Diagnosis, management and prognosis of symptomatic and incidental pulmonary embolism

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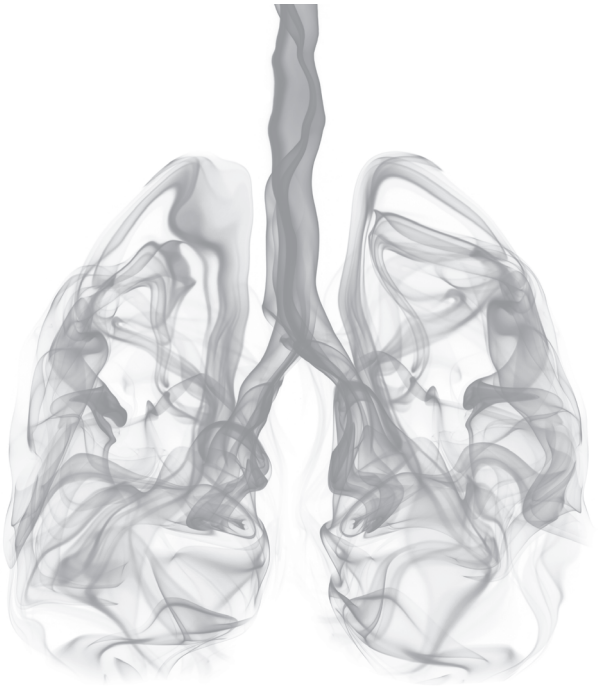
CHAPTER 2

Diagnosis of Pulmonary Embolism: Advances and Pitfalls



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ABSTRACT

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

INTRODUCTION

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

CLINICAL DECISION RULES

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

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

Table 1. Original and simplified Wells clinical decision rule

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

PE, pulmonary embolism; DVT, deep venous thrombosis.

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

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

Table 2. Revised and simplified revised Geneva score

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

PE, pulmonary embolism; DVT, deep venous thrombosis.

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

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

D-DIMER TESTING

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

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

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

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

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

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

IMAGING TESTS

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

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

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

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

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

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

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

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

SUBSEGMENTAL AND INCIDENTALLY DIAGNOSED PE

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

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

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

MAGNETIC RESONANCE ANGIOGRAPHY

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

PATIENTS WITH SUSPECTED RECURRENT PE

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

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

SUMMARY

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

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

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

REFERENCES

1. Anderson FA, Jr., Wheeler HB, Goldberg RJ et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991;151(5):933-938.
2. Ageno W, Agnelli G, Imberti D et al. Factors associated with the timing of diagnosis of venous thromboembolism: results from the MASTER registry. Thromb Res 2008;121(6):751-756.
3. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002;121(3):877-905.
4. Squizzato A, Luciani D, Rubboli A et al. Differential diagnosis of pulmonary embolism in outpatients with non-specific cardiopulmonary symptoms. Intern Emerg Med 2011.
5. Ceriani E, Combescure C, Le GG et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost 2010;8(5):957-970.
6. Wells PS, Anderson DR, Rodger M et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost 2000;83(3):416-420.
7. Le Gal G, Righini M, Roy PM et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006;144(3):165-171.
8. Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Arch Intern Med 2001;161(1):92-97.
9. Miniati M, Pistolesi M. Assessing the clinical probability of pulmonary embolism. Q J Nucl Med 2001;45(4):287-293.
10. Kline JA, Nelson RD, Jackson RE, Courtney DM. Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: a multicenter US study. Ann Emerg Med 2002;39(2):144-152.
11. Gibson NS, Sohne M, Kruip MJ et al. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. Thromb Haemost 2008;99(1):229-234.
12. Klok FA, Kruisman E, Spaan J et al. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. J Thromb Haemost 2008;6(1):40-44.
13. van BA, Buller HR, Huisman MV et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006;295(2):172-179.
14. Douma RA, Mos IC, Erkens PM et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. Ann Intern Med 2011; 154(11):709-718.
15. Stein PD, Hull RD, Patel KC et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med 2004;140(8):589-602.
16. Goekoop RJ, Steeghs N, Niessen RW et al. Simple and safe exclusion of pulmonary embolism in outpatients using quantitative D-dimer and Wells' simplified decision rule. Thromb Haemost 2007;97(1):146-150.
17. Kruip MJ, Slob MJ, Schijen JH, van der Heul C, Buller HR. Use of a clinical decision rule in combination with D-dimer concentration in diagnostic workup of patients with suspected pulmonary embolism: a prospective management study. Arch Intern Med 2002;162(14):1631-1635.
18. Wells PS, Anderson DR, Rodger M et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to

the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 2001; 135(2):98-107.
19. Pasha SM, Klok FA, Snoep JD et al. Safety of excluding acute pulmonary embolism based on an unlikely clinical probability by the Wells rule and normal D-dimer concentration: a meta-analysis. Thromb Res 2010;125(4):e123-e127.
20. Carrier M, Righini M, Djurabi RK et al. VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. Thromb Haemost 2009;101(5):886-892.
21. Righini M, Perrier A, De MP, Bounameaux H. D-Dimer for venous thromboembolism diagnosis: 20 years later. J Thromb Haemost 2008;6(7):1059-1071.
22. Gibson NS, Sohne M, Gerdes VE, Nijkeuter M, Buller HR. The importance of clinical probability assessment in interpreting a normal d-dimer in patients with suspected pulmonary embolism. Chest 2008;134(4):789-793.
23. Hager K, Platt D. Fibrin degeneration product concentrations (D-dimers) in the course of ageing. Gerontology 1995;41(3):159-165.
24. Masotti L, Ceccarelli E, Cappelli R, Forconi S. Plasma D-dimer levels in elderly patients with suspected pulmonary embolism. Thromb Res 2000;98(6):577-579.
25. Perrier A, Desmarais S, Goehring C et al. D-dimer testing for suspected pulmonary embolism in outpatients. Am J Respir Crit Care Med 1997;156(2 Pt 1):492-496.
26. Righini M, Goehring C, Bounameaux H, Perrier A. Effects of age on the performance of common diagnostic tests for pulmonary embolism. Am J Med 2000;109(5):357-361.
27. Tardy B, Tardy-Poncet B, Viallon A et al. Evaluation of D-dimer ELISA test in elderly patients with suspected pulmonary embolism. Thromb Haemost 1998;79(1):38-41.
28. Douma RA, Le GG, Sohne M et al. Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. BMJ 2010;340:c1475.
29. Bruinstroop E, van de Ree MA, Huisman MV. The use of D-dimer in specific clinical conditions: a narrative review. Eur J Intern Med 2009;20(5):441-446.
30. de Bastos M, de Bastos MR, Bogutchi T, Carneiro-Proietti AB, Rezende SM. Duration of symptoms and D-dimer testing in the ruling-out of venous thromboembolism. J Thromb Haemost 2006;4(9): 2079-2080.
31. Anderson DR, Kahn SR, Rodger MA et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA 2007;298(23):2743-2753.
32. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. JAMA 1990; 263(20):2753-2759.
33. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. Ann Intern Med 2000;132(3): 227-232.
34. Stein PD, Fowler SE, Goodman LR et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 2006;354(22):2317-2327.
35. Ghanima W, Almaas V, Aballi S et al. Management of suspected pulmonary embolism (PE) by D-dimer and multi-slice computed tomography in outpatients: an outcome study. J Thromb Haemost 2005;3(9):1926-1932.

36. Perrier A, Roy PM, Sanchez O et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med 2005;352(17):1760-1768.
37. Righini M, Le GG, Aujesky D et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. Lancet 2008;371(9621):1343-1352.
38. Mos IC, Klok FA, Kroft LJ, DE RA, Dekkers OM, Huisman MV. Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: systematic review and meta-analysis. J Thromb Haemost 2009; 7(9):1491-1498.
39. van Beek EJ, Brouwerst EM, Song B, Stein PD, Oudkerk M. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism--a critical review. Clin Radiol 2001; 56(10):838-842.
40. Aviram G, Levy G, Fishman JE, Blank A, Graif M. Pitfalls in the diagnosis of acute pulmonary embolism on spiral computer tomography. Curr Probl Diagn Radiol 2004;33(2):74-84.
41. Gotway MB, Patel RA, Webb WR. Helical CT for the evaluation of suspected acute pulmonary embolism: diagnostic pitfalls. J Comput Assist Tomogr 2000;24(2):267-273.
42. Jones SE, Wittram C. The indeterminate CT pulmonary angiogram: imaging characteristics and patient clinical outcome. Radiology 2005;237(1):329-337.
43. Abujudeh HH, Kaewlai R, Farsad K, Orr E, Gilman M, Shepard JA. Computed tomography pulmonary angiography: an assessment of the radiology report. Acad Radiol 2009;16(11):1309-1315.
44. Moores LK, Jackson WL, Jr., Shorr AF, Jackson JL. Meta-analysis: outcomes in patients with suspected pulmonary embolism managed with computed tomographic pulmonary angiography. Ann Intern Med 2004;141(11):866-874.
45. Le Gal G, Righini M, Parent F, van SM, Couturaud F. Diagnosis and management of subsegmental pulmonary embolism. J Thromb Haemost 2006;4(4):724-731.
46. Carrier M, Righini M, Wells PS et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. J Thromb Haemost 2010;8(8):1716-1722.
47. Gosselin MV, Rubin GD, Leung AN, Huang J, Rizk NW. Unsuspected pulmonary embolism: prospective detection on routine helical CT scans. Radiology 1998;208(1):209-215.
48. Dentali F, Ageno W, Becattini C et al. Prevalence and clinical history of incidental, asymptomatic pulmonary embolism: a meta-analysis. Thromb Res 2010;125(6):518-522.
49. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):454S-545S.
50. den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. J Clin Oncol 2011;29(17):2405-2409.
51. Stein PD, Woodard PK, Hull RD et al. Gadolinium-enhanced magnetic resonance angiography for detection of acute pulmonary embolism: an in-depth review. Chest 2003;124(6):2324-2328.
52. Dirk SH, Jablonski KA, Woodard PK et al. Factors in the technical quality of gadolinium enhanced magnetic resonance angiography for pulmonary embolism in PIOPED III. Int J Cardiovasc Imaging 2011.
53. Le Gal G, Righini M, Roy PM et al. Value of D-dimer testing for the exclusion of pulmonary embolism in patients with previous venous thromboembolism. Arch Intern Med 2006;166(2):176-180.

54. Nijkeuter M, Hovens MM, Davidson BL, Huisman MV. Resolution of thromboemboli in patients with acute pulmonary embolism: a systematic review. Chest 2006;129(1):192-197.
55. Mos ICM, Douma RA, Erkens PMG et al. Diagnostic outcome management study in patients with clinically suspected recurrent acute pulmonary embolism with a structured algorithm.Thromb Res. 2014 Jun;133(6):1039-44.