 498 patients who participated in the study are summarized in Table 1. The highest percentage of patients enrolled in the study were in the third trimester of pregnancy (46%). A total of 30 patients (6.0%) had previously had VTE, and 14 patients (2.8%) had known thrombophilia.

Among the 498 patients, 252 (51%) did not meet any of the three YEARS criteria, and 246 (49%) met at least one of the YEARS criteria. Of the latter 246 patients, hemoptysis was present in 19 (7.7%), clinical signs of deep-vein thrombosis were present in 47 (19%), and pulmonary embolism was considered to be the most likely diagnosis in 218 (89%).

Of the 47 patients who had clinical signs of deep-vein thrombosis, 43 underwent compression ultrasonography, which confirmed deep-vein thrombosis in 3 (7%). A total of 79 patients underwent compression ultrasonography of the legs in the absence of clinical signs of deep-vein thrombosis, of whom 1 patient (1%) received a diagnosis of deep-vein thrombosis. This patient met one YEARS criterion (pulmonary embolism was considered to be the

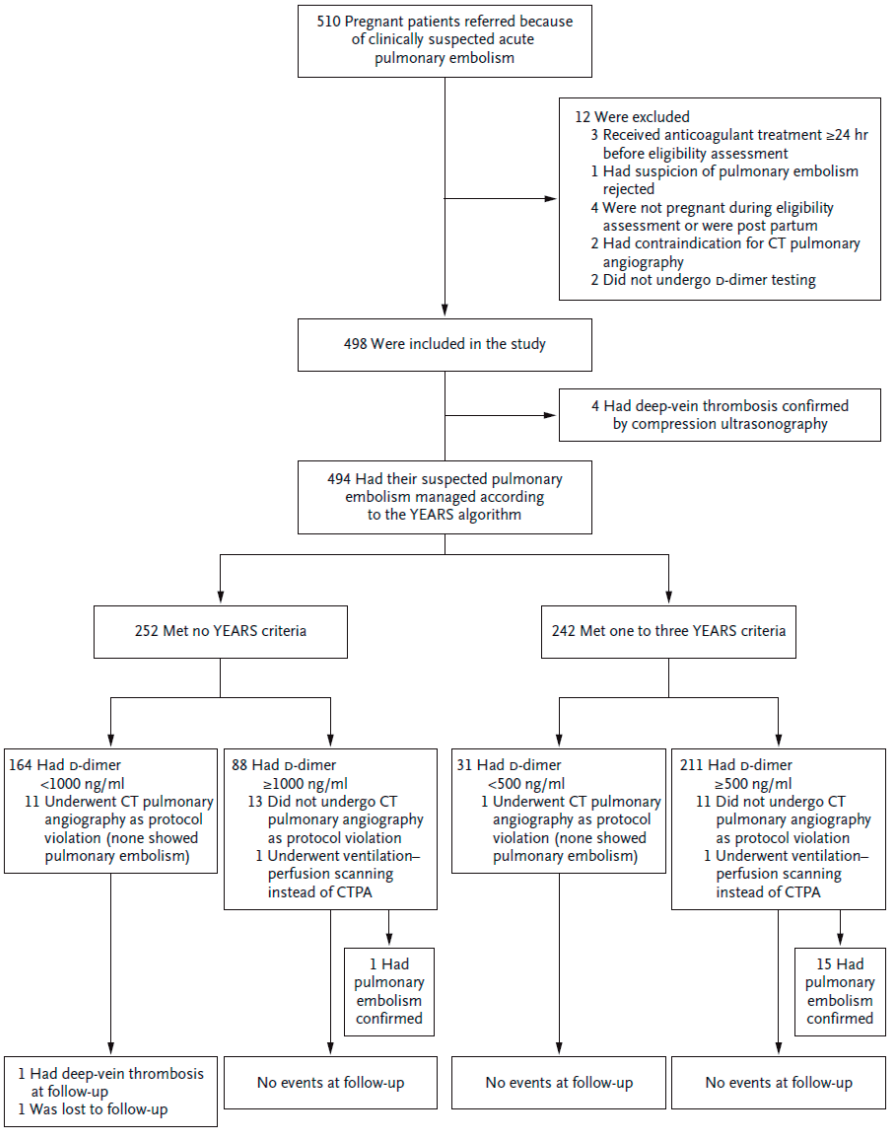

Figure 2: Flowchart of the study.
Abbreviations: DVT= deep vein thrombosis; CUS= compression ultrasonography; PE= pulmonary embolism; CTPA= computed tomography pulmonary angiography; VQ= ventilation-perfusion scan
†79 patients had CUS performed without symptoms of DVT, of which one demonstrated DVT

most likely diagnosis) and had a d-dimer level of 1480 ng per milliliter. Proximal deep-vein thrombosis was thus confirmed in a total of 4 patients (Figure 2).

The d-dimer level was below the prespecified threshold in 195 of the 494 patients (39%) who did not have confirmed deep-vein thrombosis. Of the 299 patients who had a d-dimer level

Table 1: Baseline characteristics of pregnant patients with suspected pulmonary embolism

	Included patients (n=498)
Age (years), mean (SD)	30 (5.8)
Duration of pregnancy (weeks), median (25-75IQR)	25 (17-31)
1st trimester (week 0-12+6 days), n (%)	74 (15)
2nd trimester (week 13-26+6 days), n (%)	193 (39)
3rd trimester (week 27-42), n (%)	231 (46)
YEARS items:	
Clinical signs of DVT, n (%)	47 (9.4)
Hemoptysis, n (%)	19 (3.8)
PE most likely diagnosis, n (%)	218 (44)
First pregnancy, n (%)	133 (27)
Duration of complaints (days), median (25-75IQR)	2 (1-6)
Air travel, n (%)	12 (2.4)
Surgery in the past four weeks, n (%)	5 (1.0)
Immobilization > 3 days in the last 4 weeks, n (%)	31 (6.2)
Active smoking, n (%)	37 (7.4)
Known with asthma, n (%)	62 (12)
Previous VTE, n (%)	30 (6.0)
Known thrombophilia, n (%)	14 (2.8)
Outpatient, n (%)	419(84)

Abbreviations: SD: standard deviation; IQR: interquartile range; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism

that was higher than the relevant threshold, 2 patients in whom CT pulmonary angiography was indicated were referred for ventilation–perfusion scanning, 273 patients underwent CT pulmonary angiography, and 24 patients did not undergo CT pulmonary angiography (which constituted a protocol violation). Acute pulmonary embolism was confirmed in 16 patients on the basis of CT pulmonary angiography (15 patients) or ventilation–perfusion scanning (1 patient). Of the 16 patients, 1 did not meet any of the YEARS criteria (0.4% of the 252 patients who met no YEARS criteria) but had a d-dimer level above the prespecified threshold, and 15 met at least one of the YEARS criteria (6.2% of the 242 patients who met at least one criterion) and had a d-dimer level above the threshold; none of the 16 patients had deep-vein thrombosis (Figure 2). The total number of patients who had pulmonary embolism at baseline was therefore 20 (4.0%; 95% CI, 2.6 to 6.1); this total included the 4 patients in whom proximal deep-vein thrombosis was confirmed by compression ultrasonography. No adverse reactions occurred as a result of CT pulmonary angiography.

One patient (0.20%) who did not meet any of the YEARS criteria at presentation and who had a d-dimer level of 980 ng per milliliter was temporarily lost to follow-up. Subsequent

follow-up revealed that she had not had symptomatic VTE before giving birth without incident 2 months later.

Outcomes

Among the 477 patients (96%) in whom pulmonary embolism was ruled out at baseline, who remained untreated during follow-up, and who completed the follow-up period, 1 patient received a diagnosis of VTE during follow-up (0.21%; 95% CI, 0.04 to 1.2) (Table 2). This patient, who had not met any YEARS criteria and had had a d-dimer level of 480 ng per milliliter and therefore had not undergone CT pulmonary angiography, received a diagnosis of symptomatic popliteal deep-vein thrombosis, which was confirmed by compression ultrasonography on day 90 of the follow-up period. No patient received a diagnosis of pulmonary embolism during the follow-up period. In an analysis of the worst-case scenario, which assumed that all patients who were lost to follow-up would have had a diagnosis of VTE during the 3-month follow-up period, the incidence of VTE at 3 months among patients who did not undergo CT pulmonary angiography would have been 0.42% (2 of 478 patients; 95% CI, 0.11 to 1.5).

Table 2: Primary and secondary outcomes

			All patients without DVT at baseline n = 494	
		All patients n = 498	Patients managed without CTPA n = 195	Patients managed with CTPA n = 299*
Baseline	**PE confirmed at baseline**	20/498†	0/195	16/299
		4.0%	0.0%	5.4%
		(95%CI 2.6-6.1)	(95%CI 0.0-2.0)	(95%CI 3.3-8·5)
Follow-up	**VTE during FU in patients without VTE at baseline**	1/477‡	1/195	0/283
		0.21%	0.51%	0.0%
		(95%CI 0.0-1.2)	(95%CI 0.09-2.9)	(95%CI 0.0-1.4)

Abbreviations: CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism; FU: follow-up: VTE: venous thromboembolism

*VQ-scan in 2 patients; †4 patients had CUS-confirmed DVT; ‡All patients without VTE at baseline who are not lost to follow up

Among the 195 patients who should not have undergone CT pulmonary angiography (because they did not have confirmed deep-vein thrombosis and had a d-dimer level below the prespecified threshold), 12 patients (6.2%) underwent CT pulmonary angiography, which constituted a protocol violation; no evidence of pulmonary embolism was observed in any of the 12 patients. When the intention-to-diagnose approach was used, CT pulmonary angiography was not performed in 195 of the 494 patients in whom deep-vein thrombosis was not

diagnosed at baseline (39%; 95% CI, 35 to 44); the per-protocol approach yielded similar results (40% [183 of 459 patients]; 95% CI, 35 to 45).

The results of the analyses performed in the subgroups of patients defined according to the trimester of pregnancy during which the patient was enrolled in the study are summarized in Table 3. Pulmonary embolism was diagnosed at presentation in 5 of 74 patients (6.8%; 95% CI, 2.9 to 15) in the first trimester, in 8 of 193 patients (4.2%; 95% CI, 2.1 to 8.0) in the second trimester, and in 7 of 231 patients (3.0%; 95% CI, 1.5 to 6.1) in the third trimester. The median d-dimer level was 505 ng per milliliter (interquartile range, 292 to 963) during the first trimester, 730 ng per milliliter (interquartile range, 505 to 1260) during the second trimester, and 1120 ng per milliliter (interquartile range, 818 to 1718) during the third trimester. The safety of the algorithm to rule out pulmonary embolism was similar among the three trimesters. The efficiency of the algorithm was highest during the first trimester and lowest during the third trimester; CT pulmonary angiography was avoided in 65% of the patients who began the study in the first trimester and in 32% of the patients who began the study in the third trimester.

Table 3: Subgroup analysis for the three trimesters

	First trimester (n = 74)	Second trimester (n = 193)	Third trimester (n = 231)
PE confirmed at baseline n, N% (95%CI)	5/74 6.8% (2.9-15)	8/193 4.2% (2.1-8.0)	7/231 3.0% (1.5-6.1)
Managed without CTPA* n, N % (95%CI)	48/74 65% (54-75)	89/193 46% (39-53)	74/231 32% (26-38)
Events during FU† n, N % (95%CI)	-	1/176 0.57% (0.1-3.2)	-
Median D-dimer ,ng/mL (25-75IQR)	505 (292-963)	730 (505-1260)	1120 (818-1718)

Abbreviations: PE: pulmonary embolism; CTPA: computed tomography pulmonary angiography; FU: follow-up
*intention-to-diagnose
†per-protocol

DISCUSSION

Our study showed that the pregnancy-adapted YEARS algorithm was able to safely rule out pulmonary embolism in pregnant women with suspected pulmonary embolism. CT pulmonary angiography was avoided in 39% of the patients, thus averting potential harm from radiation exposure (12, 13). Avoidance of CT pulmonary angiography occurred in 65% of patients during the first trimester (when radiation is potentially most harmful to the fetus), 46% of patients during the second trimester, and 32% of patients during the third trimester. This decreasing specificity can be explained by the physiological rise in the d-dimer level that

commonly occurs during pregnancy (7). At the time of presentation, a 4.0% incidence of pulmonary embolism was observed, whereas the incidence was 5.4% among patients referred for CT pulmonary angiography. This low incidence was expected and was consistent with the 2% incidence observed in a retrospective study that evaluated an algorithm that was based on ventilation–perfusion scanning (20). The 3-month incidence of symptomatic VTE in the current study was low, with only one patient (0.21%) receiving a diagnosis of proximal deep-vein thrombosis and no patient receiving a diagnosis of pulmonary embolism during follow-up. These data meet the proposed criteria for assessing the safety of diagnostic methods in VTE, even in the context of a low baseline prevalence of disease (19).

Our algorithm provides solid evidence for the safe management of suspected pulmonary embolism in pregnant women, with selective use of CT pulmonary angiography. In another study, an algorithm that involved pretest assessment of clinical probability with the use of the revised Geneva score, high-sensitivity d-dimer testing, compression ultrasonography of both legs in all patients irrespective of symptoms, and CT pulmonary angiography showed that pulmonary embolism was diagnosed in 7.1% of 395 pregnant women at initial presentation and in no women at follow-up (9). However, CT pulmonary angiography — or ventilation–perfusion scanning in a minority of cases — was indicated in 84% of patients in that study, as compared with only 61% in the current study, and the low 1.7% diagnostic yield of abnormal compression ultrasonography was associated with the costly approach of performing ultrasonography of both legs in all patients (9). In a recent study, the risk of early breast cancer was found to be similarly low after ventilation–perfusion scanning and CT pulmonary angiography, which supports the notion that both imaging methods are valid options in patients without cardiopulmonary disease (21).

Some issues warrant comment. First, the pregnancy-adapted YEARS algorithm was applied only in patients in whom a clear suspicion of pulmonary embolism was raised, and it was not used as a primary screening test for pulmonary embolism in pregnant women who had nonspecific chest symptoms. Second, both the pregnancy-adapted YEARS algorithm and the YEARS algorithm are driven largely by the criterion that assessed whether pulmonary embolism was considered to be the most likely diagnosis. However, the other two YEARS criteria were present in a relevant percentage of patients (19% had clinical signs of deep-vein thrombosis and 7.7% had hemoptysis). The subjective criterion that assessed whether pulmonary embolism was the most likely diagnosis is also the most decisive variable of the Wells score, which has been recommended as an initial diagnostic test for suspected pulmonary embolism in the nonpregnant population for more than a decade (22). Third, in our study, the d-dimer level could have occasionally been known to the physician when the YEARS criteria were determined, a circumstance that could potentially have led to either attributing less importance to the criterion of pulmonary embolism as the most likely diagnosis when the result of the d-dimer test was low or attributing more importance to that criterion when the d-dimer result was high. However, when the Wells clinical decision rule is used in clinical

practice, the d-dimer level is also often available before the total sum of the Wells rule is calculated (23, 24). In the YEARS and Artemis studies, close to 4000 patients with suspected pulmonary embolism had the diagnostic process managed according to a standardized algorithm in daily clinical practice conditions, often by junior physicians, in academic and teaching hospitals and across several European countries; these studies provided reassuring external validity of the YEARS approach. This measure of external validity, together with the positive results of the current study (i.e., the very low number of diagnostic failures and high efficiency of the algorithm), strongly supports the relevance and generalizability of the pregnancy-adapted YEARS approach and the YEARS approach (15). Finally, the safety of applying a d-dimer threshold on the basis of pretest probability of pulmonary embolism has been shown in other international studies (25, 26). In addition, the YEARS algorithm has been shown to be associated with a reduction in the detection of potentially clinically irrelevant subsegmental pulmonary embolism and with both a shorter visit time and reduced costs in the emergency department (27, 28).

Strengths of our study include the prospective design, large sample size, and near complete follow-up. Limitations are the nonrandomized design and the occurrence of protocol violations. However, the very low observed incidence of failure at 3 months and the near complete follow-up and the use of a standard design for evaluating diagnostic algorithms of VTE strongly support the chosen design (15, 29-32). The protocol violations reflect the great challenge of managing suspected pulmonary embolism in pregnant women, which is largely fueled by concerns of both the physician and the patient regarding radiation exposure, as well as the lack of solid evidence to guide the diagnostic strategy. Indeed, the most prevalent risk factor for improper diagnostic management of suspected pulmonary embolism has been reported to be pregnancy (33). The protocol violations did not lead to unwanted outcomes in our study population, nor did they affect our primary or secondary outcome.

In conclusion, the pregnancy-adapted YEARS diagnostic algorithm safely ruled out acute pulmonary embolism in pregnant patients who were referred for suspected pulmonary embolism. The main advantage of this approach was that CT pulmonary angiography was averted in 32 to 65% of the patients, depending on the trimester of presentation, without compromising safety.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Chapter 5

Sex-specific performance of pre-imaging diagnostic algorithms for pulmonary embolism

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SUMMARY

Background

In patients suspected of pulmonary embolism (PE), clinical decision rules are combined with D-dimer testing to rule out PE, avoiding the need for imaging in those at low risk. Despite sex differences in several aspects of the disease, including its diagnosis, these algorithms are used indiscriminately in women and men.

Objectives

To compare the performance, defined as efficiency and failure rate, of three pre-imaging diagnostic algorithms for PE between women and men: the Wells rule with fixed or with age-adjusted D-dimer cut-off, and a recently validated algorithm (YEARS). A secondary aim was to determine the sex-specific prevalence of PE.

Methods

Individual patient data were obtained from six studies using the Wells rule (fixed D-dimer, n = 5; age adjusted, n = 1) and from one study using the YEARS algorithm. All studies prospectively enrolled consecutive patients with suspected PE. Main outcomes were efficiency (proportion of patients in which the algorithm ruled out PE without imaging) and failure rate (proportion of patients with PE not detected by the algorithm). Outcomes were estimated using (multilevel) logistic regression models.

Results

The main outcomes showed no sex differences in any of the separate algorithms. With all three, the prevalence of PE was lower in women (OR, 0.66, 0.68 and 0.74). In women, estrogen use, adjusted for age, was associated with lower efficiency and higher prevalence and D-dimer levels.

Conclusions

The investigated pre-imaging diagnostic algorithms for patients suspected of PE show no sex differences in performance. Male sex and estrogen use are both associated with a higher probability of having the disease.

BACKGROUND

Diagnosing pulmonary embolism (PE) is a daily clinical challenge in which there needs to be a balance between missing the potentially fatal diagnosis and the exposure to imaging tests of many patients with a low likelihood of the disease. Hence, clinical decision rules are combined with D-dimer plasma levels to select patients who should undergo imaging of the pulmonary vasculature (1-3). The performance of these pre-imaging diagnostic algorithms can be viewed in terms of their capacity to reduce the need for imaging tests (i.e. efficiency), while at the same time minimizing the number of missed cases of PE (i.e. safety).

PE has various sex-dependent aspects. Differences between women and men in presenting signs and symptoms have been reported (4-6). Oral estrogen use is an important women-specific risk factor for PE (7). Furthermore, although the prevalence rate appears similar in both sexes at 0.3–0.5 per thousand person-years (8-10), women make up a larger proportion of the cohorts of patients suspected of PE in the various diagnostic studies (11, 12). This implies a lower prevalence among women with clinically suspected PE, which could impact the performance of diagnostic tests.

Diagnostic algorithms for PE are applied in clinical practice without taking sex into account. Yet in patients suspected of deep venous thrombosis (DVT), a meta-analysis found that a clinical decision rule performed differently in women compared to men (13). Another individual patient data meta-analysis on the diagnostic management of DVT also suggested a possible sex difference in efficiency (women 32.0% [95% CI, 22.6–43.2] vs. men 24.2% [95% CI, 16.5–34.1]) (14). For PE, a meta-analysis of three studies showed that the Geneva score and revised Geneva score have comparable performance in women and men (4). However, when the three-level Wells score was retrospectively calculated in these cohorts, there was a significant difference in risk stratification between women and men.

The aim of the current study was to compare the performance, in terms of efficiency and failure rate, of three pre-imaging diagnostic algorithms for PE in women and men: the Wells rule combined with a fixed (1) or age-adjusted (2) D-dimer cut-off and the recently validated YEARS algorithm, in which the threshold of D-dimer is increased when no YEARS items are present (3). A secondary aim was to evaluate the sex-specific sensitivity, specificity and prevalence in patients suspected of PE. We also investigated two subgroups: women younger than 50 years, in whom avoiding unnecessary imaging is especially important because of high radiation sensitivity of breast tissue (15); and women using estrogen, because estrogen use raises D-dimer levels (16, 17), potentially affecting algorithm performance.

METHODS

Data sources and study selection

The current study was conducted using individual patient data from seven studies investigating one of the algorithms mentioned above. Six studies were identified previously in a systematic review, which aimed at identifying all studies in which the diagnostic management of PE was guided by the dichotomized Wells rule followed by quantitative D-dimer testing (2, 3, 18-23). In brief, MEDLINE and EMBASE were searched from the year of introduction of the Wells score (1 January 1998) up to 13 February 2016, combining terms for 'pulmonary embolism' and 'D-dimer'. The search was restricted to original studies in adults and used an adapted search filter for diagnostic and prognostic studies without language restrictions (24). The full search strategy was published previously (23). The seventh study was the initial and thus far only prospective study evaluating the YEARS algorithm, which has recently been published (3). All studies prospectively included consecutive hemodynamically stable adult patients with a clinical suspicion of PE. In all studies, participants were followed for at least 3 months for symptomatic fatal or non-fatal venous thromboembolism (VTE).

Authors of the included original studies provided patient-level data on the following items: demographics, VTE risk factors, items of the applied decision rules, D-dimer concentrations, imaging results, anticoagulant use for other reasons than VTE, estrogen use, and completeness and outcome of follow-up. The provided data were checked against the published studies by reconstructing the baseline characteristics tables. Death was considered a case of PE if PE could not be excluded as a cause of death.

Pre-imaging diagnostic algorithms

Three pre-imaging diagnostic algorithms for PE were evaluated, which have been described in detail previously (1-3). In brief, the dichotomized Wells rule is a seven-item scoring system, classifying patients with 4 points or less as 'PE unlikely' and those with more than 4 points as 'PE likely' (1). D-dimer testing is performed in 'PE unlikely' patients, safely ruling out PE in those with a concentration of 500 μg L^{-1} or less. Patients with higher D-dimer concentrations and 'PE likely' patients should undergo pulmonary imaging. For patients over 50 years, this strategy can be adapted by adjusting the positivity threshold of D-dimer by multiplying the age of the patient by 10 μg L^{-1} (2). Recently, the YEARS algorithm has been validated, consisting of a three item decision rule with simultaneous D-dimer testing (3). Patients are assigned one point for signs of DVT, hemoptysis and PE being the most likely diagnosis. Patients with a combination of either 0 points and D-dimer ≥ 1000 ng mL^{-1} or ≥ 1 points and D-dimer ≥ 500 ng mL^{-1} are referred for pulmonary imaging.

Primary and secondary endpoints

The main outcome measures were efficiency and failure rate for the separate algorithms. Efficiency was defined as the proportion of all patients in whom the algorithm indicated that imaging was not required. We used an intention-to-diagnose approach; that is, the result of the algorithm was used as the outcome rather than the actual clinical management. The failure rate was defined as the proportion of patients with VTE, either at baseline or during 3-month follow-up, within the group of patients in whom imaging was not indicated according to the algorithm. Sensitivity was calculated by the proportion of patients with VTE at baseline or during 3-month follow-up in whom the algorithm indicated a need for imaging. Specificity was the proportion of patients without VTE in whom the algorithm did not indicate a need for imaging. Prevalence was defined as the proportion of all patients who had a VTE at baseline or during follow-up.

Analysis

Patients were only included in the analysis of the algorithm they were originally managed with (i.e. we did not calculate outcomes of the additional algorithms in a post-hoc manner for analysis purposes). Data from patients in the included studies who were not managed according to one of the three algorithms were omitted. Patients who received anticoagulation for reasons other than VTE were excluded from the failure rate analysis, as clinical follow-up could not be relied upon to identify VTE in these patients.

In the primary analysis, we compared efficiency and failure rate between women and men. In subgroup analyses we compared women using estrogen with women not using estrogen, and women younger than 50 years with men younger than 50 years. The ADJUST-PE study was excluded from the latter analysis as the threshold increase in this algorithm starts at age 50 years (2). As one of the included studies (18) exclusively enrolled patients with suspected recurrent PE, and men have a significantly higher risk of recurrence compared with women (25), we performed a sensitivity analysis for prevalence omitting this study.

We dealt with missing data through multiple imputation with 10 iterations, performed separately in each study as described previously (23). We assumed a missing at random pattern. All baseline and outcome data were used in the imputation model.

We calculated proportions, odds ratios (ORs) and 95% confidence intervals (95% CIs) using logistic regression models with sex as the independent variable. For the Wells rule combined with fixed D-dimer testing, we performed a single-stage individual patient data meta-analysis, with a random intercept effect for study to account for study level clustering. The models for the Wells rule combined with age-adjusted D-dimer testing and the YEARS algorithm were based on single studies. Models were run on 10 imputed datasets and results combined according to the Rubin rule (26).

We tested the association between estrogen use and D-dimer level in pooled data from all female participants. D-dimer levels were not imputed for this particular analysis. A multilevel

Table 1. Characteristics of included studies.

Study	Algorithm	Inclusion period	Sample size *	Population	Proportion females	Overall prevalence risk of PE	Age (years ± sd) (p for difference)**	Estrogen use among women (%)
van Belle et al. [19]	Wells rule + fixed D-dimer	Nov 2002 – Sep 2004	3296	In- and outpatients, multicentre	57.5%	21%	Women 51.6 ± 18.9 Men 54.8 ± 17.6 (p<0.001)	23.1%
Douma et al. [20]	Wells rule + fixed D-dimer	July 2008 – Nov 2009	807	In- and outpatients, multicentre	60.3%	24%	Women 51.5 ± 17.8 Men 55.4 ± 17.4 (p=0.002)	20.1%
Galipienzo et al. [21]	Wells rule + fixed D-dimer	May 2007 – Dec 2008	241	Outpatients, single centre	50.6%	27%	Women 66.9 ± 17.2 Men 63.4 ± 15.0 (p=0.094)	2.5%
Goekoop et al. [22]	Wells rule + fixed D-dimer	Mar 2002 – Mar 2004	879	Outpatients, multicentre	62.6%	13%	Women 50.4 ± 17.8 Men 52.7 ± 17.2 (p=0.057)	20.9%
Mos et al. [18]	Wells rule + fixed D-dimer	Nov 2002 – Nov 2009	281	In- and outpatients with previous PE, multicentre	58.0%	42%	Women 53.3 ± 17.1 Men 56.2 ± 15.0 (p=0.13)	6.1%
Rhigini et al. [2]	Wells rule + age-adjusted D-dimer	Jan 2010 – Feb 2013	1752	Outpatients, multicentre, aged > 50 years	57.6%	20%	Women 66.5 ± 10.8 Men 65.8 ± 10.1 (p=0.18)	3.1%
van der Hulle et al. [3]	YEARS	Oct 2013 – July 2015	3465	In- and outpatients, multicentre	62.2%	14%	Women 52.3 ± 18.5 Men 54.9 ± 17.5 (p<0.001)	15.5%

* sample sizes reflect the number of patients that could be included in the current study. ** by t-test

linear regression model with a random intercept effect for study, adjusted for age and the presence of VTE, was used. The P-value was obtained by likelihood ratio test of the full model against the reduced model with the estrogen variable omitted.

Analyses were performed in R version 3.3.3 (R Foundation for Statistical Computing; www.R-project.org). We used the mice package (version 2.22) for multiple imputation and the lme4 package (version 1.1–10) for multilevel logistic regression modelling.

RESULTS

Characteristics of included studies

The characteristics of the included studies are summarized in Table 1. Five studies evaluated the Wells rule with fixed D-dimer cut-off, one the Wells rule with age-adjusted D-dimer cut-off, and one the YEARS algorithm. Sample sizes ranged from 281 to 3465. The proportion of women ranged from 50.6% to 62.6%. The prevalence of PE ranged from 13% to 42%. Estrogen use in female patients ranged from 2.5% to 23.1%.

Algorithm performance and prevalence in women and men

For all three algorithms, the efficiency was comparable in women and men (Table 2). Similarly, the failure rate was not different in men compared with women for the Wells rule with fixed D-dimer testing and for the YEARS algorithm. For the Wells rule with age-adjusted D-dimer testing, there were two failures, both were women. When data from the studies on different algorithms were pooled, the overall efficiency was higher in women with an OR of 1.11 (95% CI, 1.02–1.2). There was no statistically significant difference in failure rate.

The prevalence of PE was lower in women than in men (Table 2). The ORs for PE for women compared with men were 0.68 (95% CI, 0.60–0.78) in the pooled studies investigating the Wells rule with fixed D-dimer, 0.74 (95% CI, 0.58–0.94) for age-adjusted D-dimer and 0.66 (95% CI, 0.55–0.81) for the YEARS algorithm. These differences remained statistically significant after adjusting for age. The pooled unadjusted overall prevalence was 18.7% in women and 25.1% in men. In the sensitivity analysis of the Wells rule with fixed D-dimer excluding the study by Mos et al.(18), the prevalence was 17.6% for women and 23.7% for men, corresponding to an OR of 0.69 (95% CI, 0.60–0.78).

Figure 1 represents the model-predicted efficiency and prevalence of the three algorithms, according to age and stratified by sex. The figure demonstrates a lower prevalence in women for each algorithm, but not different efficiencies. Although the efficiency curves for women and men intersect, there was no statistical evidence of interaction between age and sex on efficiency. Finally, none of the three algorithms showed a difference between women and men in sensitivity or in specificity (Table 3).

Table 2. Sex specific performance and prevalence of three pre-imaging diagnostic algorithms for PE.

	Efficiency			Failure rate			Prevalence of PE		
	Women	Men	Odds ratio*	Women	Men	Odds ratio**	Women	Men	Odds ratio***
Wells rule with fixed D-dimer	-	-	-	-	-	-	-	-	-
n = 5504	29.3 %	27.3 %	1.10 (0.98-1.2)	0.55 %	0.91 %	0.60 (0.20-1.9)	20.8 %	27.7 %	0.68 (0.60-0.78)
Wells rule with age-adjusted D-dimer	-	-	-	-	-	-	-	-	-
n = 1752	31.5 %	28.8 %	1.14 (0.92-1.4)	0.63 %	(n=0)	-	17.6 %	22.5 %	0.74 (0.58-0.94)
YEARS algorithm	-	-	-	-	-	-	-	-	-
n = 3465	48.5%	46.0%	1.10 (0.96-1.27)	0.39%	0.51%	0.76 (0.17-3.9)	11.8%	16.8%	0.66 (0.55-0.81)
Overall pooled estimates	-	-	-	-	-	-	-	-	-
n = 10721	29.5%	27.4%	1.11 (1.02-1.2)	0.49%	0.62%	0.78 (0.33-1.86)	18.7%	25.1%	0.69 (0.62-0.76)

* Odds of algorithm indicating that imaging was not required, women versus men ** Odds of VTE, either at baseline or during three month follow-up, within the group of patients in whom imaging was not indicated according to the algorithm, women versus men *** Odds of VTE at baseline or follow-up, women versus men

Table 3. Sensitivity and specificity.

	Sensitivity (95% CI)		Specificity (95% CI)	
	Women	Men	Women	Men
Wells rule with fixed D-dimer	99% (98-100)	99% (98-99)	38% (29-48)	38% (29-48)
Wells rule with age-adjusted D-dimer	99% (96-100)	100% (0-100)	24% (21-27)	25% (22-29)
YEARS algorithm	98% (96-100)	99% (97-100)	55% (53-57)	56% (53-59)

Abbreviations: CI: confidence interval

Subgroup analyses

In the subgroup of patients aged younger than 50 years, efficiency was not different between women and men (Table 4). Efficiency was lower in women using estrogen compared with women not using estrogen for the Wells rule with fixed D-dimer (age-adjusted OR, 0.76; 95% CI, 0.61–0.93) and YEARS algorithm (age-adjusted OR, 0.49; 95% CI, 0.37–0.64), adjusting for age. There was no statistically significant difference for the Wells rule with age-adjusted D-dimer (OR, 0.66; 95% CI, 0.29–1.5). The prevalence, adjusted for age, was higher in estrogen users with all three algorithms (Table 4). Estrogen-using women had higher D-dimer levels, with a mean difference of 144 μg L^{-1} (P = 0.037), adjusted for age and VTE diagnosis.

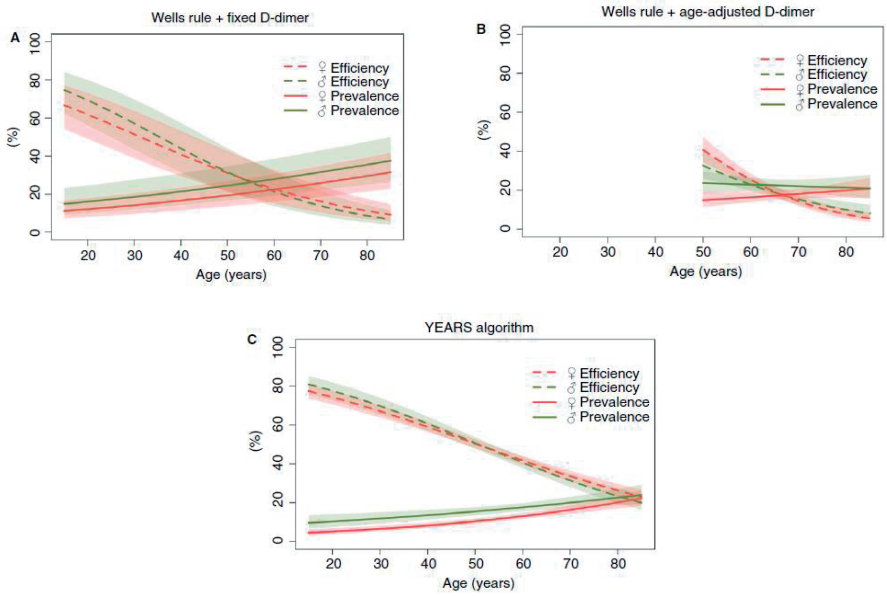

Figure 1. Age dependent predicted efficiency and prevalence of pulmonary embolism. (A) Wells rule with fixed D-dimer cut-off. (B) Wells rule with age-adjusted D-dimer cut-off. (C) YEARS algorithm

Table 4. Subgroup analyses.

	Women < 50 versus men < 50		**Estrogen use versus no estrogen use****	
	Efficiency (%)	**OR efficiency**	**OR efficiency**	**OR prevalence**
Wells rule with fixed D-dimer	♀ 44.3% ♂ 46.2%	0.92 (0.78-1.1)	0.76 (0.61-0.93)	2.4 (1.9-3.1)
Wells rule with age-adjusted D-dimer	Not applicable*	-	0.66 (0.29-1.5)	3.2 (1.4-7.0)
YEARS algorithm	♀ 61.3% ♂ 61.9%	0.97 (0.78-1.2)	0.49 (0.37-0.64)	3.6 (2.4-5.4)

Abbreviations: ♀ female. ♂ male. OR: odds ratio. All OR's presented with 95%CI. OR efficiency: outcome is imaging indication yes vs no. OR prevalence: outcome is VTE yes vs no. *D-dimer adjustment was applied > 50 years. ** Adjusted for age

DISCUSSION

In the current analysis we evaluated the sex-specific prevalence and performance of three widely used pre-imaging diagnostic algorithms for PE using individual patient data from seven prospective management studies. We found a consistently lower prevalence in women suspected of having PE as compared with men. This is congruent with the observation from the literature that the majority of participants in diagnostic studies are women, despite their PE prevalence rates being equal to those men (8-12). The higher proportion of women in all

included studies is also in line with this. Women suspected of PE thus have a lower risk of actually having the disease than men.

Both the efficiency and failure rate of the different algorithms were comparable between women and men. This similar efficiency despite a lower prevalence in women might suggest a lower specificity: there were fewer cases of PE in the women, yet the algorithm indicated the need for imaging as often as in men. However, in all three algorithms the specificity did not vary with sex. This can be explained by the fact that even though there was no statistical difference in efficiency, numerically the efficiency differed slightly. Indeed, when data from studies on the separate algorithms were pooled we found a higher efficiency in women. Substantial differences in prevalence translate into relatively small differences in efficiency. The apparent incongruity between the different prevalences and no difference in efficiency, is thus not explained by a difference in specificity but rather reflects a marginally higher efficiency in women, as should be expected with the lower prevalence.

A lower prevalence in women was not observed in a meta-analysis investigating two other diagnostic algorithms for PE (4). One possible explanation for this discrepancy is the higher age in the included cohorts compared with the current study. In a post-hoc analysis of the PIOPED study the prevalence of PE was lower in women aged 50 years or younger compared with men of the same age, but this difference disappeared at higher ages (27). In a later PE diagnostic management study with a mean age of participants comparable to that in the current study, men indeed had a higher prevalence than women (28).

Efficiency is especially important in younger women. First, these women do not benefit from the increase in efficiency of the algorithm with age-adjusted D-dimer cut-off, in which the D-dimer positivity threshold starts to increase at the age of 50 years. Second, the risk of radiation-associated breast cancer is higher at lower ages of ionizing radiation exposure (15). In our subgroup analysis of patients under 50 years, efficiency did not vary with sex. We thus found no indication of a need for a different approach in this important subgroup.

Estrogen use is a well-established risk factor for VTE (7, 29). D-dimer levels appear to rise after the initiation of oral contraceptives or hormone replacement therapy (16, 17, 30-32). Consistent with this observation, in our analysis, women taking estrogen indeed had a higher prevalence of PE, with a corresponding decrease in the efficiency of the algorithms. In an attempt to explain this decreased efficiency, we investigated whether estrogen use was associated with higher D-dimer levels, hypothesizing that exogenous estrogens raise D-dimer levels in the absence of PE, in some cases crossing the positivity threshold and thus lowering the specificity of the algorithm. Estrogen use was indeed associated with increased plasma D-dimer levels, adjusted for age and the presence of a VTE diagnosis. Specificity itself was not affected however (data not shown). We therefore do not conclude that estrogen use affects the performance of the algorithms aside from the elevated prevalence of PE.

The current study contributes to the field of PE diagnosis by reporting the sex-specific performance of the Wells rule with fixed and age-adjusted D-dimer as well as the YEARS al-

gorithm. It includes all published prospective management studies on these PE pre-imaging diagnostic algorithms in the secondary or tertiary care setting. The use of prospectively collected individual patient data, which is now considered the reference standard for meta-analyses (33), enabled investigation of relevant subgroups and the uniform definition of variables across the various studies. Pooling the results of the five studies investigating the Wells rule with fixed D-dimer provided robust estimates of the performance of this broadly used algorithm.

Given low absolute numbers of failures, the study was not powered to detect potential small sex differences in the failure rate. Nevertheless, the failure rates for both women and men remained well below 3%, which is considered a safe upper limit for the failure rate of a diagnostic test for PE, based on the failure rate of the reference standard of pulmonary angiography (34, 35). Although there was an overall high homogeneity in study design, individual studies did vary in methods and study population. For example, various D-dimer assays were used. Furthermore, the overall prevalence and the proportion of women varied between studies. In the analyses that pooled multiple studies, random effects were used to incorporate this study-level variability into the model. Nevertheless, this heterogeneity makes careful interpretation of pooled results necessary, especially of results on combined algorithms because the algorithms are in fact distinct diagnostic tests.

We chose efficiency and safety as primary outcome measures in the current study, despite the fact that the prevalence influences these parameters. Alternatively, one might focus on sensitivity and specificity. A limitation in the estimation of these parameters, however, is the risk of differential verification bias. In the included studies, patients with a positive algorithm result received a CT scan, whereas patients with a negative algorithm did not. This differential verification can be a source of bias for sensitivity and specificity (36). In addition, sensitivity and specificity tend to vary with prevalence of disease as well (37). These parameters are thus presented as secondary outcomes and should be interpreted with caution.

Given the widespread use of the Wells rule for PE diagnosis and the recent reports that the age-adjusted D-dimer and YEARS algorithm are more efficient than traditional diagnostic algorithms, the question of sex differences in algorithm performance is relevant in the context of individualized patient care. The algorithms perform equally well in women and men. Men do have a higher prevalence than women when clinically suspected of having PE, and the same goes for women using estrogen as compared with non-users. Although this should not lead clinicians to deviate from an established diagnostic strategy in these patient groups, the findings can inform future studies on diagnostic algorithms, which may investigate the added value of sex and estrogen use as risk stratifiers and D-dimer cut-off modifiers for patients suspected of PE.

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Chapter 6

No added value of the age-adjusted D-dimer cut-off to the YEARS algorithm in patients with suspected pulmonary embolism

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SUMMARY

Background

The YEARS algorithm was designed to simplify the diagnostic work-up of pulmonary embolism (PE) and to reduce the number of necessary computed tomography pulmonary angiography (CTPA) scans. An alternative strategy to reduce the number of CTPAs is the age-adjusted D-dimer cut-off (ADJUST) in patients aged 50 years or older. We aimed to investigate whether a combination of both diagnostic strategies might save additional CTPAs.

Methods

The YEARS algorithm consists of three items (clinical signs of deep venous thrombosis, hemoptysis, 'PE most likely diagnosis') with simultaneous D-dimer testing using a pre-test dependent threshold. We performed a post hoc analysis in 3465 patients managed according to YEARS to compare the number of patients managed without CTPA scans and associated diagnostic failures in hypothetical scenarios with different YEARS-ADJUST combinations.

Results

Following the YEARS algorithm, 1651 patients (48%) were managed without CTPA; PE was diagnosed in 456 (13%) patients at baseline and 18 patients with initial normal testing suffered venous thromboembolism (VTE) during 3-month follow-up (failure rate 0.61%; 95% confidence interval [CI], 0.36–0.96). If ADJUST had been fully integrated in YEARS, 1627 patients (47%) would have been managed without CTPA (absolute decrease of 0.69%; 95% CI −1.7 to 3.0), at cost of four additional missed PE diagnoses at baseline, for a projected 3-month VTE failure rate of 0.75% (95% CI, 0.49–1.13). None of the other studied scenarios showed relevant improvements in efficiency as well, but all led to more missed diagnoses.

Conclusion

In our cohort, there was no added value of implementing ADJUST in the YEARS algorithm.

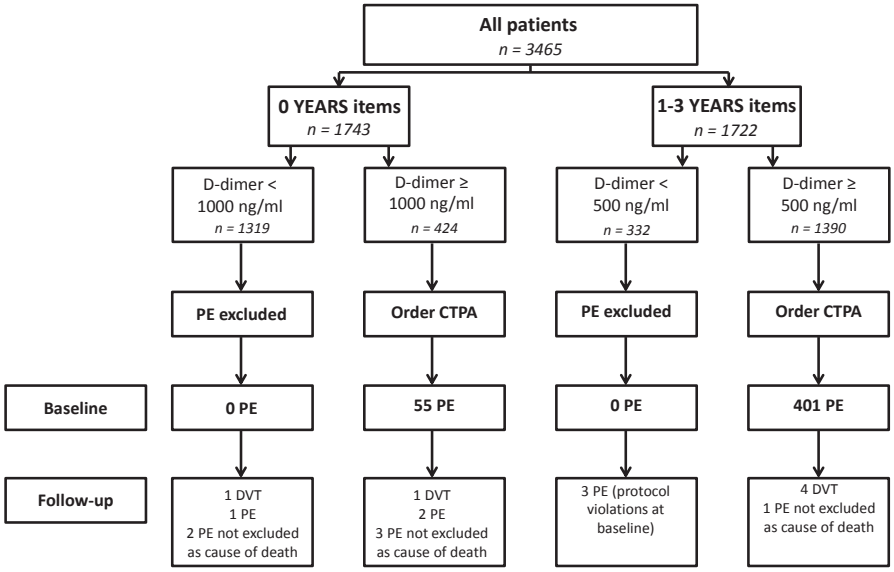
INTRODUCTION

In patients with clinically suspected pulmonary embolism (PE), a fast and accurate diagnosis is mandatory to initiate anticoagulant treatment without delay in those patients with confirmed disease and to withhold such treatment in patients in whom the disease is ruled out. The diagnostic process of PE is, however, challenging because of the non-specific and highly variable clinical presentation of PE. Routine use of clinical decision rules and the D-dimer test is therefore an important step in the standardized diagnostic approach for patients with suspected PE, because these assist in separating patients who need to be referred for imaging tests from those in whom PE can be ruled without further tests (1).

D-dimer testing has a high sensitivity for venous thromboembolism (VTE). The majority of patients, however, still require imaging tests because of its low specificity. In elderly patients the D-dimer test is even less specific than in younger patients because of a steady rise of the D-dimer with aging (2-4). To further decrease the number of required imaging tests in the diagnostic work-up of suspected PE, two novel diagnostic strategies have been suggested and validated (5, 6). The first strategy involves an age-adjusted D-dimer threshold in patients aged 50 years or older (ADJUST), defined as patients' age × 10 ng/mL (Figure 1d) (2, 5). With this strategy, the number of patients aged 50 years or older in whom PE could be safely ruled out without imaging increased from 25% to 35% without an increase in the number of missed diagnoses at baseline, for a reported 3-month failure rate of 0.3% (95% confidence interval [CI], 0.1–1.7) (5)

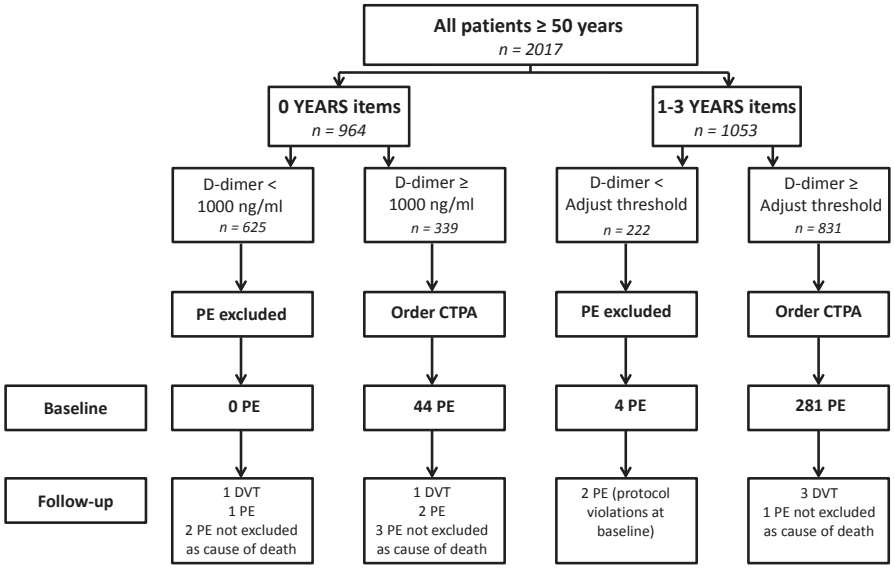
The second strategy is the YEARS algorithm, which was designed to simplify the diagnostic strategy in patients with suspected PE as well as to reduce the number of required computed tomography pulmonary angiographies (CTPAs) (Figure 1a) (7). According to YEARS, patients are managed by simultaneous assessment of the D-dimer concentration and the three YEARS items ('clinical signs deep venous thrombosis', 'hemoptysis' and 'PE most likely diagnosis'). In patients without YEARS items and a D-dimer level below 1000 ng mL^{-1}, as well as in patients with one or more YEARS items and a D-dimer level below 500 ng mL^{-1}, PE is considered to be ruled out without the need for further imaging. A recent management study demonstrated an increase in the proportion of patients managed without CTPA from 34% to 48%, for an absolute difference of 14% compared with the conventional strategy in all age categories, with a low 3-month failure rate of 0.61% (95% CI, 0.36–0.96) (6).

We hypothesized that the combination of ADJUST and YEARS could potentially further improve the efficiency of the diagnostic work-up of patients with suspected PE. We therefore set out to analyze the number of patients managed without CTPA and diagnostic failures in hypothetical scenarios with different YEARS–ADJUST combinations.



YEARS items: Clinical signs DVT, hemoptysis, "PE most likely diagnosis"

Figure 1a-d Flowcharts for four different scenarios
Figure 1a.Scenario 1: the YEARS algorithm



YEARS items: Clinical signs DVT, hemoptysis, "PE most likely diagnosis"

Figure 1b. Scenario 2: Implementing ADJUST into YEARS algorithm in patients with 1 or more YEARS items; patients aged younger than 50 years were managed according to YEARS (**Figure 1a**)

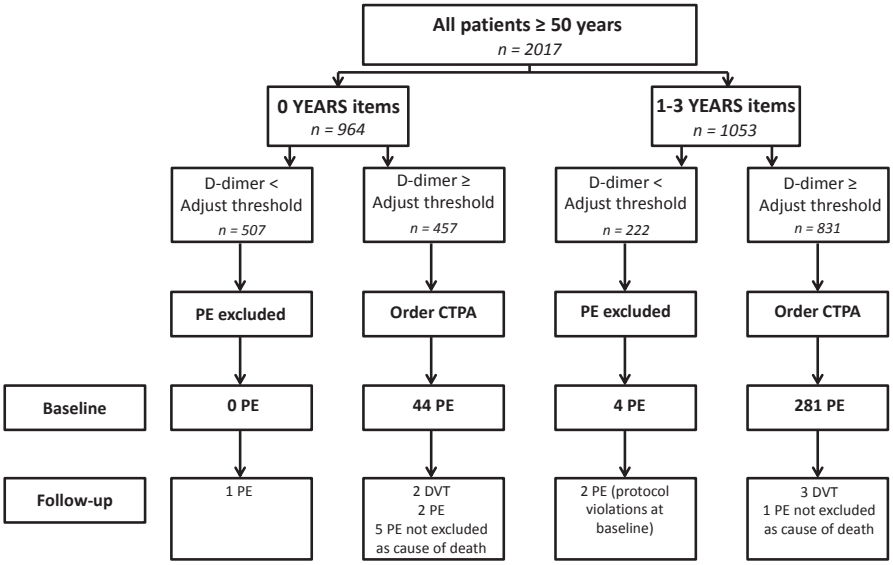


Figure 1c. Scenario 3: Implementing ADJUST into YEARS algorithm in all patients; patients younger than 50 years were managed according to YEARS (**Figure 1a**)

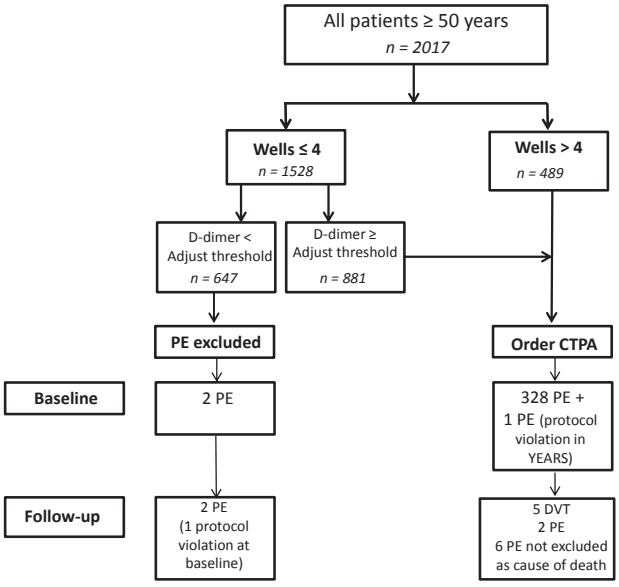


Figure 1d. Scenario 4: ADJUST

METHODS

Study population

This is a post hoc analysis of the prospective YEARS study (6). All patients were managed according to the YEARS algorithm (Figure 1a). Consecutive in- and outpatients with clinically suspected PE were included if they were 18 years or older. Exclusion criteria were pregnancy, life expectancy less than 3 months, geographic inaccessibility precluding follow-up, treatment with therapeutic doses of anticoagulants initiated ≥ 24 h prior to eligibility assessment and allergy to intravenous contrast agents. All patients were followed for 3 months for the occurrence of symptomatic recurrent or fatal VTE.

Primary aim

We studied the outcome of the algorithm in four different scenarios: (i) the YEARS algorithm, which was used to prospectively manage all patients; (ii) a hypothetical scenario with age-adjusted D-dimer threshold for patients aged ≥ 50 years and one or more YEARS items, with all other patients managed according to YEARS; (iii) a hypothetical scenario with age-adjusted D-dimer threshold for all patients aged ≥ 50 years and with all patients younger than 50 years managed according to YEARS; and (iv) all patients managed according to the conventional algorithm (i.e. using the Wells clinical decision rule, with age-adjusted D-dimer threshold for patients aged ≥ 50 years and a D-dimer threshold of 500 ng mL^{-1} for patients younger than 50 years) (Figure 1a, b, c and d). For all our scenarios, we assumed that patients would have been referred for CTPA when the D-dimer was above the predefined threshold and PE would have been considered ruled out in patients with a D-dimer below that threshold.

The YEARS algorithm is detailed in (Figure 1a). For the second and third scenario, the age-adjusted D-dimer threshold was calculated for all patients of 50 years and older. In the second scenario, we evaluated the endpoints of this study as if all patients of 50 years and older with one or more YEARS items were managed according to ADJUST (Figure 1b). For the third scenario, we evaluated the endpoints of this study as if all patients younger than 50 years were managed according to the D-dimer threshold of the YEARS algorithm and all patients of 50 years and older according to ADJUST (Figure 1c). To investigate the fourth scenario (full ADJUST algorithm), the complete Wells score was calculated for all patients to assess the clinical probability of PE (Figure 1d). All items of the Wells score were prospectively assessed in the study at baseline for post hoc analyses. Patients aged 50 years or older were managed according to the age-adjusted D-dimer cut-off and patients younger than 50 years according to the predefined threshold of 500 ng mL^{-1}. Lastly, we predefined a subgroup analysis restricted to patients aged 50 years or older for all four scenarios.

If more patients had been referred for CTPA in scenarios 2, 3 and 4, it is important to keep in mind that these CTPAs were not performed and the results of these scans, which could have detected additional PE cases, remain unknown.

Endpoints

Our safety endpoint was the failure rate of the algorithm (i.e. the number of missed PE diagnoses at baseline and recurrent or fatal VTE during the 3-month follow-up for all scenarios). The efficiency endpoint was the proportion of patients managed without CTPA.

Statistical analysis

An absolute difference with 95% confidence interval between the different scenarios was calculated to compare the proportion of patients managed without CTPA and the failure rate of the four scenarios. All analyses were performed using SPSS, version 23.0 (Chicago, IL, USA).

RESULTS

Patient characteristics

Between October 2013 and July 2015, 3465 consecutive patients were included in the YEARS study in 12 hospitals in the Netherlands (6). The mean age of these patients was 53 years, 62% were female patients and 42% of the patients were above the age of 50 years (Table 1). PE was diagnosed in 456 patients for an incidence of 13%. Contraceptive use was registered in 10% of the patients, 10% of all patients were familiar with prior VTE and 12% were immobilized or underwent surgery in the last 4 weeks.

Scenario 1: YEARS algorithm

In the YEARS study, 1651 patients (48%) were managed without CTPA, of whom 1319 patients were in the group without YEARS items and 332 patients in the group with one to three YEARS items. Pulmonary embolism was diagnosed in 456 patients (13%). During the 3-month follow-up period, nine patients with an initial negative ruling by the algorithm who remained untreated were diagnosed with VTE and PE could not be ruled out as cause of death in six additional patients. Furthermore, PE was diagnosed in three patients at baseline on CTPA that was not indicated, for a total failure rate of 18/2946 (0.61%; 95% CI, 0.36–0.96) (Table 2) (6).

Scenario 2: Implementing ADJUST into the YEARS algorithm in patients with one or more YEARS items

If the age-adjusted D-dimer threshold had been only applied in those patients with at least one YEARS item, 1747 patients (50%) could have been managed without CTPA, for an absolute difference of 2.8% (95% CI, 0.42–5.1) compared with YEARS. This higher proportion of patients managed without CTPA in this scenario corresponded to a projected failure rate of 0.75% (22/2946; 95% CI, 0.5–1.1), because of four patients with a PE that would have been missed at baseline (Table 2).

Table 1: Patient characteristics

Characteristics	All patients (n=3465)	Patients ≥ 50 years (n=2017)
Female sex, n (%)	2154 (62.2)	1183 (58.7)
Mean or median age, years (SD or 25IQR-75IQR)	53.3 (18.2)	65.0 (57.0-74.0)
Body Mass Index, mean (SD)	27.2 (7.9)	27.2 (6.0)
Outpatients, n (%)	2995 (86.4)	1727 (85.6)
Use of hormonal therapy in women, n (%)	337 (9.8)	31 (1.5)
Smoking, n (%)	830 (24.0)	409 (20.3)
Prior VTE, n (%)	359 (10.4)	229 (11.4)
Immobilisation ≥ 3 days or surgery in the last 4 weeks, n (%)	407 (11.7)	258 (12.8)
Cardiovascular comorbidity, n (%)	137 (4.0)	112 (6.0)
COPD, n (%)	423 (12.2)	378 (18.7)
Active malignancy, n (%)	336 (9.7)	276 (13.7)
YEARS items		
0 items	1743 (50.3)	964 (47.8)
1-3 items	1722 (49.7)	1053 (52.2)
YEARS items		
Clinically suspected DVT, n (%)	112 (3.2)	79 (3.9)
Hemoptysis, n(%)	137 (4.0)	69 (3.4)
"PE most likely diagnosis", n(%)	1625 (46.9)	999 (49.5)

Abbreviations: the denominator for all numbers in this table is the total number of all patients (n = 3465) or the total number of patients aged 50 years or older (n = 2017). SD: standard deviation; IQR: interquartile range; VTE: venous thrombo-embolism; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; PE: pulmonary embolism

Scenario 3: Implementing ADJUST into the YEARS algorithm in all patients

If the age-adjusted D-dimer cut-off had been used in all patients, 1627 patients (47%) would have been managed without CTPA, an absolute decrease of 0.69% (95% CI, −1.7 to 3.0) lower than YEARS (Table 2). Four patients with one to three YEARS items and a D-dimer below the age-adjusted threshold with a confirmed PE would have been missed, resulting in a projected 3-month VTE failure rate of 0.75% (22/2946; 95% CI, 0.5 to 1.1).

Scenario 4: ADJUST

If the full Wells clinical decision rule had been applied with the age-adjusted D-dimer threshold for patients of 50 years or older, 1348 patients (39%) could have been managed without CTPA at baseline, an absolute 8.7% (95% CI, 6.4–11) decrease in comparison to YEARS. According to ADJUST, two patients with PE at baseline would have been missed because of low clinical probability and a D-dimer below the age-adjusted threshold. During 3 months follow-up, 10 patients would have been diagnosed with VTE and PE could not be excluded as cause of death in six patients. On the other hand, two patients diagnosed with PE

Table 2: Overview of the 4 different scenarios in all patients

	Number of patients managed without CTPA, n (%)	Failure rate, n (%)	Absolute difference number of patients managed without CTPA compared to scenario 1: YEARS, % (95%CI)	Absolute difference failure rate compared to scenario 1: YEARS, % (95% CI)
Scenario 1: YEARS, n (%)	1651/3465 (47.7)	18/2946 (0.61)		
Scenario 2: ADJUST combined with YEARS in patients with ≥1 YEARS-item, n (%)	1747/3465 (50.4)	22/2946 (0.75)	+ 2.8 (0.42-5.1)	+ 0.14 (-0.30-0.58)
Scenario 3: ADJUST combined with YEARS in all patients, n (%)	1627/3465 (47.0%)	22/2946 (0.75)	- 0.69 (-3.0-1.7)	+ 0.14 (-0.30-0.58)
Scenario 4: ADJUST, n (%)	1348/3465 (38.9)	18/2946 (0.61)	- 8.7 (-11 – -6.4)	0

Abbreviations: CTPA: computed tomography pulmonary angiography; CI: confidence interval

at baseline by protocol violation in YEARS, had a D-dimer above the age-adjusted threshold and would therefore have been referred for CTPA by the ADJUST algorithm. Taken together, the projected 3-month VTE failure rate would therefore have been 0.61% (95% CI, 0.36–0.96) (Table 2).

Subgroup analysis restricted to patients of 50 years or older

The YEARS study included 2017 patients of 50 years or older, with a median age of 65 years (interquartile range [IQR] 57–64). PE was diagnosed in 330 patients for a PE incidence of 16%. Other patient characteristics are listed in Table 1. Following YEARS, PE was ruled out in 752 (37%) patients without CTPA. The 3-month VTE failure rate was 0.98% (16/1642; 95% CI, 0.60–1.6; Table 3). In scenario 2, the absolute difference in patients managed without CTPA would have been 4.7% (95% CI, 1.7–7.7) higher. This significant difference came at a cost of a 3-month failure rate of 1.2% (20/1642; 95% CI, 0.79–1.9) (Table 3). In scenario 3, 1.2% (95% CI, −1.8 to 4.2) fewer patients could have been managed without CTPA than in YEARS, at a cost of a 3-month failure rate of 1.2% (20/1642; 95% CI, 0.79–1.9). Lastly, if the ADJUST strategy had been used, 5.2% (95% CI, 2.3–8.1) fewer patients could have been managed without CTPA than in YEARS, at a cost of a 3-month failure rate of 0.97% (16/1642; 95% CI, 0.60–1.6).

Table 3: Overview of the four different scenarios in the subgroup analysis of patients ≥ 50 years

	Number of patients managed without CTPA, n (%)	Failure rate, n (%)	Absolute difference number of patients managed without CTPA compared to scenario 1: YEARS, % (95%CI)	Absolute difference failure rate compared to scenario 1: YEARS, % (95% CI)
Scenario 1: YEARS, n (%)	752/2017 (37.3)	16/1642 (0.97)		
Scenario 2: ADJUST combined with YEARS in patients with ≥1 YEARS-item, n (%)	847/2017 (42.0)	20/1642 (1.2)	+ 4.7 (1.7-7.7)	+ 0.24 (-0.50-1.0)
Scenario 3: ADJUST combined with YEARS in all patients, n (%)	729/2017 (36.1)	20/1642 (1.2)	- 1.1 (-4.1-1.8)	+ 0.24 (-0.50-1.0)
Scenario 4: ADJUST, n (%)	647/2017 (32.1)	16/1642 (0.97)	- 5.2 (-8.1 – -2.3)	0

Abbreviations: CTPA: computed tomography pulmonary angiography; CI: confidence interval

DISCUSSION

In this post hoc analysis of the YEARS study we found no added value of implementing ADJUST in the YEARS algorithm in different scenarios studied, as well as among the subgroup of patients older than 50 years. Only the scenario in which the age-adjusted D-dimer threshold was implemented in patients of 50 years and older with at least one YEARS item (scenario 2) was associated with a projected significant further decrease in the number of required CTPA scans, at a cost of four missed PE diagnoses at baseline.

Imaging is warranted to confirm or rule out the diagnosis of PE when the D-dimer is above the threshold in patients with suspected PE. The associated exposure to radiation, the risk of contrast-induced nephropathy, the potential for over-diagnosis and the associated costs of radiological tests are important reasons to limit the number of required scans to a minimum (8). Einstein et al. studied the lifetime attributable risk of cancer associated with radiation exposure. This study demonstrated an unneglectable lifetime attributable risk of cancer varying from 0.075% to 0.70%, with the highest risk in women and in younger patients. The highest lifetime risk of cancer was for lung and breast cancer (9). Mathews et al. performed a large population-based cohort study to assess the risk of cancer following exposure to radiation from diagnostic CT scans. The overall incidence of cancer was 24% higher after exposure to radiation compared with unexposed people (10).

The incidence of contrast-induced nephropathy varies between 2.6 and 14% after CTPA for suspected PE (11-14). Kooiman et al. demonstrated in a retrospective analysis that age over 75 years is an independent predictor for contrast-induced nephropathy, as are multiple myeloma, use of non-steroidal anti-inflammatory drugs (NSAIDs) and diabetes mellitus

(13). With increased utilization of CTPA, the incidence of other adverse reactions to iodinated contrast media has increased as well. For instance, the incidence of hypersensitivity reactions has been estimated to be between 0.1 and 0.6% of patients injected with non-ionic iodinated contrast media (15, 16). The majority of hypersensitivity reactions are mild, but the less frequent moderate and severe reactions may be life threatening (17).

Based on previous studies (18), we hypothesized that combining the age-adjusted threshold with the YEARS algorithm would be associated with a further reduction in the number of CTPAs in elderly patients. Our hypothesis was, however, rejected by the results of this study, with similar findings across almost all scenarios and in the subgroup analysis of patients aged 50 years or older. Only in scenario 2, was the proportion of patients managed without CTPA higher, with an absolute difference of 4.7% (95% CI, 1.7–7.7) compared with YEARS. Even so, this reduction of CTPAs came at a cost of four additional failures, with missed diagnosis of PE at baseline, which is in our opinion an unacceptably high failure rate to save this limited number of CTPAs. Moreover, implementing scenario 2 in a busy clinical practice would introduce a large amount of complexity into the YEARS algorithm, which was designed to simplify the diagnostic work-up of patients with suspected PE. Prior studies demonstrated poor adherence of clinicians to pre-test probability rules and following algorithms, with an even higher risk of inappropriate management in patients older than 75 years (19, 20). Use of the age-adjusted D-dimer cut-off only in patients of 50 years and older with at least one YEARS item will likely to increase the risk of inappropriate management of patients with suspected PE, compromising the safety of the algorithm.

The main strength of our study is the inclusion of a large number of consecutive in- and outpatients with suspected PE. Data were prospectively collected and all events during follow-up were adjudicated by an independent committee. Moreover, we studied the potential improvement of the algorithm in different scenarios.

The main limitation of this post hoc analysis is that patients were not randomized between the four studied strategies. Only patients with a D-dimer above the established threshold of YEARS were referred for CTPA. Hence, we could not directly compare the results of the scenarios. For this reason, it is not known if all diagnosed PEs that would have been missed in the different scenarios were clinically relevant (i.e. that the relevant patients indeed would have benefited from treatment with oral anticoagulants). Vice versa, it is not known whether the extra CTPA scans that would have been made in the different scenarios would not have shown additional PEs. Even so, we consider the low risk of events during the study follow-up as a strong argument that important PE diagnoses were not missed by the YEARS algorithm. Moreover, these post hoc analyses were performed without a sample size calculation and may have been underpowered. Therefore, our findings should be regarded as hypothesis generating. Nevertheless, our findings do not justify a prospective study to find a more definite answer to our research question. The second limitation is the somewhat lower incidence of PE in the YEARS study compared with other European studies, although our subgroup

analysis in patients of 50 years and older demonstrated a low failure rate despite the higher incidence of PE of 16% in this group.

In conclusion, there was no added value of implementing ADJUST in the YEARS algorithm in our cohort. Reduction in the proportion of patients managed without CTPA was only found in scenario 2, although at the unacceptable cost of four additional diagnostic failures. In our cohort both for patients under 50 years and those over the age of 50 years, YEARS was associated with the most beneficial safety and efficiency profile of all the studied diagnostic scenarios.

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Chapter 7

Combination of pulmonary embolism rule-out criteria (PERC) and YEARS algorithm in a European cohort of patients with suspected pulmonary embolism

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ABSTRACT

Background

Both the YEARS algorithm and the pulmonary embolism (PE) rule-out criteria (PERC) were created to exclude PE with limited diagnostic tests. A diagnostic strategy combining both scores might save additional computed tomography pulmonary angiography (CTPA) scans, but they have never been evaluated in conjunction.

Aim

The aim of this study was to determine the safety and efficiency of combining YEARS and PERC in a single diagnostic strategy for suspected PE.

Methods

The PERC rule was assessed in 1,316 consecutive patients with suspected PE who were managed according to YEARS. We calculated the absolute difference (with 95% confidence interval [CI]) in failure rate and the number of 'saved' CTPAs for the scenario that PE would have been ruled out without CTPA in the absence of all PERC items.

Results

Using the YEARS algorithm, PE was diagnosed in 189 patients (14%), 680 patients (52%) were managed without CTPA and the 3-month rate of venous thromboembolism in patients in whom PE was ruled out was 0.44% (95% CI: 0.19–1.0). Only 6 of 154 patients (3.9%; 95% CI: 1.4–8.2) with no YEARS items who were referred for CTPA would have been PERC negative, of whom none were diagnosed with PE at baseline or during follow-up (0%; 95% CI: 0–64). Applying PERC before YEARS in all patients would have led to a failure rate of 1.42% (95% CI: 0.87–2.3%), 0.98% (95% CI: 0.17–1.9) more than shown in patients managed by YEARS.

Conclusion

Combining YEARS with PERC would have yielded only a modest improvement of efficiency in patients without a YEARS item and an unacceptable failure rate in patients with ≥1 YEARS item.

INTRODUCTION

The diagnostic management of suspected pulmonary embolism (PE) remains challenging, due to the nonspecific clinical presentation of acute PE in combination with the potential harmful imaging test that is required in most cases of suspected PE to rule out the disease (1). It has been widely demonstrated that PE can be ruled out in patients with an unlikely clinical probability in combination with a normal high-sensitive D-dimer test, without any imaging tests (1, 2, 3). The best validated and most widely used clinical decision rules are the Wells rule and revised Geneva score (4, 5). The YEARS algorithm, designed to further decrease the number of required imaging tests that includes parallel D-dimer and pretest probability assessment, was recently evaluated in a large outcome trial (Figure 1) (6). It was shown to safely rule out acute PE with a low failure rate of 0.61% (95% confidence interval [CI]: 0.36–0.96). Only 52% of all patients were referred for computed tomography pulmonary angiography (CTPA), a reduction of 14% points compared with the traditional diagnostic algorithm (6).

The PE rule-out criteria (PERC) are based on eight criteria (age < 50 years, heartbeat < 100/min, SaO_2 > 94%, no unilateral leg swelling, no haemoptysis, no recent trauma or surgery, no hormone use and no previous venous thromboembolism) and patients are considered to be negative when all these criteria were met (Table 1). This rule was designed to identify patients with respiratory or chest symptoms who have a very low risk of PE and do not need further

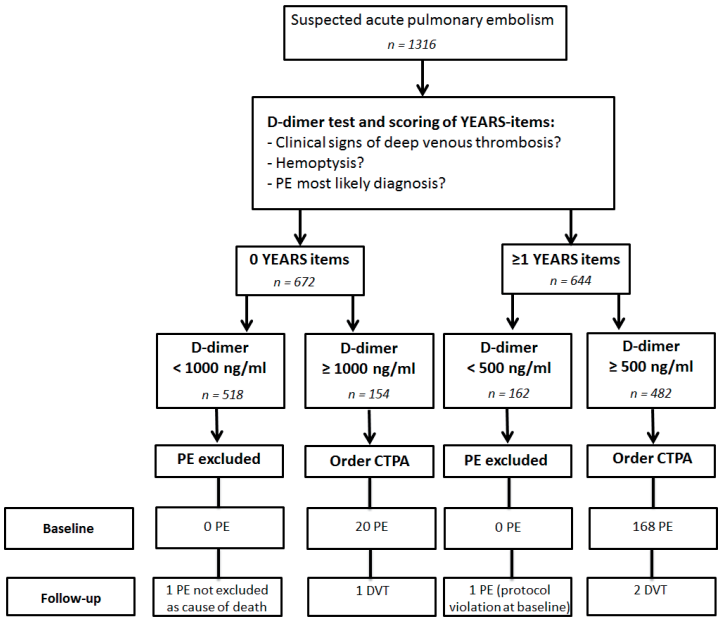

Figure 1. The YEARS algorithm with numbers of patients analyzed in this study. CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 1: The pulmonary embolism rule-out criteria (PERC)

Age < 50 years
Heartbeat < 100 beats per minute
SO_2 > 94%
No hemoptysis
No estrogen use
No surgery or trauma requiring hospitalization in the last four weeks
No unilateral leg swelling
No previous venous thrombo-embolism

clinical evaluation with clinical prediction rule, D-dimer test or imaging (7). The most recent American College of Physicians guideline suggests application of PERC in all patients judged to be at low risk for PE after initial clinical evaluation (Class II recommendation) (8).

The aim of this study was to evaluate whether the PERC rule has incremental diagnostic value to the YEARS algorithm, that is, whether the application of PERC as a standard test before the YEARS items are assessed and D-dimer levels are measured, further reduces the number of necessary CTPA examinations without compromising the safety of the algorithm.

METHODS

Study Population

This study is a post hoc analysis of the YEARS study in which consecutive in- and outpatients with clinically suspected PE were included if they were aged 18 years or older (6). All patients were managed according to the YEARS diagnostic algorithm for suspected PE (Figure 1). Patients who were referred for CTPA without an indication following the YEARS algorithm were regarded as protocol violations. Only outpatients who presented at the emergency department were included in this post hoc analysis. Exclusion criteria were allergy to intravenous contrast, pregnancy, treatment with anticoagulants initiated $\geq$ 24 hours before eligibility assessment, geographic inaccessibility precluding follow-up and life expectancy less than 3 months. All patients who were hospitalized at date of inclusion or in patients in whom the PERC items were not available were also excluded from this analysis. The follow-up consisted of a 3-month period for the occurrence of recurrent and/or fatal venous thromboembolism.

The current analysis was restricted to two of the participating hospitals of the YEARS study, that is, the Leiden University Medical Center (Leiden, the Netherlands) and the Haga Teaching Hospital (The Hague, the Netherlands) because PERC items were prospectively assessed along with the YEARS items by an independent researcher for all patients. Results of the PERC score were not registered in the patient charts and these results were therefore not used for initial management decisions.

Study Objectives

The primary aim of this study was to investigate the safety of applying the PERC rule before the YEARS algorithm in our cohort. The secondary aim of this study was to determine the efficacy of applying the PERC rule before the YEARS algorithm in our cohort. Our primary outcome was the absolute difference in the hypothetical failure rate of the algorithm when PERC would have been applied before the YEARS algorithm and the actual observed failure rate. The secondary outcome was the absolute difference in the number of required CTPA examinations between the combination of PERC and YEARS and the YEARS algorithm alone.

Statistical Analysis

The total score of the PERC rule was calculated for all patients. The PERC rule was negative when none of the eight items were present. If one or more items were present, the PERC rule was scored positive. After categorizing all patients as PERC negative or positive, the hypothetical number of diagnostic failures and required CTPAs were calculated. Diagnostic failures were defined as patients with confirmed PE at baseline or during 3-month follow-up. The proportion of required CTPAs and the 3-month venous thromboembolism (VTE) failure rate of the algorithm were calculated. The absolute differences and 95% CIs between the combination of PERC and YEARS and YEARS alone were calculated. All analyses were performed using SPSS, version 23.0 (Chicago, Illinois, United States).

RESULTS

Study Population

A total number of 1,443 patients with suspected PE were included in the YEARS study in the two hospitals. Of these patients, 111 patients were excluded because they were hospitalized at the moment of inclusion, as were 16 patients in whom the PERC rule could not be calculated due to missing data. After exclusion of these patients, 1,316 patients were entered in the current analysis. PE was confirmed in 188 patients for a PE prevalence of 14%. The mean age was 53 years (standard deviation [SD]: 18.8), the majority of patients were female (64%), 11% of the patients were known with a prior VTE, 9% were diagnosed with a malignancy before inclusions and 12% underwent surgery in the last 4 weeks or immobilization for more than 3 days (Table 2).

YEARS Algorithm

According to the YEARS algorithm, 672 patients had no YEARS items and 644 patients had a least one YEARS item. CTPA was required in 636 patients (48%) to confirm or rule out the diagnosis of PE, of whom 188 patients were diagnosed with PE at baseline (Figure 1).

Table 2 Demographical characteristics

	All patients	PERC negative patients	PERC positive patients
Number of patients (n)	1316	250	1066
Age (years), mean ± SD	53.4 ± 18.8	36.7 ± 9.4	57.4 ± 18.3
Women, n (%)	838 (63.7)	159 (63.6)	679 (63.7)
Pulmonary embolism confirmed, n (%)	188 (14.3)	11 (4.4)	178 (16.7)
Risk factors			
Previous PE, n (%)	144 (10.9)	0 (0)	144 (13.5)
Active malignancy, n (%)	119 (9.0)	11 (4.4)	108 (10.1)
Use of exogenous hormones, n (%)	127 (9.7)	0 (0)	127 (11.9)
Immobilization or surgery in last 4 weeks, n (%)	156 (11.9)	0 (0)	156 (14.6)
YEARS-score			
D-dimer < 1000 ng/ml and 0 items, n (%)	518 (39.4)	156 (62.4)	362 (34.0)
D-dimer > 1000 ng/ml and 0 items, n (%)	154 (11.7)	6 (2.4)	148 (13.9)
D-dimer < 500 ng/ml and ≥ 1 item, n (%)	162 (12.3)	37 (14.8)	125 (11.7)
D-dimer > 500 ng/ml and ≥ 1 item, n (%)	482 (36.6)	51 (20.4)	431 (40.4)

Abbreviations: PERC: pulmonary embolism rule-out criteria; SD: standard deviation; PE: pulmonary embolism

During 3-month follow-up, five patients suffered from VTE (three with deep vein thrombosis (DVT), one PE diagnosed at baseline due to protocol violation and one patient in whom PE could not be excluded as cause of death; Figure 1]. The 3-month VTE failure rate of the algorithm was 0.44% (5 out of 1,128, 95% CI: 0.19–1.0).

Applying PERC before YEARS

Of all patients, 250 (19%) would have been PERC negative. The mean age of this PERC-negative cohort was 36.7 years (SD: 9.4) and 159 patients were female (64%). PE was confirmed in 11 of these 250 patients at baseline by CTPA for a prevalence of 4.4%. A total of 1,066 patients were PERC positive. PE was confirmed in 178 of these patients at baseline (16.7%). Their mean age was 57.4 years (SD: 18.3), 64% were female and 14% was known with a history of VTE (Table 2).#

PERC-Negative Patients

From the PERC-negative patients, 162 had zero YEARS item and 88 patients had one to three YEARS items (Figure 2a; Table 2). Of the 162 patients without YEARS items, 156 patients had a D-dimer < 1,000 ng/mL and 6 patients had a D-dimer ≥ 1,000 ng/mL and were referred for CTPA (3.7%, 95% CI: 1.7–7.8). None of these PERC-negative patients without YEARS items were diagnosed with PE at baseline or during follow-up for a failure rate of 0.0% (95% CI: 0.0–2.3). From the 88 PERC-negative patients with at least one YEARS item, 37 patients had

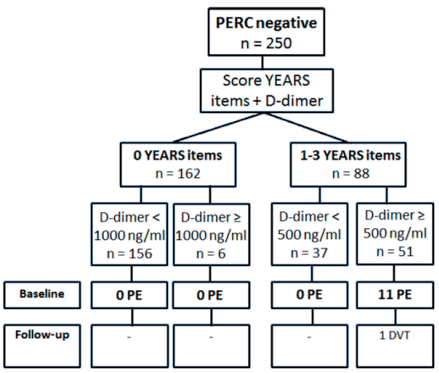

Figure 2a

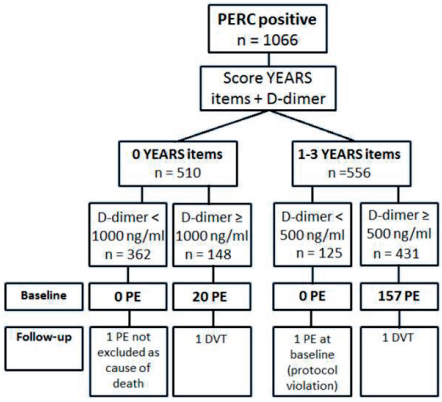

Figure 2b

Figure 2. Outcome of hypothetical situation of the application of PERC before YEARS, with (a) PERC-negative patients and (b) PERC-positive patients. PERC, pulmonary embolism rule-out criteria.
Abbreviations: PE = pulmonary embolism, DVT = deep venous thrombosis

a D-dimer < 500 ng/mL, none of these patients was diagnosed with PE at baseline and there were no events during follow-up in this group. A total of 51 patients had a D-dimer ≥ 500 ng/mL and were referred for CTPA. PE was diagnosed in 11 of these latter patients at baseline and 1 patient suffered from DVT during follow-up (Figure 2a). In patients who were PERC negative, the absolute difference in the number of required CTPAs was 2.4% (95% CI: −9.6 to 4.8) lower than by using the YEARS algorithm at the cost of a failure rate of 4.8% (12 out of 250, 95% CI: 2.8–8.2).

PERC-Positive Patients

From all PERC-positive patients, 510 patients had no YEARS item and 556 patients had at least one YEARS item (Figure 2b). In the group of PERC-positive patients without YEARS items, 362 patients had a D-dimer < 1,000 ng/mL. None of these patients was diagnosed with PE at baseline and in one patient, PE could not be excluded as a cause of death during follow-up. A total number of 148 patients had a D-dimer ≥ 1,000 ng/mL and were referred for CTPA, PE was confirmed in 20 patients at baseline. One patient was diagnosed with a DVT during follow-up. In the group of patients with at least one YEARS item, 125 patients had a D-dimer < 500 ng/mL of which 1 patient was diagnosed with PE at baseline as protocol violation in YEARS; 431 patients had a D-dimer ≥ 500 ng/mL and were referred for CTPA, 157 patients were diagnosed with PE at baseline (Figure 2b). During 3-month follow-up, one patient was diagnosed with DVT.

Combination of PERC and YEARS

Compared with the YEARS diagnostic strategy, the absolute difference in 3-month VTE failure rate of the combination of PERC and YEARS was 0.98% (95% CI: 0.17–1.9) higher compared with YEARS alone (Table 3). When PERC would have been applied before YEARS, only 579 patients (44%) would have been referred for CTPA for an absolute difference of 4.3% (0.52–8.1) in favour of the PERC/YEARS combination (Table 3).

Table 3 Overview of primary and secondary study outcome.

	Failure rate	Number of required CTPAs
YEARS, n **% (95%CI)**	5/1128, 0.44 (0.19-1.0)	636/1316, 48 (46-51)
PERC + YEARS, n **% (95%CI)**	16/1128, 1.4 (0.87-2.3)	579/1316, 44 (41-47)
Absolute difference compared to YEARS, n % (95%CI)	11/1128 + 0.98 (0.17-1.9)	57/1316 - 4.3 (0.52-8.1)

Abbreviations: CTPA: computed tomography pulmonary angiography; CI: confidence interval; PERC: pulmonary embolism rule-out criteria

DISCUSSION

In this post hoc analysis of the YEARS study, we demonstrated a modest decrease in the number of required CTPAs when the PERC rule would have been applied before the YEARS algorithm. The small 4.3% (95% CI: 0.52–8.1) increase in efficiency came at the cost of a higher failure rate of 0.98% (95% CI: 0.17–1.9). PERC was designed for patients who have a low suspicion on PE according to the treating physician's gestalt. In our analysis, we hypothetically applied PERC to all patients with suspected PE as initial diagnostic test. With all diagnostic failures by PERC at baseline in patients with at least one YEARS item, it could be argued that these failures did not occur in the patient category for which PERC was developed. Nevertheless, when we would apply PERC as extension to YEARS in patients without any YEARS items, the efficacy improvement was very modest, thus supporting our conclusion that PERC has no added value to YEARS in diagnostic management of patients with suspected PE in a Western European emergency ward setting.

The PERC rule was derived with the intention of defining a group of patients who have such a low risk of PE that PE can be ruled out without further diagnostic tests (7). One of the largest performed studies to evaluate the PERC rule was performed in the United States by Kline et al. A total number of 8,183 patients were enrolled in this study, with a PE prevalence of 6.3% at baseline. The PERC rule was found to be negative in 20% of all patients. In this subgroup, only 1.0% of patients suffered VTE during a 45-day follow-up, with an upper limit

of the 95% CI of 1.6% (9). These findings were confirmed in other studies from the North American continent (7, 10, 11).

Clearly, the reported low failure rate justified implementation of PERC in the U.S. emergency setting. Nevertheless, the reported PE prevalence is lower in the United States than in countries outside the United States (12). However, the specificity of the PERC rule appears to increase as the risk of PE in the population decreases, in accordance with Bayes' theorem (13). In other words, PERC rule can be safely applied in a population with a low to very low baseline pretest probability of PE, but may be unsafe in populations with higher PE prevalence (14). This hypothesis was confirmed in our analysis as well in several previous European studies (15-17). Hugli et al demonstrated a PE prevalence of 5.4% (95% CI: 3.1–9.3) in patients who were PERC negative in a cohort with a PE prevalence of 21.3% (16). Righini et al evaluated the use of the PERC rule as well in a cohort with a high PE prevalence of 25.6% (95% CI: 23–39) (17). Of all the PERC-negative patients in this study, 6.7% (95% CI: 3–14) were diagnosed with PE and would have been missed by the PERC rule. Moreover, these studies demonstrated that only a small proportion of patients was PERC negative, ranging from 7.7 to 13.2%, in contrast to the prevalence of 20% PERC-negative patients with a low false-negative rate of 1.0% (95% CI upper limit of 1.6%) in the U.S. studies (9, 15, 16).

A recent report of a large European study focusing on the safety of PERC concluded that PERC can exclude acute PE with a low percentage of false-negative results (18). Importantly, as in our study, PERC was not used as a primary diagnostic test but as a second test in patients with an estimated low clinical probability of PE based on assessment by the physician and calculation of the revised Geneva score. In these patients with a very low PE prevalence of 4.7% and no PERC item, the 3-month risk of symptomatic VTE was 1.2% (95% CI upper limit of 2.9%). From this study, the overall accuracy of a negative PERC score ruling as single test could not be extracted. A current prospective study in France is recruiting patients to implement and evaluate the PERC rule in a cluster randomized trial in 15 different hospitals (NCT02375919) (19). Each centre will be randomized for the sequence of a 6-month intervention period (using the PERC strategy), followed by a control period of 6 months where usual care will be applied. Awaiting the results of this trial, current evidence does not allow standard application of the PERC rule in an emergency setting in European countries.

Recently, the combination of the age-adjusted D-dimer threshold and the YEARS algorithm was analysed to reduce the number of required CTPAs further (20). Different scenarios, even in subgroup populations of patients aged 50 years and older, showed, however, no safe reduction in the number of required CTPAs. It is therefore possible that the limit of required CTPAs has been reached with YEARS.

Strengths of this post hoc analysis are the large sample size, the accurate follow-up of the included patients as well as the adjudication of the end points by an independent committee. The PE prevalence in our cohort was representable and comparable to other European cohorts of patients with suspected PE. The main limitation of our analysis is that this is a post

hoc analysis and patients were not managed according to the hypothetical scenario of using PERC before YEARS. Also, despite our large sample size of the total study cohort, a relatively small number (250 patients) would have been PERC negative. In our opinion, our results of this analysis do not justify a further prospective study to answer the research question more precise.

In conclusion, applying PERC before the start of the YEARS algorithm would have yielded a modest decrease in the proportion of required diagnostic tests at the cost of a higher failure rate of the algorithm.

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Chapter 8

The YEARS algorithm for suspected pulmonary embolism: Shorter visit time and reduced costs at the Emergency department

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SUMMARY

Background

Recently, the safety of the YEARS algorithm, designed to simplify the diagnostic work-up of pulmonary embolism (PE), was demonstrated. We hypothesize that by design, YEARS would be associated with a shorter diagnostic emergency department (ED) visit time due to simultaneous assessment of pre-test probability and D-dimer level and reduction in number of CT scans.

Aim

To investigate whether implementation of the YEARS diagnostic algorithm is associated with a shorter ED visit time compared with the conventional algorithm and to evaluate the associated cost savings.

Methods

We selected consecutive outpatients with suspected PE from our hospital included in the YEARS study and ADJUST-PE study. Different time-points of the diagnostic process were extracted from the to-the-minute accurate electronic patients' chart system of the ED. Further, the costs of the ED visits were estimated for both algorithms.

Results

All predefined diagnostic turnaround times were significantly shorter after implementation of YEARS: patients were discharged earlier from the ED; 54 min (95% CI, 37–70) for patients managed without computed tomography pulmonary angiography (CTPA) and 60 min (95% CI, 44–76) for the complete study population. Importantly, patients diagnosed with PE by CTPA received the first dose of anticoagulants 53 min (95% CI, 22–82) faster than those managed according to the conventional algorithm. Total costs were reduced by on average €123 per visit.

Conclusion

YEARS was shown to be associated with a shorter ED visit time compared with the conventional diagnostic algorithm, leading to faster start of treatment in the case of confirmed PE and savings on ED resources.

INTRODUCTION

Crowding of emergency departments (EDs) is a worldwide increasing concern, leading to longer duration of the ED visit, which may negatively impact the quality of care as well as access to healthcare (1). In the Netherlands 1.9 million ED visitors are registered per year, corresponding to 110 visits per 1000 persons (2). The mean duration of stay in the ED in the Netherlands is 130 min (1). An increasing length of stay in the ED has been associated with treatment delay, decreased patient satisfaction and higher risk of suboptimal or incomplete diagnostic evaluation and/or treatment (1, 3).

Most patients with acute pulmonary embolism (PE) are diagnosed in the ED (4, 5). PE-associated symptoms are non-specific and may mimic other acute cardiopulmonary conditions. This non-specific presentation is associated with an excess of diagnostic tests and diagnostic delay in the ED (6). Importantly, it is widely acknowledged that patients with PE benefit from rapid diagnosis and treatment (7-9).

The YEARS study recently demonstrated a novel diagnostic algorithm for the management of patients with suspected PE, which consists of simultaneous assessment of the YEARS items and D-dimer measurement (Figure 1). Compared with patients managed according to the conventional algorithm, the YEARS algorithm led to a 14% reduction in the need for computed tomography pulmonary angiography (CTPA), without compromising safety (10). Whether the YEARS algorithm also allows for a shorter length of stay in the ED is unknown.

The aim of this study was to investigate whether implementation of the YEARS diagnostic algorithm would lead to a shorter ED visit time than before implementation of the YEARS algorithm, when the conventional diagnostic algorithm, consisting of consecutive Wells rule

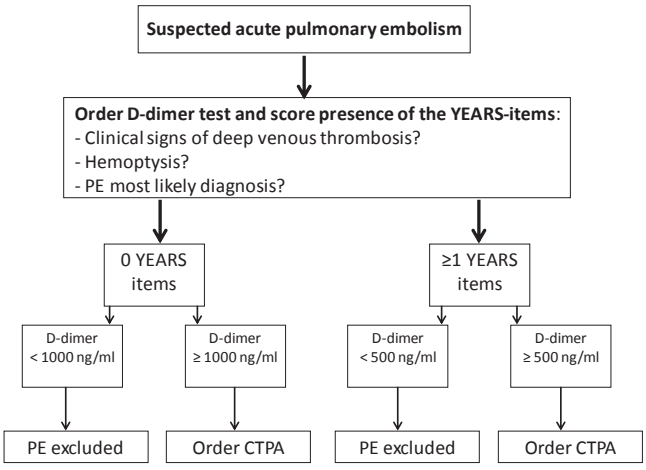

Figure 1. The YEARS algorithm. PE = pulmonary embolism; CTPA = computed tomography pulmonary angiography.

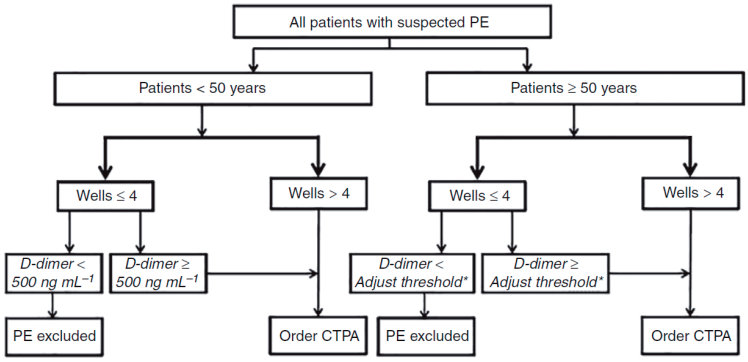

Figure 2. The ADJUST algorithm. PE = pulmonary embolism; CTPA = computed tomography pulmonary angiography. * D-dimer adjusted threshold = age x 10 (ng/mL)

and D-dimer testing in the case of unlikely clinical probability, was applied. To do so, total ED visit times of patients included in the YEARS study were compared with ED visit times of patients included in the ADJUST study, where patients were managed according to the conventional Wells rule (Figure 2). In addition, we analyzed and compared costs associated with ED visits for both diagnostic approaches.

METHODS

Study population

A post hoc analysis was performed of the combined data of patients from the Leiden University Medical Center, Leiden, the Netherlands, included in two prospective outcome studies (10, 11). The YEARS study included consecutive in- and outpatients with suspected PE between October 2013 and July 2015. All patients were managed according to the YEARS algorithm (Figure 1) (10).

The ADJUST study included consecutive outpatients with suspected PE from January 2010 to February 2013 (11). All patients were managed according to the Wells clinical decision rule and in patients with an unlikely clinical probability, a D-dimer test was performed (Figure 2). In both studies, all patients were followed for a 3-month period, and all suspected VTE events and deaths occurring in this period were adjudicated by an independent committee (10, 11).

From both studies, all patients with confirmed PE and the 265 most recently included consecutive patients with excluded PE were eligible for study inclusion (10, 11). Patients were excluded if they were transferred to another hospital from the emergency ward for logistical reasons (because of the associated excess of ED visit time) or if acute PE was not the primary suspected diagnosis at presentation, leading to clinical evaluation by more than one specialist for a broad differential diagnosis at the emergency ward, because the latter could

have led to a longer duration of stay. Patients from the ADJUST cohort were also excluded if they presented before 1 May 2011 at the emergency department, because the accurate to-the-minute time-registration system had not yet been implemented before this date. The final patient selection is illustrated in Figure 3.

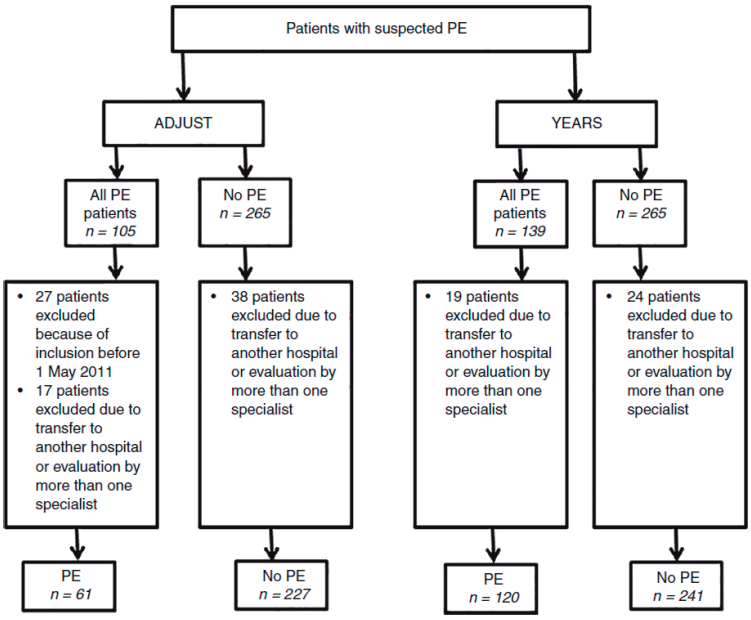

Figure 3. Flow chart of inclusion of patients

Time registration

The patients' chart system of the emergency ward consists of an accurate to-the-minute time registration of all management steps, including time of arrival, all hemodynamic and respiratory measurements, ordering of all diagnostic tests and administration of any medication. This registration system was implemented in May 2011. Different time-points of the diagnostic process were extracted from this electronic patients' chart system: start of diagnostic evaluation (defined as time of connection of the patient to the cardiac monitor, which is the first step of management of all patients after they enter the ED), time of D-dimer request (moment of electronic order), time of CTPA request (moment of electronic order), time of medication administration (moment of electronic order), time of discharge from the emergency ward and overall time spent in the emergency ward (time from start of diagnostic algorithm until discharge).

To evaluate whether the overall duration of an ED visit changed during the study period (May 2011 until February 2015), the same data were collected for all patients who presented

with suspected myocardial infarction during the month of March of the years 2012–2015, as this is a cardiovascular emergency as well.

To study other relevant factors associated with an ED visit, we also collected data on the type of referral (physician-based referral vs. self-referral), time of presentation (during office hours vs. evening/night shifts), day of presentation (weekdays vs. weekend) and presence of comorbidities such as heart failure, chronic obstructive pulmonary disease (COPD) and/or cancer.

Costs analysis

Costs during the ED visit were estimated for both algorithms in euros at the 2017 price level, including D-dimer use, CTPA use and ED capacity costs. The average number of required D-dimer tests and CTPAs to confirm or rule out PE were measured for both cohorts using the YEARS diagnostic algorithm (YEARS) or the conventional diagnostic strategy (ADJUST). Costs per D-dimer and per CTPA were set at €5 and €182, respectively (12). Capacity costs were estimated from the patients' time spent in the ED and were valued at €110 per hour, which was estimated as the average Dutch costs per ED visit (i.e. €234 per visit divided by the average Dutch ED visit time, which has been established at 130 min) (1, 12). No costs were counted for ED specialist time and subsequent healthcare (assumed identical for both strategies).

Aim of the study

Our primary aim was to determine the total turnaround time in the ED for patients with suspected PE in the YEARS cohort compared with patients from the ADJUST cohort. Our secondary aims were to evaluate factors predictive for a shorter or longer duration of stay in the emergency department and to determine whether the total turnaround time during the study period of 2012–2015 had changed.

Our primary endpoint was the time-to-diagnose in patients with suspected PE, defined as the time from start of the diagnostic algorithm to the moment of final PE diagnosis, in patients with suspected PE managed according to the YEARS algorithm compared with patients managed with the conventional algorithm (ADJUST). The turnaround time between start of the diagnostic algorithm and order for CTPA was calculated for all patients who were referred to CTPA, as were the turnaround time between start of the diagnostic algorithm and initial dose of anticoagulant treatment for all patients with proven PE, and the turnaround time between start of the diagnostic algorithm and discharge from the ED for all patients regardless of final diagnosis.

Our secondary aims were to evaluate factors predictive for a shorter or longer duration of stay in the emergency department and to determine whether the total turnaround time during the study period of 2012–2015 had changed. Also, the costs of the ED visit of patients managed according to the YEARS algorithm were compared with those costs associated with the conventional diagnostic algorithm.

Statistical analysis

Odds ratios (ORs) with 95% confidence intervals were calculated for differences in baseline characteristics between both cohorts. The independent t-test was used to evaluate differences in mean age at baseline. All time-points during the emergency ward visit are presented as median with 25–75 interquartile ranges (IQR). Absolute differences and 95% confidence intervals between medians were measured using the Hodges–Lehmann test. The association between time to diagnose and factors associated with shorter or longer stay in the emergency department were evaluated using multivariate logistic regression analysis in the combined cohorts adjusted for all identified differences in the baseline characteristics between the two cohorts, and expressed by odds ratios with 95% confidence intervals. The association of presentation during the different days of the week with ED visit time was calculated with a multinomial logistic regression analysis with a longer duration of stay as reference category. The 75th percentile was used as cut-off for a shorter or longer duration of stay. Linear regression analysis was performed to adjust the results of our primary endpoint for all identified differences in baseline characteristics between the two cohorts.

The overall duration of stay of patients with suspected myocardial infarction during the years 2012–2015 was presented as median with 25–75 interquartile ranges. The Kruskal–Wallis test was used to compare these time-points. All time-points used for the analysis of the costs of an ED visit are presented as mean time-points. The costs were calculated as proportion of patients per cohort times the cost of the utilized tests. All costs are displayed in euros. P-values < 0.05 were considered statistically significant. All analyses were performed using SPSS software version 23.0 (Chicago, IL, USA).

RESULTS

Patient selection

Among the eligible patients from the YEARS study, 19 of the 139 patients with confirmed PE and 24 patients with PE ruled out were excluded due to transfer to another hospital or evaluation by more than one specialist, leaving 120 patients with confirmed PE and 241 patients with PE ruled out for analysis (Figure 3) (10). The mean age of these patients was 53 years (standard deviation 18) and 147 (41%) patients were male (Table 1). The majority of patients presented during weekdays (78%), 126 patients (35%) were self-referrals and 205 (57%) patients were discharged from the emergency ward without hospital admission.

These 361 patients were compared with 288 patients from the ADJUST cohort (11). Among the eligible patients from the ADJUST cohort, 27 patients with PE were excluded because of inclusion before 1 May 2011, and 17 patients with confirmed PE and 38 patients with PE ruled out were excluded due to transfer to another hospital or evaluation by more than one specialist in the emergency department, leaving 61 patients with confirmed PE and 227 pa-

Table 1: Baseline characteristics

	YEARS n = 361	ADJUST n = 288	
Age, mean (SD)	53 (18)	65 (10)	p < 0.01
Male sex, n (%)	147 (41)	109 (38)	1.13 (0.82-1.6)
Co-morbidities, n (%)			
COPD	18 (5.0)	23 (8.0)	0.60 (0.32-1.1)
Heart failure	2 (0.6)	14 (5.0)	0.11 (0.02-0.48)
Cancer	47 (13)	49 (17)	0.73 (0.47-1.1)
Confirmed pulmonary embolism, n (%)	120 (33)	61 (21)	1.9 (1.3-2.6)
Self-referral patients, n (%)	126 (35)	124 (43)	1.4 (1.0-1.9)
Presentation in weekend, n (%)	79 (22)	60 (21)	1.1 (0.73-1.6)
Presentation during office hours, n (%)	231 (64)	173 (60)	1.18 (0.86-1.6)
Discharge from ED without hospital admission, n (%)	205 (57)	208 (72)	0.51 (0.36-0.70)

Abbreviations: SD: standard deviation; COPD: chronic obstructive pulmonary disease; ED: emergency department

tients without PE from the ADJUST cohort (Figure 3). The mean age of these patients was 65 years (SD 10) and 109 (38%) were male. Of the patients, 124 (43%) were self-referrals, 79% presented during weekdays and 208 patients (72%) were discharged from the emergency ward without hospital admission (Table 1).

Patients from the YEARS cohort were significantly younger, were less often discharged from the ED without hospital admission, for an OR of 0.51 (95% CI, 0.36–0.70) and were less often known to have heart failure, for an OR of 0.11 (95% CI, 0.02–0.48). Other baseline characteristics were comparable between both cohorts.

ED visit time

The overall time spent in the emergency ward for all patients, defined as the time of start of the diagnostic algorithm to discharge from the emergency ward, was 203 min (interquartile ratio [IQR], 135–270) in the YEARS cohort vs. 260 min (IQR, 183–355) in the ADJUST cohort, for an absolute difference of 60 min (95% CI, 44–76). In patients managed without a CT scan, the overall time in the emergency ward in the YEARS cohort was 119 min (IQR, 87–170 min), compared with 174 min (IQR, 136–220 min) in the ADJUST cohort, for an absolute difference of 54 minutes (95% CI, 37–70). In the patients diagnosed with PE, the turnaround time between start of the diagnostic algorithm and initial dose of anticoagulants was 200 min (25–75 IQR, 163–262) in the YEARS cohort, compared with 260 min (25–75 IQR, 193–337) in the ADJUST cohort, for an absolute difference of 53 min (95% CI, 22–82). The turnaround time between the start of the diagnostic algorithm and the order for CT scan was 75 min (25–75 IQR 55–106) in the YEARS cohort, compared with 132 min (25–75 IQR, 96–180) in the ADJUST cohort, for an absolute difference of 52 min (95% CI, 42–62) (Figure 4a, Table 2). The breakdown of turnaround times per algorithm per patient category is demonstrated in Figures S1 and S2.

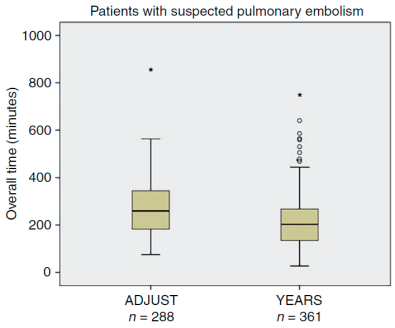

Figure 4a

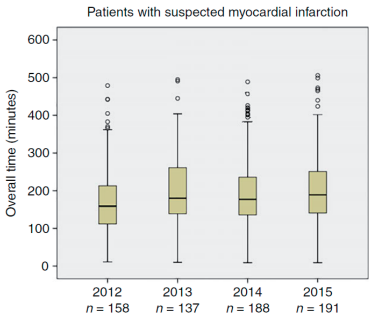

Figure 4b

Figure 4 Total emergency department (ED) visit time for patients with suspected pulmonary embolism (PE) (A) and suspected myocardial infarction (B)

After adjustment for age, all studied time-points remained significantly different and shorter for patients managed according to the YEARS algorithm; the adjusted total ED visit time for all patients was 40 min (95% CI, 22–58) shorter and the adjusted total ED visit time for all patients managed without CTPA was 46 min (95% CI, 2071) shorter, the adjusted time between start of the diagnostic algorithm and the initial dose of anticoagulants in all patients with confirmed PE was 54 min (95% CI, 24–84) shorter, and the adjusted difference in time between start of the diagnostic algorithm and the order for CTPA in patients who were referred for CT was 53 minutes (95% CI, 42–64) shorter. Adjustment for the comorbidities COPD and heart failure did not change our results.

Table 2: Turnaround time in emergency ward in ADJUST and YEARS cohort with absolute difference

		ADJUST (Conventional)		Years			
Turnaround time between:	**Patient cohort:**	**Number of patients**	**Median time, minutes (25-75IQR)**	**Number of patients**	**Median time, minutes (25-75IQR)**	**Absolute difference in time (min), (95% CI)**	**Absolute difference after adjustment for age, in time (min) (95% CI)**
Start of diagnostic algorithm and order for CT scan	All patients referred for CT scan	193	132 (97-180)	247	75 (55-106)	52 (42-62)	53 (42-64)
Start of diagnostic algorithm and initial dose of anticoagulant	All patients with proven PE	61	260 (193-337)	120	200 (163-262)	53 (22-82)	54 (24-84)
Start of diagnostic algorithm and discharge from emergency ward	All patients managed without CT	95	174 (136-220)	114	119 (87-170)	54 (37-70)	46 (20-71)
	All patients	288	260 (183-355)	361	203 (135-270)	60 (44-76)	40 (22-58)

Abbreviations: CT= computed tomography, PE = pulmonary embolism, min = minutes

Table 3. Factors associated with a longer duration of stay on the emergency ward with calculated odds ratio (OR) and 95% confidence interval, using the 75th interquartile range as cut-off value in patients from the combined cohorts. Multivariate regression analysis was used to adjust for all relevant baseline characteristics.

	Long vs short stay OR (95% CI)	After multivariate regression analysis, OR (95% CI)
Referral by medical specialist/general practitioner versus self-referral	0.90 (0.63-1.3)	1.0 (0.70-1.5)
Presentation during business hours versus during evening/night shift	1.5 (1.1-2.2)	1.7 (1.1-2.5)
Presentation during weekdays versus weekend	0.74 (0.48-1.1)	0.78 (0.50-1.2)
Heart failure	4.1 (1.5-11)	2.2 (0.76-6.3)
COPD	1.8 (0.94-3.5)	1.6 (0.81-3.3)
Active malignancy	1.4 (0.86-2.2)	1.2 (0.75-2.1)
Discharge vs hospital admission	0.53 (0.37-0.76)	0.43 (0.28-0.64)
Male versus female	1.2 (0.84-1.7)	1.2 (0.83-1.8)
Age < 50 years versus age ≥ 50 years	0.34 (0.20-0.59)	0.73 (0.39-1.4)
ADJUST cohort versus YEARS cohort	2.8 (1.9-4.1)	3.0 (1.9-4.8)

Abbreviations: OR: odds ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease

Predictive factors for ED visit time

Discharge from the ED without hospital admission was significantly associated with a shorter duration of the ED visit, for an OR of 0.53 (95% CI, 0.37–0.76) using the 75th percentile as cut-off for a longer duration of stay. Age younger than 50 years was also associated with a shorter duration of the ED visit, for an OR 0.34 (95% CI, 0.20–0.59). All other studied factors were not associated with a longer or shorter duration of the emergency ward visit (Table 3).

Duration of ED visit during 2012–2015

The overall time of an ED visit for patients with suspected myocardial infarction was 159 min (IQR, 112–215) in 2012, compared with 180 minutes (25IQR–75IQR, 138–261) in 2013, 177 min (IQR, 136–237) in 2014 and 189 (IQR, 141–251) in 2015 (Figure 4b). These time-points are significantly different (P = 0.004), with a shorter duration of stay in the emergency ward in 2012. There was no significant difference between the turnaround times during 2013–2015 (P = 0.68).

Costs analysis

Compared with the conventional algorithm, the YEARS algorithm increased the use of the D-dimer test by 23% (77% vs. 100%, Table 4) and decreased the use of CTPAs by 9% (61% vs. 52%). Total time of the ED visit on average decreased by more than an hour. The impacts on per-visit costs associated with D-dimer tests were an increase of €1 and for CTPAs and ED capacity costs a decrease of €16 and €132, respectively. Total per-visit costs during the ED visit decreased on average by €123 (€612 vs. €489; Table 4). Table S1 demonstrates the costs for both algorithms in patients with confirmed PE vs. those with PE ruled out.

Table 4. Average costs during the ED visit (in euro) per algorithm.

		Conventional algorithm		YEARS algorithm		Difference	
	Unit price	Volume	Costs	Volume	Costs	Volume	Costs
D-dimer test	€ 5	77%	€ 4	100%	€ 5	23%	€ 1
CT-thorax	€ 182	61%	€ 111	52%	€ 95	-9%	€ -16
ED capacity (in hours)	€ 110	4.52 h	€ 497	3.53h	€ 389	- 0.59h	€ -108
Total costs			€ 612		€ 489		€ -123

Abbreviations: CT: computed tomography with contrast infusion; ED: emergency department

DISCUSSION

This analysis demonstrated a significantly shorter turnaround time for patients with suspected PE using the YEARS algorithm than the conventional algorithm for all different predefined time-points, without a general tendency to shorter ED stay for other acute cardiovascular conditions. This shorter turnaround time is very relevant because an early start with anticoagulant treatment in patients with confirmed PE reduces mortality and morbidity (13-15). The overall time of the ED visit decreased by as much as 60 min. Overall costs during the ED visit were estimated to decrease by €123 per patient. The main explanation for our findings is that in the YEARS algorithm, the decision to perform D-dimer testing can be made directly instead of after initial evaluation of the patient and calculating a clinical decision rule when using the conventional algorithm (4, 11, 16). The mean duration of a D-dimer measurement is 45–60 min; this represents the whole logistic process in the Leiden University Medical Center from taking the blood from the patient to publication of the results in the electronic chart system of the patient. On the other hand, however, D-dimer measurement is not necessary in all patients in the conventional diagnostic approach: patients with a high clinical probability must be directly referred for imaging. The reduction of the required number of CTPAs in the YEARS study is an additional explanation for the shorter duration of the ED visit. Apart from the great advantage of faster initiation of anticoagulant treatment, the introduction of YEARS also resulted in a decrease in costs associated with the ED visit. The small increase in costs for

more D-dimer tests was more than offset by the savings of CTPAs. Although less tangible, the €108 savings on shorter ED capacity were considerable as well, for a total average net saving of €123. These savings represent the value of ED capacity that could be effectively used to provide better care to other patients. It is acknowledged that the costs of diagnostic tests and ED capacity can differ by hospital and country. For example, the mean length of an ED visit has been estimated at 245 min in the USA, as compared with only 130 minutes in the Netherlands (1, 17). Despite such differences, we do expect savings in all settings, as the small additional costs for extra D-dimers are far outweighed by the savings on CTPAs and ED capacity.

In this paper we used two different summary measures for the ED visit times. When analyzing predicting factors, we focused on the typical patients and used the median and 25–75 interquartile range to summarize the skewed distributed ED visit times. When analyzing costs we used the mean as a summary measure because possible outliers can have a considerable impact on costs.

The only predictive factors for a shorter duration of the ED visit we found were age younger than 50 years and discharge from the ED without admission to the hospital. These two variables were reported to be of relevance to length of stay in the ED in the Netherlands. In two Dutch studies, the median time of an ED visit was also found to be longer for patients who presented during weekdays and patients referred by medical professionals (compared with self-referrals) (1, 7). It is likely that our study was underpowered to identify these predictors as well.

An important strength of this analysis is that our hospital is equipped with a to-the-minute registration system on the emergency ward, which is accurate and precise. This registration system makes it possible to accurately extract data at different time-points during the emergency ward visit. Further, the inclusion and exclusion criteria of both the YEARS and ADJUST study were comparable (10, 11). Also, we were able to show that the overall time of an ED visit did not decrease between 2012 and 2015, which underlines the relevance and validity of the faster diagnostic turnaround time using the YEARS algorithm. The used CT scanners were comparable for both study cohorts; all patients were scanned with a multi-detector CT scan.

The main limitation of this study is that our analyses may be underpowered to detect subtle differences in the predictive factors for a shorter or longer duration of stay. The subgroup of patients with comorbidities such as heart failure or COPD is too small to draw firm conclusions. Because other hospitals work with other ED registration systems, we were not able to seek external validation of our findings. Also, the mean age of patients in the YEARS cohort was significantly lower than that of patients from the ADJUST study ($P < 0.01$) and YEARS patients had a lower incidence of heart failure. Even so, after adjustment for age and comorbidities, all different measured time-points during the ED visit remained significantly different between both cohorts. Moreover, more patients from the ADJUST cohort were discharged without hospital admission from the ED than was the case in the YEARS cohort (OR, 0.51; 95% CI, 0.36–0.74). We did not adjust for this potential confounder because discharge from the ED is associated with a shorter ED visit time. Even so, because we did not

perform a randomized controlled trial with direct comparison of both diagnostic strategies, our results may be subject to bias. Further, because more data on recent ED visits or recent hospitalizations were unfortunately not available, we were not able to correct for these potential confounders. Lastly, we only studied the total ED visit time in one academic hospital. We could not test whether our findings may be extrapolated to other hospitals. Nonetheless, our expectation is that other hospitals will find similar effects using the YEARS algorithm because of the simultaneous assessment of the D-dimer test and the assessment of clinical probability as well as the established reduction of required CTPA scans.

In conclusion, we demonstrated a shorter ED visit time for patients with suspected PE using the YEARS diagnostic algorithm than using the conventional diagnostic algorithm, leading to faster treatment initiation in cases of confirmed PE and savings on emergency ward resources. A shorter ED visit time creates important capacity to treat other patients and lowers the risk of crowding in the ED, which is a benefit for all patients visiting the ED.

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Chapter 9

Chest X-ray not routinely indicated prior to the YEARS algorithm in the diagnostic management of suspected pulmonary embolism

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ABSTRACT

Background

The YEARS algorithm was designed to simplify the diagnostic process of suspected pulmonary embolism (PE) and to reduce the number of required CTPA-scans. Chest X-ray (CXR) is often used as initial imaging test in patients suspected for PE.

Aim

To determine if CXR results differ between patients with confirmed PE and with PE ruled out, and to investigate whether CXR provides incremental diagnostic value to the YEARS criteria that is used for selecting patients with CTPA indication.

Methods

This post-hoc analysis concerned 1473 consecutive patients with suspected PE who were managed according to YEARS and were subjected to CXR as part of routine care. The prevalence and likelihood ratios of seven main CXR findings for a final diagnosis of PE were calculated.

Results

214 patients were diagnosed with PE at baseline (15%). Abnormal CXR occurred more often in patients with confirmed PE (36%, 77/214) than in patients without PE (26%; 327/1259), for an odds ratio of 1.60 (95%CI 1.18-2.18). Only the unexpected finding of a (rib)fracture or pneumothorax, present in as few as six patients (0.4%), significantly lowered the post-test probability of PE to an extent that CTPA could have been avoided.

Conclusion

The incremental diagnostic value of CXR to the YEARS algorithm to rule out PE was limited. CXR was more frequently abnormal in patients with PE than in those in whom PE was ruled out. These data do not support to perform CXR routinely in all patients with suspected PE, prior to CTPA imaging.

INTRODUCTION

The diagnostic management of suspected acute pulmonary embolism (PE) is challenging due its non-specific signs and symptoms. The clinical suspicion of PE must therefore be followed by objective testing. Current guidelines recommend applying clinical decision rules to categorize patients in accordance with their pre-test probability of PE (1, 2). In case of non-high probability of PE, D-dimer testing is warranted because PE can be safely ruled out if the D-dimer test result is normal. In case of abnormal D-dimer or high clinical probability, computed tomography pulmonary angiography (CTPA) should be performed (1-3). In recent years, attempts have been made to increase the number of patients in whom imaging is not required to rule out PE, for instance by introduction of an age-dependent D-dimer threshold. A recently published strategy is the simple and straightforward YEARS algorithm that includes simultaneous D-dimer and clinical pre-test probability assessment and the application of a pre-test probability D-dimer threshold (4, 5)). The YEARS algorithm was shown to safely rule out acute PE (failure rate of the overall algorithm 0.61%, 95%CI 0.36-0.96) and reduce the need for CTPA examinations by 14% compared to the conventional diagnostic strategy (5).

CXR is a commonly performed test in the initial evaluation of suspected cardiopulmonary disease and has the advantage of being associated with lower radiation exposure than CTPA (6). Since 40-88% of patients with PE have mostly non-specific abnormal CXR findings, CXR cannot be used to confirm and/or exclude the diagnosis of PE (6-8), although it may indicate other cardiopulmonary conditions (6). Most prevalent abnormal CXR findings in PE patients are cardiomegaly, atelectasis, elevated hemi diaphragm, pleural effusion, pulmonary infarction and parenchymal areas of increased opacity (6, 7, 9-12). Interestingly, the NICE-guideline recommends to start the diagnostic management of patients with suspected PE with a chest X-ray (CXR) to exclude other conditions than acute PE (13). Strong evidence supporting this recommendation is lacking. The aim of the current analysis was to investigate whether a CXR provides incremental diagnostic value to the YEARS algorithm in the diagnostic work-up of suspected acute PE.

METHODS

Study population

For this post-hoc analysis, 1711 consecutive patients with suspected PE from the YEARS study from three Dutch hospitals, in which a CXR was performed as part of routine clinical care, were evaluated. All patients were managed according to the YEARS algorithm (Figure 1) (5). Exclusion criteria for the YEARS study were treatment with anticoagulants in therapeutic doses initiated ≥ 24 hours before inclusion, life expectancy less than three months, pregnancy or allergy to intravenous contrast agents (5). Patients with confirmed PE were treated with anticoagulants according to international guidelines. Follow-up consisted of a scheduled outpatient clinic visit or telephone interview after three months.

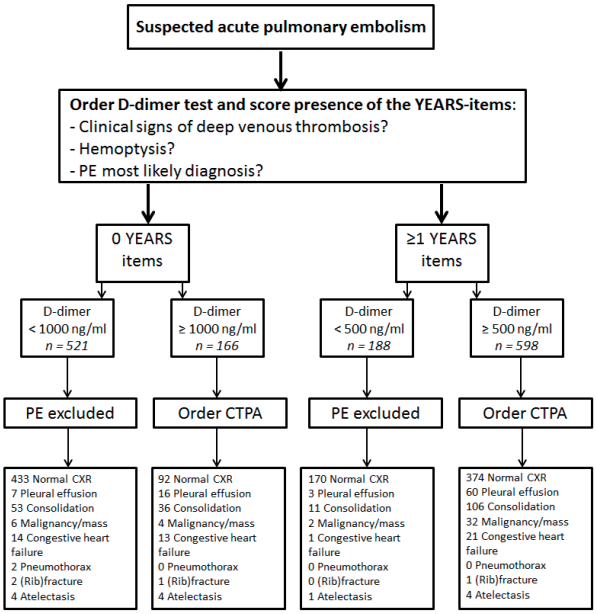

Figure 1: The YEARS algorithm

Chest X-rays

All patients included in this analysis underwent a CXR in the diagnostic work-up for suspected PE before they were referred for CTPA. The results of the CXR were reported by the local attending radiologist, who was either a certified radiologist or a resident under supervision of a certified radiologist. For this analysis, CXRs were classified as normal or abnormal. The following abnormalities were recorded: pleural effusion, consolidation, malignancy/mass, congestive heart failure, pneumothorax, (rib)fracture and atelectasis.

Aims and endpoints of this analysis

The aim of this analysis was to determine the prevalence of CXR abnormalities among patients with suspected PE and to evaluate if CXR results differ in patients with confirmed PE versus patients with PE ruled out. Further aims were to investigate the potential incremental value of performing a CXR routinely in all patients with suspected PE, i.e. whether the post-test probability of PE after certain CXR findings would allow for changing the decision to perform CTPA as indicated by YEARS.

The endpoints of this analysis included the odds ratios (with 95% CI) between the rate of abnormalities on CXR for patients with confirmed PE versus patients with PE ruled out, and for patients with an indication for CTPA according to the YEARS algorithm versus patients without CTPA-indication. Further, we assessed the positive and negative likelihood ratios for the specific predefined CXR abnormalities mentioned above, to calculate the post-test probability for each abnormality.

Statistical analysis

To compare the rate of abnormalities on CXR for patients with PE versus those without PE, an odds ratio (OR) with corresponding 95% CI was calculated. To evaluate whether the post-test probability of PE changed after the CXR result, positive and negative likelihood ratios (LR) with 95% confidence intervals (CI) were calculated for each different abnormality on CXR and for a normal CXR. The pre-test probability was dependent of the PE-prevalence, which was calculated in all patients and in patients who were referred for CTPA according to the YEARS algorithm. All analyses were performed using SPSS, version 23.0, Chicago, USA.

RESULTS

Patient characteristics

From the 1711 eligible patients, CXR was not performed in 238 patients for unknown reasons. After excluding these patients, 1473 were left for analysis. Their mean age was 54 years, 62% were female, 14% of patients had COPD, 2% had chronic heart failure and 9% had an active malignancy. Dyspnea was present in 71% of these patients, 40% presented with coughing and 74% with thoracic pain (Table 1). The patients who were managed without CXR had numerical but not significant less co-morbidities than the included patients: 6.3% of these patients were known with COPD and 1.1% of these patients had a history of heart failure, the majority were women (72%) and the mean age was 53 years. Following the YEARS algorithm, CTPA was indicated to rule out or confirm the diagnosis of PE in 763 (52%) of all patients. PE was diagnosed in 214 patients at baseline for a prevalence of 15%. PE prevalence among the 238 excluded patients without CXR was 17%.

CXR results in all patients

The majority of patients had a normal CXR (73%). Abnormal CXR was more frequent among patients with confirmed PE (36%) than in patients without PE (26%; Table 2) for an OR of 1.60 (95%CI 1.18-2.18). Consolidation was the most frequent abnormality which was present in 23% of patients with PE versus 13% of patients without PE for an OR of 2.08 (95%CI 1.45-2.99). Other CXR abnormalities were quite similar between the group of patients with and without PE (Table 2). The distribution of specific CXR results in different patients groups are illustrated in Figure 2.

CXR results in patients with an indication for CTPA

From the 763 patients with an indication for CTPA according to the YEARS algorithm, the CXR was normal in 465 patients (61%) compared to 604 of the 710 patients (85%) in whom CTPA was not indicated for an OR of 3.65 (95% CI 2.84-4.70). Consolidation was the most frequent abnormality found on CXR in all four different YEARS groups (Figure 2).

Table 1: Baseline characteristics

	All patients (n=1473)
Mean age, years (SD)	54.4 (18.6)
Female sex, n (%)	922 (62.6)
Pulmonary embolism, n (%)	214 (14.5)
CTPA indicated following YEARS, n (%)	763 (51.8)
Prior VTE, n (%)	146 (9.9)
COPD, n (%)	208 (14.1)
Heart failure, n (%)	30 (2.0)
Malignancy, n (%)	133 (9.0)
Immobilisation or recent surgery, n (%)	159 (10.8)
Use of estrogen in women, n (%)	131 (14.2)
Smoking, n (%)	250 (23.8)
Symptoms, n (%)	
Dyspnoea	1045 (70.9)
Coughing	579 (39.3)
Thoracic pain	1086 (73.7)
Palpitations	115 (7.8)
Fever (>38.5 °C)	47 (3.2)

Abbreviations: COPD: chronic obstructive pulmonary disease; CTPA: computed tomography pulmonary angiography; VTE: venous thromboembolism

Pre- and post-test probability after CXR

Table 3 illustrates the different LRs with 95%CI for all predefined CXR abnormalities. Pneumothorax and rib fracture were rare, with prevalence's of only 0.1% and 0.3% respectively. For the overall population, only these two latter rare findings significantly lowered the post-test probability of PE with a positive likelihood ratio (LR) of 0.00 (Table 3). Most of the other LRs were around 1.00, indicating that the result of the CXR did not change the post-test prob-

Table 2: Overview of CXR findings in different patient groups

Result of CXR	All patients (n = 1473)	PE (n = 214)	No PE (n = 1259)	CTPA indicated (n = 763)
Normal CXR, n (%)	1069 (72.6)	137 (64.0)	932 (74.0)	465 (60.9)
Pleural effusion, n (%)	86 (5.8)	14 (6.5)	72 (5.7)	76 (10.0)
Consolidation, n (%)	206 (14.0)	49 (22.9)	157 (12.5)	142 (18.6)
Malignancy/mass, n (%)	44 (3.0)	6 (2.8)	38 (3.0)	36 (4.7)
Congestive heart failure, n (%)	49 (3.3)	7 (3.3)	42 (3.3)	34 (4.5)
Pneumothorax, n (%)	2 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)
(Rib) fracture, n (%)	4 (0.3)	0 (0.0)	4 (0.3)	2 (0.3)
Atelectasis, n (%)	13 (0.9)	1 (0.5)	12 (1.0)	8 (1.0)

Abbreviations: CXR: Chest X-ray; PE: pulmonary embolism; CTPA: computed tomography pulmonary angiography

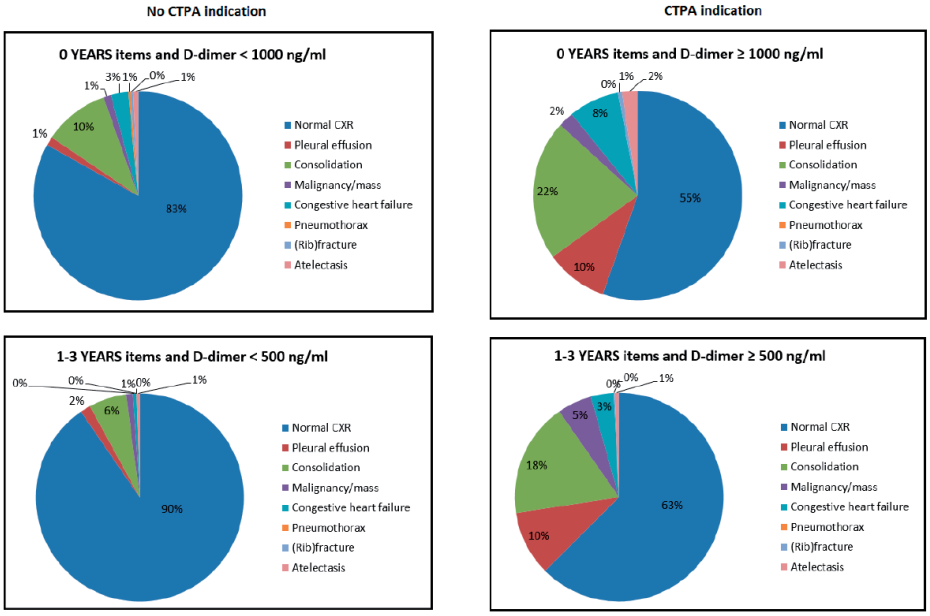

Figure 2: CXR findings per YEARS group

ability of a PE diagnosis. For patients with an indication for CTPA, only the CXR finding of a rib fracture, which was present in two patients, lowered the post-test probability to such an extent that CTPA could have been avoided (Table 3). Atelectasis on the CXR in patients with an indication for CTPA lowered the post-test probability on PE with a LR of 0.37 although with a broad 95% confidence interval (0.05-3.0), consistent with a 8% (1/13) prevalence of PE in patients with atelectasis.

DISCUSSION

In our cohort of patients with suspected PE, CXR was more frequently abnormal in patients who were diagnosed with PE than in those in whom PE was ruled out. The post-test probability of PE was only relevantly changed in patients with a (rib)fracture and/or a pneumothorax, which were rare findings. The incremental diagnostic value of CXR to the YEARS algorithm to rule out PE was therefore limited.

Previous studies have shown conflicting results for abnormalities on CXR observed in patients with PE. Two studies reported cardiomegaly as most common abnormality with a prevalence of 38% (19/50 patients) and 27% (622/2315 patients) respectively (6, 10). Robin et al. found interstitial lung disease or consolidation as most prevalent abnormality (28%) (11) and two other retrospective studies, of which one was the PIOPED study, reported atelectasis/

Table 3: Overview of LRs and CXR results in two groups; all patients and patients in whom CTPA was indicated according to the YEARS algorithm

	All patients (n=1473)		Patients in whom CTPA was indicated according to the YEARS algorithm (n=763)	
Results CXR	**Positive LR (95%CI)**	**Negative LR (95%CI)**	**Positive LR (95%CI)**	**Negative LR (95%CI)**
Normal CXR	0.86 (0.78-0.96)	1.4 (1.1-1.7)	1.1 (0.95-1.2)	0.89 (0.73-1.1)
Pleural effusion	1.1 (0.66-2.0)	0.99 (0.95-1.0)	0.58 (0.33-1.0)	1.1 (1.0-1.1)
Consolidation	1.8 (1.4-2.4)	0.88 (0.82-0.95)	1.4 (0.99-1.8)	0.93 (0.86-1.0)
Malignancy/mass	0.93 (0.40-2.2)	1.0 (0.98-1.0)	0.51 (0.22-1.2)	1.0 (1.0-1.1)
Congestive heart failure	0.98 (0.45-2.2)	1.0 (0.97-1.0)	0.67 (0.29-1.5)	1.0 (0.99-1.1)
Pneumothorax	0.00	1.0 (0.99-1.0)	n.a.	n.a.
(Rib)fracture	0.00	1.0 (0.99-1.0)	0.00	1.0 (0.99-1.0)
Atelectasis	0.49 (0.06-3.8)	1.0 (0.99-1.0)	0.37 (0.05-3.0)	1.0 (0.99-1.0)

Abbreviations: CI: confidence interval; CTPA: computed tomography pulmonary angiography; CXR: chest X-ray; LR: likelihood ratio; n.a.: not applicable; PE: pulmonary embolism
Example: Assuming that the pre-test probability of PE is 28% in a certain patient with suspected PE and an indication for CTPA according to YEARS, the post-test probability of PE in case of a normal CXR result would be 28%*1.1 = 31%. The post-test probability of PE in this patient with any abnormality on CXR would be 28%*0.89 = 25%

parenchymal areas with increased opacity as most common abnormality with a prevalence of 68% (7, 12). This heterogeneity in CXR findings demonstrates that a suspicion of acute PE may cause different non-specific abnormalities on CXR. Considering this, the diagnostic value of CXR for the diagnosis of PE is therefore poor.

In the past, CXR was used as standard imaging test in the approach of patients with suspected PE to find alternative diagnosis and as useful tool for the interpretation of the ventilation/perfusion scan (V/Q scan) (7, 11, 12). Nowadays, CTPA is the first-choice imaging test in the diagnostic work-up for patients with suspected PE due the ability to directly visualize emboli, as well as alternative diagnosis. CXR is not needed for interpretation of the CTPA. Reasons why CXR is often used in clinical practice are its wide availability, the fast execution, the low radiation exposure compared to CTPA or VQ scan, and the low costs (14). Patients without an indication for CTPA, and thus a lower probability on PE, had more often a normal CXR in our cohort than patients referred for CTPA. However, normal CXR as well as abnormal CXR could not distinguish patients with from those without CTPA indication, nor could CXR distinguish between patients with or without PE.

CXR may have two different roles in the diagnostic work-up of patients with suspected PE. First of all, CXR is an important diagnostic modality at the emergency department for the initial assessment of patients with respiratory and/or chest symptoms. The result of the CXR could lead to change suspected PE to another diagnosis or to moving PE higher up in the differential diagnosis. Moreover, the results of CXR, which were likely available for some of

the patients when the physician completed the YEARS algorithm, could have led to assigning less or more YEARS items to the patient. This may have influenced the final YEARS classification and associated D-dimer threshold. For those reasons, CXR could therefore have contributed to the efficiency of the YEARS algorithm (5). Second, the CXR may be used as a routine test to exclude alternative diagnosis before performing a CTPA.

A study limitation is that because of the retrospective design of our study and the lack of detailed information on the differential diagnosis of each individual patient, we were not able to explore the reason why the CXR was ordered, especially because no CXR is no longer recommended nor considered among the useful tools for this specific clinical setting in recent guidelines. Also, for unknown reasons, not all patients in our cohort were referred for CXR which may have caused selection bias. Even so, CXR results hardly influenced the post-test probability of PE in any of the YEARS categories. Therefore, our data do not support routine use of CXR in all patients before CTPA. Also, for unknown reasons, not all patients in our cohort were referred for CXR which may have caused selection bias.

In conclusion, CXR shows non-specific abnormalities in patients with confirmed PE more frequently than in patents with PE ruled out. Only the rare findings of a (rib)fracture or pneumothorax significantly lowered the post-test probability to such extent that CTPA could have been avoided according to the YEARS algorithm. Although CXR may play an important role in the initial diagnostic management in patients with suspected PE, our data do not support routine CXR in all patients with suspected PE, especially not in patients with an established indication for CTPA by YEARS.

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Chapter 10

Lower prevalence of subsegmental pulmonary embolism after application of the YEARS diagnostic algorithm

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ABSTRACT

Background

The rate of identified isolated subsegmental pulmonary embolism (ssPE) has doubled with advances in CTPA technology, but its clinical relevance is debated. YEARS was shown to safely reduce the number of required CTPAs in the diagnostic management of PE. We hypothesized that the higher threshold for performing CTPA in YEARS was associated with a lower prevalence of ssPE compared to the conventional diagnostic algorithm.

Methods

We compared 2291 consecutive patients with suspected PE managed according to YEARS to 3306 consecutive control patients managed according to the Wells for the prevalence of isolated ssPE.

Results

In the YEARS cohort, 52% were managed without CTPA, 12% had PE of which 10% were isolated ssPE, and the 3-month diagnostic failure rate was 0.35%. In the control cohort, 32% were managed without CTPA, 20% had PE of which 16% were isolated ssPE, and the 3-month failure rate was 0.73%. The isolated ssPE prevalence was significantly lower in YEARS (absolute difference 6.2% (95%CI 1.4-10), OR 0.58 (95%CI 0.37-0.90).

Conclusion

YEARS is associated with a lower prevalence of isolated ssPE, due to reduction in CTPAs by the higher D-dimer threshold. This was however not associated with a higher risk of recurrent VTE during follow-up.

INTRODUCTION

Since the introduction of multi-detector computed tomography pulmonary angiography (CTPA), the sensitivity of this diagnostic technique for visualizing smaller pulmonary embolism (PE) has noticeably advanced. These advances have led to a more frequent detection of filling defects in subsegmental pulmonary arteries - with diameters as small as 2-3 mm - by multi-detector computed tomography (MDCT) compared to single detector computed tomography (SDCT; Figure 1) (1, 2). The rate of isolated subsegmental PE (ssPE) diagnosis has doubled since the introduction of the MDCT from 4.7% (95%CI: 2.5-7.6%) to 9.4% (95%CI: 5.5-14.2%) (1, 3). Despite this increase in isolated ssPE diagnoses, the risk of fatal PE has remained unchanged, suggesting that not all isolated ssPE may be clinically relevant (1, 4).

Recently, a number of studies designed to optimizing diagnostic strategies for suspected acute PE. Ultimately they aimed at lowering the number of necessary CTPAs, thereby reducing the number of patients exposed to ionizing radiation and simplifying diagnostic management in busy clinical practices (5, 6). The YEARS algorithm involves a D-dimer test that is combined with three clinical variables, i.e. clinical signs of deep venous thrombosis, haemoptysis and "PE most likely diagnosis". In the absence of YEARS items, the D-dimer threshold to rule out PE without CTPA is 1000 ng/ml and in patients with one or more YEARS items the D-dimer threshold remains 500ng/ml. All patients with D-dimer levels higher than these D-dimer thresholds require a CTPA-examination (Figure 2). We have shown that this algorithm is safe with a failure rate of the overall algorithm of 0.61% (95%CI 0.36-0.96) and

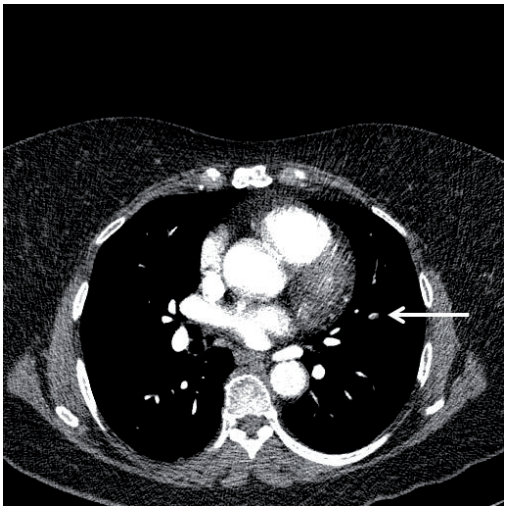

Figure 1 Isolated subsegmental pulmonary embolism (arrow) on computed tomography pulmonary angiography (CTPA)

a resultant 14% reduction in CTPA-examinations compared to the standard algorithm with the conventional Wells rule and fixed D-dimer threshold of <500ng/ml (6).

We hypothesized that this reduction in CTPA-examinations has led to a decreased rate of smaller more distal emboli diagnosis without a higher incidence of recurrent VTE during 3-month follow-up. To test this hypothesis, we compared the percentage of isolated ssPE diagnoses in patients managed according to the YEARS algorithm to patients managed according to the conventional algorithm that is currently recommend to be used in clinical practice [7].

METHODS

Study population

This was a post-hoc analysis with the combined data of two prospective outcome studies, i.e. the YEARS study and the Christopher study, in which consecutive, hemodynamically stable in- and outpatients with clinically suspected PE had been included in the same Dutch Hospitals (6, 8). We used the Christopher population as proxy for current clinical practice.

The YEARS study evaluated the safety and efficiency of the YEARS algorithm in 3465 consecutive in- and outpatients aged 18 years or older from October 2013 to July 2015 (Figure 2) (6).

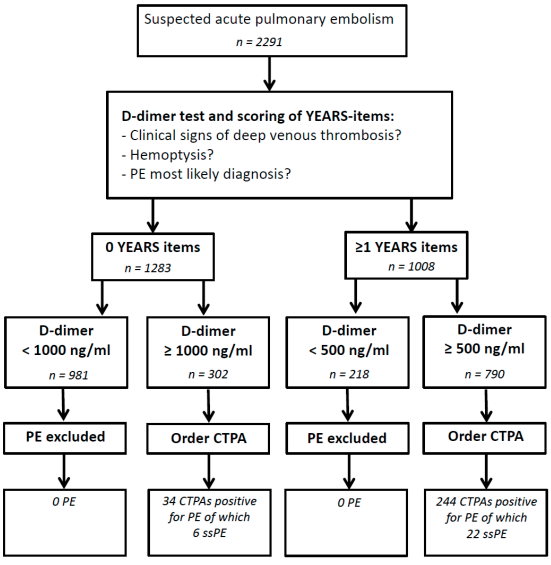

Figure 2 Years algorithm and study flowchart
Abbreviations: PE = pulmonary embolism, CTPA = computed tomography pulmonary angiography, ssPE = subsegmental pulmonary embolism

Exclusion criteria were treatment with therapeutic doses of anticoagulants initiated ≥ 24 hours prior to eligibility assessment, pregnancy, allergy to intravenous contrast agents, life expectancy less than three months or geographic inaccessibility precluding follow-up. Patients were managed according to the YEARS algorithm (Figure 2). D-dimer concentrations were measured with automated well validated high-sensitive quantitative D-dimer assays (Tinaquant, Roche Diagnostica, Mannheim, Germany; Innovance, Siemens, Malburg, Germany and STA-LIA DiagnosticaStage, Asnieres, France) according to local practice. Patients in whom PE was ruled out were left untreated. In patients with a confirmed PE diagnosis anticoagulant treatment was started. Results were reported using an intention-to-diagnose approach. All patients were followed for a 3-month period for the occurrence of (fatal) recurrent venous thromboembolism (VTE)(6). The current study was restricted to 2291 patients from four study sites participating in the YEARS study, i.e. Leiden University Medical Center (Leiden), Academic Medical Center (Amsterdam), Flevo Hospital (Almere) and Haga Teaching Hospital (The Hague). We restricted our analysis to these four hospitals since they comprised the majority of included patients and all original CTPA examinations were readily available for analysis.

The Christopher study included 3306 normotensive consecutive in- and outpatients with clinically suspected PE (8). Patients were included from November 2002 to September 2004. The probability of PE was classified as "unlikely" with a Wells clinical decision rule score of 4 points or less, and likely with a Wells score of more than 4 points. In all patients with an "unlikely" score, a D-dimer was measured and PE was considered to be ruled out if the D-dimer was < 500 ng/ml. Anticoagulant treatment was withheld in these latter patients. Patients with a D-dimer ≥ 500 ng/ml and all patients with a "likely" score were directly referred for CTPA. Exclusion criteria were treatment with therapeutic doses of unfractionated or low-molecular-weight heparin, life expectancy less than three months, allergy to intravenous contrast agents, renal impairment (creatinine clearance < 30ml/min) or hemodynamic instability. All patients were followed for three months for the occurrence of symptomatic (fatal/recurrent) VTE(8).

Radiological Evaluation

An MDCT was performed in all patients from the YEARS cohort with an indication for CTPA (6). In the Christopher study, CTPA was performed using either SDCT or MDCT (8). In both studies, the pulmonary arteries were evaluated up to at least the subsegmental vessels by the attending radiologist. PE was diagnosed if a filling defect was detected or if a vessel was totally occluded by low-attenuation material on at least 2 adjacent slices.

For all patients in this analysis, we used the previously reported frequencies of isolated ssPE by the local attending radiologist, who was either a certified radiologist, or a resident under supervision of certified radiologist. The definition of isolated ssPE was dependent on this local attending radiologist.

To assess the accuracy of the clinical ssPE diagnosis, all CT scans of the YEARS study were reassessed by an independent reader who was blinded for the original CT report by the local attending radiologist, as well as for patient characteristics, clinical presentation, treatment decisions and outcome. For the patients from the Christopher study, we used previously reported frequencies of isolated ssPE (8). These CT scans were not available for re-evaluation.

Endpoints

This analysis was performed to determine the absolute difference in isolated ssPE prevalence between the YEARS cohort and the Christopher cohort. Other endpoints were the number of required CTPA-examinations to safely confirm or rule out PE between both cohorts and the difference in failure rate (occurrence of VTE during 3-month follow-up).

A second analysis was performed in patients from both cohorts to evaluate if subsegmental thrombus location was associated with a lower D-dimer level than more proximal PE. Also, we determined if isolated ssPE diagnoses would have been missed if YEARS would have been applied in the Christopher cohort.

Statistical analysis

To compare the prevalence of isolated ssPE, the required number of CTPA-examinations and the failure rate in the YEARS study versus the Christopher study, absolute difference and the Odds Ratio's (OR) with exact 95% confidence intervals were calculated. To evaluate the association between D-dimer level and location of the thrombus, we compared the median D-dimer level in the patients with isolated ssPE versus more proximal PE from both patient cohorts. The Mann-Whitney-U test was performed to determine the level of significance between both groups. To evaluate if ssPE diagnoses would have been missed when applying YEARS in the Christopher cohort, the YEARS score was calculated post-hoc for all patients of the Christopher cohort. For measurement of inter-observer agreement between the independent reader and the local attending radiologist for isolated ssPE, Cohen's kappa was calculated in two different cohorts: 1) for the adjudication of isolated ssPE in the complete cohort, 2) for adjudication of isolated ssPE within the group of patients with confirmed and treated PE. The kappa value for agreement was interpreted as follows: poor (< 0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or very good (0.81–1.00) (9). P-values < 0.05 were considered statistically significant. All analysis were performed using SPSS version 23.0, Chicago, USA.

RESULTS

YEARS cohort

The median age of the 2291 patients in the YEARS cohort was 53 years (25-75 interquartile range (IQR) 40-67), 39% of these patients were men and 88% were outpatients (6). The median age of patients with confirmed isolated ssPE was 66 years (IQR 48-77), 36% of these patients were men and 89% were outpatients (Table 1).

According to the intention-to-diagnose approach, 1092 out of 2291 patients (48%) underwent CTPA and the diagnosis of PE was confirmed in 278 patients (12%). In 28 patients (10% of all PE diagnosis) PE was limited to only the subsegmental arteries, leaving 250 patients with PE localized in at least one segmental or central branch of the pulmonary artery (Table 2). The Cohen's kappa statistic comparing the assessment of the local attending radiologist and the independent blinded reviewer for isolated ssPE within the complete patient cohort (n=2291) was 0.80 and for ssPE within the PE cohort (n=278) 0.78, indicative of 'good' agreement. Of all patients with isolated ssPE, 22 patients had 1-3 YEARS-items and a D-dimer above 500 ng/ml and 6 patients had 0 YEARS-items and a D-dimer above 1000 ng/ml (Figure 2).

Of the 1924 patients in whom PE was ruled out at baseline, who remained untreated and completed the follow-up period of three months, 8 patients were diagnosed with recurrent VTE (2 fatal PE) during follow-up for a failure rate of 0.42% (95%CI 0.21-0.82).

Table 1 Baseline characteristics

	YEARS COHORT		CHRISTOPHER COHORT	
	All patients (n=2291)	**ssPE-patients (n=28)**	**All patients (n=3306)**	**ssPE-patients (n=110)**
Age, median (IQR25-75)) or mean (SD)	53 (40-67)	66 (48-77)	53 (18.4)	57 (17.0)
Male sex, n (%)	891 (38.9)	10 (35.7)	1409 (42.6)	60 (54.5)
Outpatients, n (%)	2023 (88.3)	25 (89.3)	2701 (81.7)	81 (73.6)
Duration of complaints, days, median (IQR25-75)	3 (1-9)	3 (1.0-18.5)	2 (1-5)	1 (0-4)
VTE risk factors				
Immobilization/surgery, n (%)	255 (11.1)	6 (21.4)	610 (18.5)	38 (34.5)
Previous venous thrombo-embolism, n (%)	234 (10.2)	4 (14.3)	480 (14.5)	15 (13.6)
Active malignancy, n (%)	212 (9.3)	3 (10.7)	476 (14.4)	21 (19.1)
Estrogen use, women, n (%)	193 (8.5)	1 (3.6)	438 (23.1)	16 (32.0)
Comorbidities				
Heart failure, n (%)	92 (4.0)	1 (3.6)	243 (7.4)	9 (8.2)
COPD, n (%)	270 (11.8)	3 (10.7)	341 (10.3)	11 (10.0)

Abbreviations: COPD: chronic obstructive pulmonary disease; IQR: interquartile range; SD: standard deviation; ssPE: subsegmental pulmonary embolism; VTE: venous thromboembolism

Christopher cohort

A total of 3306 consecutive patients were included in the Christopher study with a mean age of 53 years (SD 18.4), 43% were male patients and 82% were outpatients (Table 1) (8). A total of 1057 patients (32%) were managed without CTPA. PE was diagnosed in 676 patients for a PE-prevalence of 20% (Table 2). MDCT was performed in 1939 patients and SDCT in 260 patients. Among all patients with confirmed PE, 110 (16%) patients were diagnosed with isolated ssPE. Of all patients who remained untreated, 23 were diagnosed with recurrent VTE (7 fatal PE) during the 3-month follow-up period for a failure rate of 0.73% (95%CI 0.49-1.1).

Table 2 Prevalence and 3-month VTE-rate of both cohorts

	Years cohort (n = 2291)	Christopher cohort (n=3306)	Absolute difference, % (95% CI)
PE-prevalence, n (%)	278 (12)	676 (20)	8.3% (6.4-10)
Isolated ssPE prevalence, n (%)	28 (10)	110 (16)	6.2% (1.4-10)
CTPA indicated, n (%)	1092 (48)	2249 (68)	20.4% (18-23)
3-months VTE-rate, % (95% CI)	0.42 (0.21-0.82)	0.73 (0.49-1.1)	0.32 (-0.15-0.74)

Abbreviations: CI: confidence interval; CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism; ssPE: subsegmental pulmonary embolism; VTE: venous thromboembolism

Difference between both cohorts

The prevalence of isolated ssPE was significantly lower in the YEARS cohort, with an absolute difference of isolated ssPE prevalence in patients with confirmed PE of 6.2% (95%CI 1.4-10) for an odds ratio of 0.58 (95%CI 0.37-0.90). The absolute difference of isolated ssPE prevalence between both cohorts among all included patients was 2.1% (95% CI 1.3-2.9) for an odds ratio of 0.36 (95% CI 0.24-0.55). CTPA was indicated in 48% of the YEARS cohort versus 68% in the Christopher cohort for an absolute difference of 20% (95%CI 18-23) in favour of the YEARS algorithm. The 0.32% difference in the 3-month recurrent VTE rate in untreated patients between the cohorts was not statistically significant (95%CI -0.15 -0.74; Table 2).

Secondary endpoints

D-dimer levels were not measured in 185 patients with confirmed PE from the Christopher cohort because they had a likely probability, i.e. a Wells score of more than 4 points, and were referred for CTPA without D-dimer measurement. In all other patients with available D-dimer test results from both studies, the median D-dimer level of patients with isolated ssPE was 1571 ng/ml (IQR 1010-3025) compared to 3205 ng/ml in patients with more proximal PE

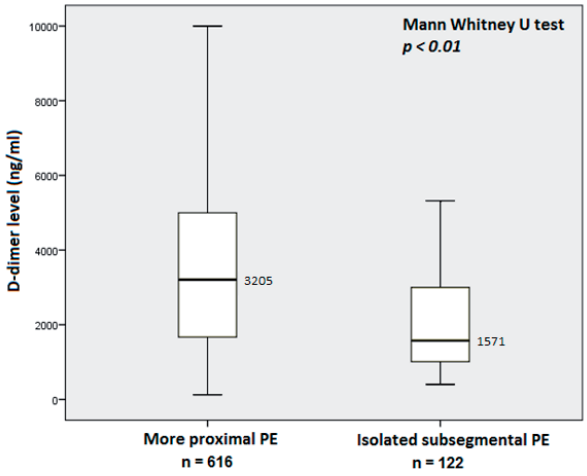

Figure 3 D-dimer levels and location of pulmonary embolism (PE) in the YEARS- and Christopher study

(IQR 1666-5000, p<0.01; Figure 3). Of all 110 patients diagnosed with isolated ssPE in the Christopher cohort, 11 patients (10% of ssPE diagnosis and 2% of all PE diagnoses) would have remained undetected if the YEARS algorithm would have been applied: 7 patients with 0 YEARS items and a D-dimer below 1000 ng/ml and 4 patients with 1-3 YEARS items and a D-dimer below 500ng/ml.

DISCUSSION

This analysis demonstrates a lower prevalence of isolated ssPE in patients managed according to the YEARS algorithm compared with a traditional algorithm, without compromising the safety of the diagnostic work-up. This difference was the consequence of a lower sensitivity of YEARS for smaller more distal emboli due to the higher threshold for performing CTPA scans because of the pre-test probability dependent D-dimer cut-off. This is explained in two ways.

First, we confirmed the previously described association between D-dimer level and location of PE, where isolated ssPE is associated with a lower median D-dimer level than more proximal PE (10-12). De Monye and colleagues demonstrated the correlation between D-dimer level and thrombus location in a prospective cohort study in patients with clinically suspected PE: D-dimer levels were clearly lower in the group of patients with isolated ssPE (11). Another study confirmed this observation (12). Second, we showed that 10% of all isolated ssPE diagnoses would have remained undetected if the YEARS algorithm would have been used instead of the standard diagnostic algorithm in the Christopher study. This

notable reduction was not associated with a higher rate of symptomatic VTE events among the untreated patients of the YEARS study with an initial negative ruling by the diagnostic algorithm during the 3-month follow-up period. These findings support the hypothesis that some isolated ssPE cases may safely remain untreated, although our results should be regarded as hypothesis generating.

To date, there is limited, uncontrolled, evidence in a little over 50 patients with confirmed isolated ssPE without deep venous thrombosis (DVT) who remained untreated and none suffered recurrent PE during follow-up (4, 13). Based on these observations, international guidelines suggest clinical surveillance over treatment with anticoagulants in patients with isolated ssPE and no proximal DVT in the legs who have a low risk for recurrent VTE, i.e. patients who are not hospitalized or have reduced mobility and those without active cancer (Class IIb, Grade 2C) (3, 14, 15). A currently active outcome study evaluates the safety of withholding anticoagulant therapy in 300 patients without a history of VTE or cancer, with confirmed isolated ssPE without proximal DVT on bilateral lower extremity ultrasound (NCT01455818). Until the results of this study are available, the decision whether to start anticoagulant treatment in patients with isolated ssPE should be made on an individual basis, taking into account the risk of recurrent PE versus the risk of major bleeding with or without anticoagulant treatment.

We found a good inter-observer agreement of isolated ssPE diagnosis in the cohort of all PE-patients of 0.78. Prior studies using the same comparison have suggested that the inter-observer agreement of the presence of PE depends on the location of the thrombus, with a fair to moderate inter observer agreement for isolated ssPE versus high agreement for more proximal PE. Miller et al demonstrated a moderate inter-observer agreement for subsegmental pulmonary artery defects of 0.53, especially in CTPA degraded with technical artefacts, such as breathing motion artefact, artefacts due to cardiac pulsation or beam-hardening from adjacent high-density structures (16, 17). Ghanima et al found a low inter-observer agreement of 25%, with a kappa of 0.38 (95%CI 0.0-0.89) (18) . Although our data do not allow firm conclusions on the reasons for the difference between the current and prior studies, we hypothesize that the further advancements in CT technology since 2002-2008 (inclusion period of the studies by Ghanima and Miller) and the very low number of technically inadequate CT scans in the YEARS study may have contributed to the good inter-observer agreement found in the current analysis.

Strengths of our study include the prospective data collection and comparison of two large cohorts of consecutive in- and outpatients with suspected PE with similar in- and exclusion criteria from the same Dutch hospitals. Moreover, we could clearly explain the cause of the observed lower isolated ssPE prevalence among patients managed according to YEARS, supporting the biologic plausibility of our conclusion.

The fact that only half of the study population of the YEARS study was subjected to CTPA prevents accurate assessment of the actual number of patients with ssPE that were not de-

tected and remained untreated. The other way around, it remains unclear if patients with isolated ssPE from the Christopher study who would not have been referred for CTPA according to YEARS, would have had an uneventful follow-up without treatment. Limitations of this post-hoc analysis are that not all patients from the YEARS study were included. We restricted our analysis to four of the participating centers in which 66% of the total study patients were included and in which all original CTPA-examinations were readily available for analysis. Second, the association between D-dimer level and location of the thrombus was made with data from both study cohorts and from all four hospitals which included patients in the YEARS study. Bias could have been introduced in the analysis of the association of D-dimer level and PE localisation because different D-dimer assays were used in the participating hospitals and within the hospitals over time. Third, the PE prevalence in YEARS was lower than in Christopher. Although this difference can be partly explained by the lower prevalence of isolated ssPE, we cannot rule out bias towards overestimation of the primary endpoint. Further, the two studies were performed in different time periods (2002-2004 and 2013-2015), allowing for bias due to for instance differences in CT technology. Indeed, where only state-of-the-art MDCT machines were used in the YEARS study, 260 patients from the Christopher cohort were managed with SDCT. Even so, because MDCT allows better visualization of segmental and subsegmental pulmonary arteries, making it easier to detect smaller more distal emboli, the prevalence of isolated ssPE was still lower in the YEARS cohort than in the Christopher cohort, supporting the validity of our findings.

In conclusion, we demonstrated a lower prevalence of isolated ssPE in patients managed according to the YEARS algorithm compared with the conventional diagnostic strategy mainly used in daily clinical practice. This lower prevalence of isolated ssPE is a consequence of the lower sensitivity of YEARS for ssPE due to the higher D-dimer threshold. Our study provides further indirect evidence that some isolated ssPE may be left untreated in selected patients, although definite proof will only be provided by outcome studies in which patients with ssPE are left untreated. Further, these findings support the relevance of the YEARS, due to easy applicability, the reduction in number of required CTPAs, the low failure rate and -last but not least- the associated lower prevalence of isolated ssPE. This was however not associated with a higher risk of recurrent VTE during follow-up which provides indirect evidence that some ssPE may be left untreated in selected patients, although our study was underpowered to detect a small differences.

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Chapter 11

General discussion and future perspectives

This thesis contains different studies that are focused on improving the diagnostic management of patients with suspected acute pulmonary embolism (PE). Chapter 1 contains a general introduction on the condition 'acute pulmonary embolism' and its current diagnostic management.

PART I: THE DIAGNOSTIC MANAGEMENT OF SUSPECTED PULMONARY EMBOLISM DURING PREGNANCY

Chapter 2 provides an overview on the use of clinical prediction rules and D-dimer tests in the diagnostic work-up of suspected pulmonary embolism during pregnancy. The most often used clinical prediction rule in the non-pregnant setting is the Wells score, which consists of seven clinical items. Pregnant women were excluded in the main clinical derivation and validation studies of the Wells score. Therefore, this clinical prediction score is not validated for this specific population. In the 1990s, several studies have shown that D-dimer levels physiologically increase steadily during pregnancy, making this test less useful to rule out venous thrombo-embolism (lower specificity). During the first trimester of pregnancy, 50-100% of all patients have D-dimer levels less than the most used threshold of 500 ng/mL, and 0-76% of all patients during the third trimester. Different studies investigated an alternative D-dimer threshold during pregnancy, but suggested new threshold varied among the studies and were never prospectively (externally) validated.

There are contradicting recommendations in different international guidelines for the use of clinical decision rules and D-dimer testing for the diagnostic work-up of suspected PE during pregnancy. Even so, the majority of guidelines clearly indicates that only imaging tests – CT-scan or ventilation perfusion scintigraphy – are currently available to safely exclude or confirm this diagnosis during pregnancy.

Chapter 3 is a systematic review and meta-analysis of the safety, efficiency and the maternal and fetal radiation exposure of two different imaging modalities that are widely used to confirm or rule out PE were compared, i.e. ventilation perfusion scan and the CT-scan. The pooled number of false negative scans was 0.0% (95%CI 0-0.04) for ventilation perfusion scan and 0.0% (95%CI 0.0-0.16) for CTPA, showing comparable sensitivity. The pooled rate of non-diagnostic results with ventilation perfusion scan and CT-scan were 14% (95%CI 10-18) and 12% (95%CI 8-17) respectively, which was unexpectedly high for CT. The maternal and fetal radiation exposure was well below the safety threshold for both imaging modalities, although they could not be compared given the lack of high quality data. Notably, none of the included studies in this meta-analysis have used state-of-the-art imaging techniques as currently used in clinical practice. Hence, our pooled estimates are likely outdated and contemporary CT and VQ sequences involve less radiation exposure and less non-diagnostic

tests. In conclusion, this meta-analysis demonstrates that both imaging modalities are safe and can be applied to use to rule out PE during pregnancy.

The results of a multinational, multicenter, prospective diagnostic management study for suspected PE during pregnancy are presented in chapter 4. The YEARS algorithm was validated in this study in a pregnant population. The YEARS algorithm was adapted for pregnancy; all patients with clinical signs of deep venous thrombosis were referred for ultrasonography of the symptomatic leg, and if DVT was confirmed, treatment with anticoagulants was initiated without further CTPA imaging. The YEARS algorithm consists of assessment of three clinical items; haemoptysis, clinical signs of deep venous thrombosis and PE the most likely diagnosis, in combination with D-dimer measurement. A total number of 498 patients were included in 17 different hospitals in the Netherlands, France and Ireland. The PE-prevalence was 4.0% (20/498) with a 3-month VTE failure rate was 0.21% (95%CI 0.0-1.2) with one patient who developed a popliteal DVT after twelve weeks of follow-up. CTPA could be avoided in 40% (95%CI 35-44) of all patients. Subgroup analysis demonstrated that 65% of all patients could be managed without CTPA during the first trimester compared to 32% of patients in the third trimester. The conclusion of this study is that the pregnancy adapted YEARS algorithm safely ruled out PE in pregnant patients across all three trimesters. This study is the largest management study ever performed in the setting of pregnant patients with suspected PE, and its results will certainly change clinical practice since potential harmful imaging was avoided in a large proportion of patients.

PART II: THE DIAGNOSTIC MANAGEMENT OF SUSPECTED PE IN NON-PREGNANT PATIENTS

Part II of this thesis encompasses analyses on the diagnostic management of suspected PE in non-pregnant patients. In current clinical practice, different diagnostic algorithms for confirming or excluding PE are used indiscriminately in women and men. Men and women can present with different clinical presentations for acute PE and there are also sex-specific risk factors for venous thrombo-embolism such as use of estrogens in female patients. Three different diagnostic algorithms for acute PE, the Wells rule with fixed D-dimer threshold, the Wells rule with age-adjusted D-dimer cut-off (calculated as age x 10) and the YEARS algorithm, were compared in chapter 5 for safety and efficiency between men and women. Individual patient data were obtained from seven prospective studies that enrolled consecutive adult patients with suspected PE. The pooled prevalence of PE was lower in women (18.7%) than in men (25.7%) for an odds ratio of 0.69 (0.62-0.76). The overall efficiency was higher in women with an OR of 1.11 (95%CI 1.02-1.2) when data from the studies were pooled. The failure rate was comparable for men and women for all different algorithms,

so the investigated pre-imaging diagnostic algorithms are more efficient for women with a similar failure rate.

In the next chapters, we investigated if combinations of different strategies could improve their efficiency by further reducing the number of required CT-scans in the diagnostic work-up for patients with suspected PE even further. Chapter 6 describes a study of the combination of the YEARS algorithm with the age-adjusted D-dimer cut-off. In this analysis, four hypothetical scenarios were analysed to investigate if this combination could improve the efficiency further without compromising safety. Only one scenario proved to be more efficient than the YEARS algorithm alone. . In 847 of the 2017 patients of 50 years and older with at least 1 YEARS item, a CTPA was not necessary to exclude PE using the combination of YEARS and the age-adjusted D-dimer cut-off, compared to 752 of the 2017 patients using the YEARS algorithm alone for an absolute difference of 4.7% (95%CI 1.7-7.7). This improvement in efficiency came at the cost of a higher failure rate of 0.75% (95% CI 0.49-1.13). Due to this safety issue, we concluded that there is no added value of implementing the age-adjusted D-dimer cut-off in the YEARS algorithm in the studied patients.

Another strategy to simplify the diagnostic work-up for suspected PE is the Pulmonary Embolism rule out criteria (PERC-rule). This rule consists of seven clinical items. When all items are absent, no further diagnostic tests are required to exclude the diagnosis of PE. In chapter 7 we investigated whether the PERC rule could be used in combination with the YEARS algorithm. A total of 250 out of 1316 patients were PERC negative. The combination of these two strategies reduced the number of required CT-scans with 57 scans (4.3%, 95%CI 0.52-8.1), although eleven patients with PE would have been missed. These missed diagnoses were mostly seen in patients with at least one YEARS-item. The absolute 0.98% increase of the failure rate of the algorithm forces us to conclude that the combination of the YEARS algorithm with the age-adjusted D-dimer cut-off is not safe.

Chapter 8 describes a comparison of total visit time in the emergency department for patients with suspected PE with two different diagnostic algorithms, the YEARS algorithm and the conventional diagnostic strategy with the Wells rule and fixed D-dimer threshold. This was compared on different time points during the diagnostic process, and estimated associated costs of the emergency department visit were calculated. The hypothesis that the YEARS algorithm would be faster due to simultaneous assessment of the three YEARS items and the D-dimer measurement was confirmed in this analysis: the YEARS algorithm was associated with a significantly shorter emergency department visit time of ~60 minutes. Consequently, treatment with anticoagulants was initiated 53 minutes faster using the YEARS algorithm than the conventional algorithm. The estimated costs were reduced with 123 euros per visit for YEARS. Thus, YEARS was shown to be associated with a shorter visit time than the conventional diagnostic strategy, leading to faster start of treatment in case of confirmed PE and savings on emergency department sources.

Chapter 9 describes an evaluation of the added value of chest X-ray in the diagnostic work-up of suspected PE. Currently, almost all patients with suspected PE are referred for chest X-ray and many also for CTPA. However, this is not in accordance with recommendations of in international guidelines, in which the use of chest X-ray is not recommended at all. Reasons why a chest X-ray is often used in clinical practise are its wide availability, the fast execution, the low radiation exposure and the low costs. The aim of this study was to investigate whether chest X-ray provides incremental diagnostic value to the YEARS criteria that is used for selecting patients with CTPA. Further, we aimed to assess differences in chest X-ray results between patients with confirmed PE and patients with PE ruled out. Our results demonstrated that chest X-ray examinations were more frequently abnormal in patients with confirmed PE than in those with PE ruled out, 36% versus 26% respectively (OR 1.60, 95%CI 1.18-2.18). The most frequent chest X-ray abnormalities were 'consolidation' in both patient groups. Only the finding of a rib fracture or pneumothorax, which were present in only 6 out of 1473 patients (0.4%), significantly lowered the post-test probability of PE to an extent that CTPA could have been avoided. The conclusion of this analysis was that the incremental value of chest X-ray in the diagnostic work-up of patients with suspected PE is limited and our data do not support routine chest X-ray in all patients with suspected PE, especially not in patients with an established indication for CT-scan.

Chapter 10 evaluated the prevalence of subsegmental pulmonary embolism – small emboli in the subsegmental vessels – in the YEARS study compared to the Christopher study, where the conventional diagnostic strategy was used. Over the past years, the rate of identified isolated subsegmental pulmonary embolism has doubled with advances in technology, although the clinical relevance of these small emboli is debated and the indication for anticoagulation is questionable in selected patients. A total number of 2291 patients from the YEARS cohort were compared to 3306 patients from the Christopher study. The prevalence of PE was 12% in the YEARS patients (278/2291) with 28 patients diagnosed with isolated subsegmental PE (10% of all PE diagnoses), compared to a prevalence of 20% (676/3306) in the Christopher study with 110 patients with isolated subsegmental PE (16% of all PE diagnoses) for an absolute difference of 6.2% (95% confidence interval 1.4-10). We concluded that application of the YEARS algorithm was associated with a lower prevalence of subsegmental PE, most likely due to the lower sensitivity of YEARS for smaller more distal emboli due to the higher D-dimer threshold without a compromising safety of the diagnostic work-up. These findings indirectly lend support to the hypothesis that some of the isolated subsegmental PE cases may safely remain untreated.

FUTURE PERSPECTIVES

The diagnostic management of patients with suspected acute PE has greatly evolved over the last decades. Diagnostic algorithms with combinations of clinical decision rules and D-dimer tests have significantly and safely decreased the number of required imaging tests to confirm or exclude PE. An important benefit of this reduction is a decrease in CT-associated complications and costs.

The Artemis study demonstrated that the pregnancy adapted YEARS algorithm was safe to use in pregnant patients with suspected PE during all trimesters in a Western European population. Further validation in external cohorts of pregnant women in different continents and for different D-dimer assays than used on the Artemis study will support wide application of the algorithm. Moreover, the algorithm may be further improved. The levels of D-dimer will rise during pregnancy. It is interesting to investigate whether higher D-dimer thresholds than 1000 ng/ml can be used safely during the second and third trimester of pregnancy, to further increase the efficiency of the pregnancy adapted YEARS algorithm and reduce the number or required imaging tests. The very low prevalence of PE among the patients in the Artemis study as well as other studies would support such an approach. The first step would be to evaluate and compare the D-dimer levels during the three different trimesters in patients in whom PE is excluded and in patients with confirmed PE. When new D-dimer thresholds can be established, these should be validated in a new study before it may be applied in clinical practice.

Further research in other patient subgroups who are often excluded from trials -or were only present in small numbers- is necessary, such as elderly patients, inpatients and patients with active cancer. As in pregnant women, D-dimer levels are higher in these groups than in patients without such comorbidities . Hence, further increase of the D-dimer threshold could potentially decrease the use of CTPA in this subgroup too.

The emergency departments of hospitals are crowding with the aging population and the threshold to test for presence of PE has decreased over the past years. Another step to increase the efficiency of the diagnostic management of patients with suspected acute PE is to investigate whether general practitioners could also apply YEARS. If this practice would prove safe, the number of unnecessary referrals and health care costs would decrease in addition to the number of imaging tests ordered.

A final option to improve the specificity of the diagnostic algorithms for suspected PE would be to develop advanced models that allow a personalized D-dimer threshold for each individual patient. The main limitation of such models would be that scores can no longer be easily calculated nor remembered. Prospective management studies evaluating the safety (sensitivity) of such algorithms should therefore also focus on applicability in daily practice.

Lastly, future studies should also investigate the role of the magnetic resonance imaging (MRI) in diagnosing PE, since MRI does not involve use of radiation. Especially the non-

contrast enhanced MR direct thrombus imaging (MRDTI) technique is of particular interest. MRDTI is currently not validated to rule out VTE, but results of ongoing studies with this very purpose are expected shortly. MRI techniques in general could be especially beneficial for patients with a relative contra-indication to CTPA, such as those with contrast allergies or severe renal failure. Up till now, technical issues have prevented the extensive spread introduction of MRI in the work-up of suspected PE.

Chapter 12

Nederlandse samenvatting

Dit proefschrift beschrijft verschillende studies die gericht zijn op het verbeteren van de diagnostiek bij patiënten met een verdenking op een acute longembolie. Het doel van deze studies is om de diagnostische strategieën bij patiënten met verdenking acute longembolie te optimaliseren en efficiënter te maken. Hoofdstuk 1 bevat een algemene introductie over acute longembolie, de diagnostiek en de verrichte studies die beschreven staan in dit proefschrift.

DEEL 1: DIAGNOSTIEK BIJ VERDENKING ACUTE LONGEMBOLIE TIJDENS ZWANGERSCHAP

Hoofdstuk 2 betreft een overzicht van het gebruik van klinische beslisregels en het gebruik van de D-dimeer concentratie bij verdenking acute longembolie tijdens de zwangerschap. De meest gebruikte klinische beslisregel bij de niet zwangere patiënten was tot voorheen de Wells score, welke bestaat uit 7 items die gescoord moeten worden. Helaas is deze score nooit gevalideerd in de zwangere populatie en wordt daarom het gebruik hiervan tijdens de zwangerschap niet aangeraden. Een andere methode, die gebruikt wordt in de diagnostiek bij verdenking longembolie, is het bepalen van de D-dimeer concentratie in het bloed: bij een lage concentratie in combinatie met een vastgestelde lage voorafkans is een longembolie uitgesloten. Gedurende een normale zwangerschap stijgt de concentratie van de D-dimeer in het bloed geleidelijk. In de jaren 90 is onderzoek verricht naar het gebruik van D-dimeer concentraties in gedurende de zwangerschap, echter met wisselende resultaten. Tijdens het eerste trimester heeft 50-100% van de gezonde zwangeren een D-dimeer concentratie onder de meest gebruikte afkapwaarde van 500 ng/mL, dit in tegenstelling tot gezonde zwangeren in het derde trimester van de zwangerschap, wanneer slechts 0-76% van de patiënten een D-dimeer concentratie kleiner dan de afkapwaarde heeft. Verschillende studies keken naar de optimale afkapwaarde van de D-dimeer concentratie tijdens zwangerschap, maar ook hier zijn erg wisselende resultaten gepubliceerd variërend van 640 – 3120 ng/ml in het derde trimester. Vanwege het gebrek aan sluitend bewijs geven richtlijnen tegenstrijdige aanbevelingen omtrent het gebruik van de D-dimeer concentratie gedurende de zwangerschap, waardoor op dit moment beeldvormende diagnostiek met CT pulmonalis angiografie (CTPA) of ventilatie-perfusie scan nog altijd de enige manier is om een longembolie uit te sluiten gedurende de zwangerschap.

In hoofdstuk 3 is naar het gebruik van beeldvorming bij de diagnostiek van acute longembolie tijdens de zwangerschap gekeken. In dit hoofdstuk wordt een meta-analyse verricht die de voor- en nadelen van twee verschillende beeldvormende modaliteiten – de ventilatie-perfusie scan en de CT-scan – vergelijkt. Daarnaast wordt een overzicht gegeven van de blootstelling aan straling voor zowel moeder als de foetus. Uit deze meta-analyse blijkt dat beide technieken veilig zijn te gebruiken voor het aantonen of uitsluiten van een acute longembolie tijdens de zwangerschap. De gemiddelde kans op een fout-negatieve

scan was 0.0% (95% betrouwbaarheidsinterval 0-0.04) voor de ventilatie-perfusie scan en 0.0% (95% betrouwbaarheidsinterval 0.0-0.16) voor de CT-scan. De gemiddelde kans op een niet-diagnostisch resultaat voor de ventilatie perfusie scan was 14% (95% betrouwbaarheidsinterval 10-18) en 12% (95% betrouwbaarheidsinterval 8-17) voor de CT-scan. Helaas werden in geen van de geïncludeerde studies in deze meta-analyse moderne technieken gebruikt, die in de huidige klinische praktijk toegepast worden en zeer waarschijnlijk veel minder vaak een niet-diagnostische uitslag hebben. Concluderend laat deze meta-analyse zien dat beide modaliteiten veilig zijn en gebruikt kunnen worden om een longembolie uit te sluiten gedurende de zwangerschap.

Hoofdstuk 4 geeft de resultaten weer van een prospectieve studie verricht ter validatie van het aangepaste YEARS algoritme in de zwangere populatie met verdenking op een acute longembolie. Het YEARS algoritme voor zwangerschap was zodanig aangepast, dat bij patiënten met klinische verschijnselen van een trombosebeen eerst een compressie-echografie van het symptomatische been werd verricht. Wanneer een diepe veneuze trombose vastgesteld werd, volgde meteen behandeling met anticoagulantia en werd er niet alsnog een CTPA gemaakt. Wanneer geen diepe veneuze trombose aangetoond werd, werd het normale YEARS algoritme gevolgd. Het YEARS algoritme is een klinische beslisregel die bestaat uit score van 3 klinische criteria : klinische verschijnselen van een diepe veneuze trombose, hemoptoë en of longembolie de meest waarschijnlijke diagnose is, in combinatie met een D-dimeer test. In totaal werden 498 patiënten geïncludeerd in 17 verschillende ziekenhuizen in Nederland, Frankrijk en Ierland. De prevalentie van longembolieën was 4.0% (20/498) met een risico op een gemiste DVT of longembolie bij initieel normale testen van 0.21% (95% betrouwbaarheidsinterval 0.04-1.2). Het gebruik van een CT-scan kon in 40% van alle patiënten vermeden worden. Een subgroep analyse toonde dat in het eerste trimester van de zwangerschap 65% van de patiënten geen indicatie voor CTPA had, vergeleken met 32% in het derde trimester. De conclusie was dat het aangepaste YEARS algoritme voor zwangeren veilig gebruikt kan worden gedurende alle drie de trimesters. Deze studie is op dit moment de grootste management studie die ooit verricht is in zwangere patiënten met verdenking op acute longembolie en deze resultaten zullen de klinische praktijk veranderen, mede gezien het feit dat mogelijk schadelijke beeldvorming vermeden kan worden in een groot deel van de patiënten.

DEEL 2: DIAGNOSTIEK BIJ VERDENKING ACUTE LONGEMBOLIE

In het tweede deel van het proefschrift worden verschillende studies besproken, die proberen de diagnostiek bij verdenking acute longembolie in niet zwangere patiënten te verbeteren. In hoofdstuk 5 is gekeken naar de verschillen in prevalentie en efficiëntie van drie verschillende diagnostische strategieën voor het vaststellen van een longembolie tussen man en vrouw. De volgende diagnostische strategieën werden met elkaar vergeleken: Wells regel met standaard

D-dimeer afkapwaarde van 500 ng/ml, Wells regel met leeftijdsafhankelijke D-dimeer afkapwaarde voor patiënten van 50 jaar en ouder (berekend als leeftijd x 10 ng/ml) en het YEARS algoritme. Resultaten van deze studie tonen aan dat de prevalentie van een acute longembolie bij alle drie de strategieën lager is bij vrouwen dan bij mannen, namelijk 18.7% bij vrouwen tegenover 25.1% bij mannen (odds ratio van 0.69; 95% betrouwbaarheidsinterval 0.62-0.76). De totale efficiëntie, waarmee bedoeld wordt hoeveel CT-scan bespaard konden worden, van de drie verschillende diagnostische strategieën was in vrouwen iets hoger met een odds ratio van 1.11 (95% betrouwbaarheidsinterval 1.02-1.2), terwijl de failure rate van de diagnostische algoritmes gelijk was tussen mannen en vrouwen. Concluderend zijn de onderzochte diagnostische strategieën in het gebruik efficiënter bij vrouwen.

In de volgende hoofdstukken worden een aantal combinaties van verschillende diagnostische strategieën onderzocht, die het aantal benodigde CT-scans in de praktijk bij patiënten met verdenking op een acute longembolie verder zouden kunnen reduceren.

Hoofdstuk 6 beschrijft een post-hoc analyse die gekeken heeft of het YEARS algoritme te combineren is met de leeftijdsafhankelijke D-dimeer afkapwaarde (ADJUST) in patiënten van 50 jaar en ouder. In deze analyse zijn verschillende hypothetische scenario's bekeken, die beide diagnostische strategieën combineren. Slechts één scenario leverde een kleine winst in efficiëntie op, dit was als het YEARS algoritme gecombineerd werd met de leeftijdsafhankelijke D-dimeer afkapwaarde in patiënten van 50 jaar en ouder met minimaal 1 YEARS item. In dit hypothetische scenario was een CT-scan in 847 van de 2017 patiënten niet nodig voor het uitsluiten van een longembolie, in tegenstelling tot 752 patiënten wanneer het YEARS algoritme alleen werd toegepast. Dit komt overeen met een absoluut verschil van 4.7% (95% betrouwbaarheidsinterval 1.7-7.7) in benodigde CT-scans. Ondanks de afname van het aantal nodige CT-scans voor het veilig uitsluiten van een acute longembolie, werden meer acute longembolieën gemist met een risico op een gemiste diagnose van 0.75% (95% betrouwbaarheidsinterval 0.49-1.13). Dit is 0.24% hoger (95% betrouwbaarheidsinterval -0.50 – 1.0) in vergelijking met het normale YEARS algoritme. Hierdoor is geconcludeerd dat een combinatie van deze twee strategieën YEARS en ADJUST niet veilig genoeg is en daarom ook niet toepast moet worden in de klinische praktijk.

In hoofdstuk 7 is retrospectief onderzocht of de "pulmonary embolism rule-out criteria" (PERC regel) gebruikt kan worden, voordat het YEARS algoritme wordt toegepast bij de klinische verdenking acute longembolie. De PERC regel bestaat uit zeven verschillende klinische items. Wanneer deze allemaal afwezig zijn, is vooral in Noord-Amerikaanse studies gezien dat een longembolie veilig kan worden uitgesloten zonder dat aanvullend diagnostisch onderzoek nodig is. Het belangrijkste verschil met Noord-Amerikaanse studies is, dat in Europese studies naar longembolieën een prevalentie van 15-20% gevonden wordt, terwijl dit in Noord-Amerika slechts 6-8% is. Wanneer deze PERC regel toegepast zou zijn voor start van het YEARS algoritme, zou een besparing van 57 benodigde CT-scans gezien zijn in 1316 patiënten (4.3%, 95% betrouwbaarheidsinterval 0.52-8.1), maar dit zou ten koste gaan van

11 extra gemiste longembolie diagnoses, voornamelijk bij patiënten met minimaal 1 YEARS item. De absolute toename van gemiste diagnoses met 0.98% is daarom reden om de PERC regel in de Europese setting niet te gebruiken voor het YEARS algoritme.

Hoofdstuk 8 is een vergelijking gemaakt van de totale behandelduur op de spoedeisende hulp bij verdenking acute longembolie tussen twee verschillende diagnostische strategieën, de conventionele Wells-regel met D-dimeer test in vergelijking met het YEARS algoritme. Naast totale behandelduur werden ook de gemaakte kosten voor patiënten geschat voor beide scenario's. Resultaten van deze studie laten zien dat het gebruik van het YEARS algoritme geassocieerd is met een tijdsbesparing van ongeveer 60 minuten in alle patiënten. Patiënten met een vastgestelde acute longembolie werden 53 minuten eerder behandeld wanneer het YEARS algoritme toegepast werd. Daarnaast werden de gemiddelde kosten van het bezoek aan de spoedeisende hulp met 123 euro per bezoek gereduceerd. Het YEARS algoritme is dus geassocieerd met een kortere bezoektijd aan de spoedeisende hulp, en resulteert in een snellere start van behandeling van patiënten met een bewezen longembolie en lagere zorgkosten.

Hoofdstuk 9 beschrijft de aanvullende waarde van een thoraxfoto (X-thorax) op de spoedeisende hulp bij patiënten met verdenking op een longembolie. Op dit moment wordt vaak een thoraxfoto bij patiënten met deze klinische verdenking verricht, ook al maakt een thoraxfoto geen deelt uit van de aanbevolen diagnostische algoritmes voor verdenking longembolie. Gezien de overlap tussen symptomen bij een longembolie en andere cardiopulmonale ziekten, zoals hartfalen , pneumothorax of een pneumonie, wordt vaak toch initieel een thoraxfoto gemaakt. Het doel van deze studie was om te kijken of er verschil in resultaten is van deze thoraxfoto tussen patiënten die een longembolie hebben en patiënten waarbij een longembolie uitgesloten wordt. Er werd vastgesteld dat patiënten met een acute longembolie vaker een afwijkende thoraxfoto hebben dan patiënten zonder een longembolie, 36% versus 26%, met een odds ratio van 1.60 (95% betrouwbaarheidsinterval 1.18-2.18). De frequentste afwijking op de thoraxfoto was in beide groepen een consolidatie. Alleen de weinig voorkomende afwijking pneumothorax en ribfractuur, aanwezig in 6 van de 1473 patiënten (0.4%), verminderde de post-test kans op een longembolie zodanig dat het verrichten van een CT-scan niet nodig zou zijn geweest. Deze analyse laat zien dat de toegevoegde waarde van een thoraxfoto bij patiënten met verdenking op longembolie zeer beperkt is, vooral bij patiënten die toch verwezen moeten worden voor een CT-scan.

In hoofdstuk 10 wordt de prevalentie van longembolie in de subsegmentale arteriën – subsegmentale longembolieën – vergeleken tussen de YEARS studie en de Christopher studie waarbij de conventionele Wells regel gebruikt is. Door verbeteringen in de techniek van CT-scans, zijn longembolieën in de allerkleinste longslagaders steeds beter zichtbaar. Er is echter discussie of deze subsegmentale longembolieën een klinische betekenis hebben en of ze in alle gevallen behandeld moeten worden. In totaal werden 2291 patiënten uit de YEARS studie vergeleken met 3306 patiënten uit de Christopher studie. De prevalentie van longembolieën in de YEARS patiënten was 12% (278/2291), waarvan 28 patiënten gediagnosticeerd werden

met een geïsoleerde subsegmentale longembolie (10% van alle longemboliepatiënten), vergeleken met een prevalentie van 20% (676/3306) in de Christopher studie met 110 patiënten met een geïsoleerde subsegmentale longembolie (16% van alle longembolie patiënten). Het absolute verschil was 6.2% (95% betrouwbaarheidsinterval 1.4-10). Geconcludeerd werd dat het YEARS algoritme geassocieerd is met een lagere prevalentie van subsegmentale longembolieën, wat mogelijk verklaard kan worden door de lagere sensitiviteit van het algoritme voor kleinere, meer distale, embolieën door een hogere D-dimeer afkapwaarde. Dit had echter geen consequenties voor de veiligheid in de zin van meer recidief VTE tijdens follow-up. Deze bevindingen onderbouwen indirect de hypothese dat niet alle subsegmentale longembolieën klinisch relevant zijn en behandeling met anticoagulantia behoeven.

TOEKOMSTPERSPECTIEVEN

De afgelopen decennia is er een enorme ontwikkeling geweest in het diagnostische proces van patiënten met verdenking op een acute longembolie. Diagnostische algoritmes in combinatie met klinische beslisregels en D-dimeer testen hebben het aantal benodigde CT-scans significant en veilig gereduceerd met een vermindering van CT-geassocieerde complicaties en kosten tot gevolg.

De Artemis studie heeft aangetoond dat het aangepaste YEARS algoritme voor zwangeren veilig te gebruiken is gedurende alle drie trimesters van de zwangerschap in een West-Europese patiënt populatie. Verdere validatie in externe cohorten van zwangere vrouwen in verschillende continenten, en met verschillende D-dimeer afkapwaarden zullen een wereldwijde applicatie van dit Artemis algoritme verder ondersteunen. Daarnaast kan het algoritme mogelijk nog verder verbeterd worden. Gedurende zwangerschap stijgt de D-dimeer concentratie. Het zou daarom interessant zijn om te onderzoeken of hogere D-dimeer afkapwaardes van 1000 ng/ml in het tweede en derde trimester veilig te gebruiken zijn, en of dit het aantal benodigde CT-scans nog verder kan reduceren. De lage prevalentie van longembolieën in de Artemis studies, en ook in vergelijkbare studies, kan deze benadering ondersteunen. De eerste stap zou zijn om D-dimeer concentraties te evalueren en die te vergelijken gedurende de drie trimesters in zwangere patiënten met bewezen én met uitgesloten longembolie. Na het vaststellen van deze geschatte nieuwe D-dimeer afkapwaardes zouden deze uiteraard eerst gevalideerd moeten worden in een nieuwe studie voordat deze gebruikt kunnen worden in de dagelijkse klinische praktijk.

Ook is extra onderzoek nodig in andere patiënten subgroepen die vaak uitgesloten worden van grote onderzoeken, of die slechts in kleine aantallen geïncludeerd worden, zoals bijvoorbeeld de oudere patiënt, opgenomen klinische patiënten en patiënten met kanker. In deze patiëntgroepen zijn de D-dimeer concentraties ook hoger in vergelijking met patiënten zonder co-morbiditeit, en kan in deze patiëntgroepen de afkapwaarde van de D-dimeer concentratie verhoogd worden om gebruik van beeldvorming verder te reduceren.

Met de toenemende vergrijzing en de lage drempel om diagnostiek naar een acute longembolie in te zetten zijn de spoedeisende hulpen in Nederland erg druk bezocht. Een mogelijkheid om de druk te verminderen van patiënten met verdenking op een longembolie in deze setting, zou toepassing van het YEARS algoritme in de 1e lijn (huisartsenzorg) zijn. Wanneer dit gebruik veilig blijkt te zijn, zal het aantal onnodige verwijzingen naar de spoedeisende hulp met de geassocieerde kosten erg dalen.

De mooiste oplossing om de specificiteit van de diagnostische strategieën te verbeteren zou een gepersonaliseerde D-dimeer drempel zijn. Dit is een model dat echter nog ontwikkeld moet worden. De grootste beperking voor het ontwikkelen van zo'n model is dat scores in algoritmes niet langer makkelijk berekend noch onthouden kunnen worden.

Tenslotte zouden toekomstige studies de rol van de MRI (magnetische resonantie imaging) in het diagnostische proces voor het vaststellen van longembolieën verder onderzocht moeten worden. De MR direct trombus imaging (MRDTI) waarbij geen contrast gebruikt wordt is in dit verband interessant. Deze techniek is momenteel nog niet gevalideerd om longembolie uit te sluiten, maar resultaten van lopende studies met dat doel worden binnenkort verwacht. MRI-technieken zouden vooral interessant zijn voor patiënten met een contra-indicatie voor CT-scans, zoals contrast-allergie of (ernstig) nierfalen. Tot nu toe hebben technische problemen en ruime beschikbaarheid de introductie van MRI in het diagnostisch proces van longembolieën in de weg gestaan.

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CURRICULUM VITAE

Liselotte Myrthe van der Pol werd geboren op 18 oktober 1987 te Dirksland en groeide op in Ouddorp. In 2005 behaalde zij haar atheneum diploma aan C.S.G. Jacob van Liesveldt te Hellevoetsluis. Zij startte met de studie Geneeskunde aan de Universiteit Leiden in september 2005. In 2010 begon zij met haar coschappen, met onder andere een keuze coschap op de spoedeisende hulp in het St. Elisabeth Hospital te Willemstad, Curaçao en haar semi-arts stage op de afdeling Algemene Interne geneeskunde van het HagaZiekenhuis. Liselotte behaalde in augustus 2012 haar artsendiploma. In oktober 2012 startte zij als arts-assistent niet in opleiding (ANIOS) op de afdeling Interne geneeskunde van het HagaZiekenhuis te Den Haag. Per 1 januari 2014 is zij gestart met de opleiding tot internist in het HagaZiekenhuis (opleiders dr. M.O. van Aken, dr. M. van Buren). In mei 2016 heeft zij haar opleiding gedurende 2 jaar onderbroken om promotie onderzoek te verrichten in zowel het HagaZiekenhuis als het Leids Universitair Medisch Centrum onder begeleiding van Prof. Dr. M.V. Huisman. Tijdens het afronden van haar promotie heeft zij per mei 2018 haar opleiding vervolgd waarbij zij vanaf 1 januari 2019 werkzaam is in het Leids Universitair Medisch Centrum (opleider Prof. Dr. De Fijter).