IMPROVING THE DIAGNOSTIC STRATEGY OF PULMONARY EMBOLISM

Improving the diagnostic strategy of pulmonary embolism

ISBN 90-9021179-9

Graphic design

Megla | www.megla.nl

Printing

Littera Picta

Publication of this thesis was financially supported by

Wyeth Pharmaceuticals bv, GlaxoSmithKline bv, Bayer bv HealthCare Pharmaceuticals,

Novo Nordisk Farma bv, Roche Nederland bv, ZLB Behring nv

2006 Rotterdam

IMPROVING THE DIAGNOSTIC STRATEGY OF PULMONARY EMBOLISM

Optimalisering van de diagnostische strategie bij longembolie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het college voor Promoties.

de openbare verdediging zal plaatsvinden op
vrijdag 15 december 2006 om 11.00 uur

door

Maria Johanna Helma Agnes Kruip

geboren te Roermond

PROMOTIECOMMISSIE

Promotores	**Prof.dr. B. Löwenberg**
	Prof.dr. H.R. Büller
Overige leden	**Prof.dr. H.A.P. Pols**
	Prof.dr. M.H. Prins
	Prof.dr. P.M.T. Pattynama
Co-promotor	**Dr. F.W.G. Leebeek**

Niets is dwazer dan wijs te zijn op het verkeerde moment.

Erasmus (1469-1536)

Ter herinnering aan mijn vader

Voor Evert

INDEX

Chapter 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Deep venous thrombosis is caused by pathological thrombus formation in the deep veins of the leg, pelvis or arm. In case a part of the thrombus is dislodged and migrates through the venous system to the pulmonary arteries, a pulmonary embolism may arise. Depending on the size, these thrombi can be located in central, segmental or subsegmental arteries.

Pulmonary embolism is a common disease with an estimated incidence of 30 per 100.000 inhabitants per year (< 70 years) increasing to 250 per 100.000 inhabitants per year among patients of older age (≥ 70 years) [1]. Clinical symptoms are diverse. The most common symptoms are dyspnoe, (pleuritic) chest pain that worsens with breathing and (less frequent) hemoptysis and cough. On physical examination signs that accompany pulmonary embolism are tachycardia, pleuritic rub, an accentuated second heart sound and neck vein distention [2]. Diagnosing or excluding pulmonary embolism on clinical signs and symptoms is difficult since none of these clinical manifestations are specific [3]. In less than 30% of patients presenting with clinically suspected suggestive of pulmonary embolism the disease can actually be confirmed by objective testing [4-6]. Therefore, the need for accurate diagnostic tests to exclude or confirm pulmonary embolism is obvious.

Pulmonary embolism if untreated is associated with high morbidity and mortality; even if treated adequately it remains it is the third cause of cardiovascular mortality after coronary artery disease and stroke [7]. In 1966 Barrit and Jordan compared in a randomized study anticoagulant treatment with no treatment in patients with clinically suspected pulmonary embolism. In this landmark study 26% of the untreated patients had fatal thromboembolic events and another 26% developed nonfatal recurrent emboli in the first weeks after the diagnosis. There were no fatalities in the group receiving anticoagulants [8]. Nowadays anticoagulant treatment provides effective prophylaxis of fatal and non-fatal recurrences, since the rate of recurrent thromboembolic events has been estimated at 4% during the first 3 months of treatment, although the risk of recurrence of pulmonary embolism remains present and gradually increases to 30% over the ten year after presentation [9,10]. The mortality rate due to fatal pulmonary embolism during 3 months of anticoagulant treatment is 1-2.2% [11,12]. However, anticoagulant treatment carries a substantial risk of bleeding. With vitamin-K antagonists, the risk of bleeding has been estimated at 16.5 per 100 treatment-years. Of these bleedings, approximately 1 per 100 treatment-years is an intracranial bleeding and about 2 per 100 treatment-years are other major bleedings with a case-fatality rate of 13% [13,14]. Given the high mortality in the absence of anticoagulant treatment on one hand, and the risk of bleeding with anticoagulant treatment on the other hand, it is important to rapidly confirm or exclude pulmonary embolism in patients who present with suspicion of pulmonary embolism.

Development of diagnostic tests

Prior to the development of accurate diagnostic tests, clinical history and physical examination have been the main diagnostic tools in patients with suspected pulmonary embolism. Even when the clinical evaluation was combined with results from arterial blood gas measurements, electrocardiogram and chest x-ray, the overall results were still inaccurate in confirming or ruling out pulmonary embolism [15,16].

Pulmonary angiography, which was introduced in the 1960s, has long been considered the gold standard for the diagnosis of pulmonary embolism [17,18]. Pulmonary angiography is sometimes difficult to interpret, with disagreement more often about the absence of pulmonary embolism (17% of angiograms) than about its presence (8% of angiograms) [4]. Despite these difficulties in interpretation, the 3 months thromboembolic risk in patients in whom anticoagulant treatment was withheld after a normal pulmonary angiogram was 1.7% (95% CI 1.0-2.7%) in a meta-analysis of eight studies based on a total of 1050 patients [19]. Three of these recurrences were fatal (0.3%; 95% CI 0.02-0.7%). A pulmonary angiogram is an invasive procedure and costly. At present with improved technology and with the assistance of experienced radiologists the complication rate has been low with a major non-fatal complication rate of 0.4% and a mortality rate of 0.1% [20]. The role of pulmonary angiography in the diagnosis of pulmonary embolism nowadays is limited, because of the availability of alternative non-invasive strategies. As a consequence the practical experience with angiography in hospitals has declined. Nevertheless, in patients with inconclusive non-invasive test results pulmonary angiography remains an excellent diagnostic method.

Also in the 1960s the lung perfusion scintigraphy was introduced [21]. Perfusion lung scintigraphy is a noninvasive technique allowing the visualization of pulmonary perfusion through intravenous injection of albumin macroaggregates labeled with Technetium 99m. A normal perfusion scan can safely rule out pulmonary embolism and anticoagulant treatment can be withheld [4,22]. Not all perfusion defects are specific for the diagnosis pulmonary embolism. A perfusion defect corresponding to a (large part of a) segment is more specific. The specificity can be increased by adding ventilation scintigraphy (with Xenon 133, Krypton 81m, or aerolized Technetium 99m). A high probability scan, defined as at least one segmental perfusion defect with locally normal ventilation (a mismatch) confirms pulmonary embolism with a specificity of 97% [4]. The major disadvantage of lung scanning is that in 50-60% of patients pulmonary embolism can be excluded nor confirmed (non-diagnostic scan result), so that further testing is needed.

Since the late 1990s the diagnostic strategy for pulmonary embolism has changed. As stated before, pulmonary embolism is present in 20-30% of patients presenting with signs and symptoms suggestive of the disease, hence the first goal of the diagnostic work up should be to distinguish those individuals who have the disease and should be treated with anticoagulants from the majority who do not. For this purpose standardized clinical probability assessments have been introduced in combination with D-dimer testing, a marker of coagulation activation [23-27]. Using pre-test clinical probability, either as a probability assessment or as a standardized clinical decision rule, patients can be classified into three categories corresponding to the prevalence of pulmonary embolism: in patients with a low, intermediate or high probability, the prevalence of pulmonary embolism is 6-10%, 27-30%, or 63-68%, respectively [7]. More recently a dichotomized clinical decision rule has been introduced with the categories pulmonary embolism unlikely of likely [28].

D-dimer is a degradation product of cross-linked fibrin. The finding of a normal plasma D-dimer concentration was shown to be able to exclude pulmonary embolism accurately in most patients presenting with clinical suspicion. The sensitivity and negative predictive value vary depending on the type of D-dimer assay. With the current rapid tests, both sensitivity and specificity are usually high (90-100% and 94-100%, respectively) [27,29-31]. To safely exclude pulmonary embolism the sensitivity should preferably approach 100%. This is important because, for every 2% decrease in sensitivity 1 in 1000 patients presenting with symptoms of pulmonary embolism will die of recurrent pulmonary embolism as a result of unjustly withholding anticoagulant treatment [32]. Most D-dimer assays lack a sufficiently high sensitivity to justify their use as the sole test. In patients with a low clinical probability and a normal D-dimer concentration, present in 20-30% of patients with clinically suspected pulmonary embolism, pulmonary embolism seems safely excluded, however this has to be further documented in large cohort studies [6,23,33-35].

In the remaining proportion of patients, who are more likely to have pulmonary embolism, diagnostic imaging is necessary. Since 2002 the clinical utility of single slice spiral CT has been studied as part of several diagnostic strategies. In these strategies spiral CT was not used as the sole diagnostic test, but it was combined with other diagnostic imaging techniques, mostly compression ultrasonography [6,36,37]. The main drawback of single slice spiral CT has been the limitation to detect peripheral emboli, and therefore is not able to safely exclude pulmonary embolism without further testing [38,39]. Multi slice CT has become available since 2004 and has improved the detection rate of peripheral emboli. It is possible that multi slice CT indeed might be safely used as the sole imaging test to confirm or exclude pulmonary embolism, however for the time being large studies are also lacking that document the validity of this approach [34].

Outline of the thesis

The aim of this thesis is to investigate diagnostic strategies for patients with suspected pulmonary embolism. For this purpose several studies addressing different aspects of the diagnostic work up have been performed. In **Chapter 2** we reviewed the current status of pulmonary embolism diagnosis. Thereafter, the clinical usefulness of D-dimer testing, the clinical decision rule, and radiological imaging techniques are studied. In **Chapter 3** the safety of withholding anticoagulant treatment in patients with a low clinical probability, using an extended clinical decision rule, in combination with a normal D-dimer concentration is evaluated. In the remaining patients a diagnostic strategy using compression ultrasonography and pulmonary angiography was evaluated. The clinical decision rule has been simplified and dichotomized. In a large management study in **Chapter 4** this simple clinical decision rule in combination with a normal D-dimer concentration is used to exclude pulmonary embolism. In this study spiral CT was used as the sole diagnostic imaging technique to exclude or diagnose pulmonary embolism. Whether this strategy can also be used in hospitalized patients or other subgroups of patients at risk for pulmonary embolism is assessed in **Chapter 5** and **Chapter 6**, respectively.

Clinical decision rules are frequently used in diagnostic strategies. The observer variability in the assessment of clinical probability is assessed in **Chapter 7** and further simplification of the Wells clinical decision rule is studied and validated in **Chapter 8**.

D-dimer testing has a central role in excluding pulmonary embolism. Many assays are available and in **Chapter 9** a fast assay is evaluated. Finally, in **Chapter 10,** the potential clinical utility of C-reactive protein, alone or in combination with a clinical decision rule and D-dimer in excluding pulmonary embolism is evaluated for its use as a diagnostic variable in patients with suspected pulmonary embolism.

REFERENCES

1. Stein PD, Hull RD, Kayali F, Ghali WA, Alshab AK, Olson RE. Venous thromboembolism according to age: the impact of an aging population. Arch Intern Med. 2004;164:2260-2265.
2. Stein PD, Terrin ML, Hales CA, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest. 1991;100:598-603.
3. Kearon C, Hirsh J. The diagnosis of pulmonary embolism. Haemostasis. 1995;25:72-87.
4. 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;263:2753-2759.
5. Stein PD, Hull RD, Saltzman HA, Pineo G. Strategy for diagnosis of patients with suspected acute pulmonary embolism. Chest. 1993;103:1553-1559.
6. Perrier A, Roy PM, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med. 2004;116:291-299.
7. Bounameaux H, Perrier A. Diagnosis of Venous Thromboembolism. Hemostasis and Thrombosis; basic principles and clinical practice (ed 5th). Philadephia: Lippincott Williams & Wilkins; 2006:1279-1297.
8. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet. 1960;1:1309-1312.
9. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. Arch Intern Med. 2000;160:3431-3436.
10. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000;160:761-768.
11. Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. N Engl J Med. 1997;337:663-669.
12. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators. N Engl J Med. 1997;337:657-662.
13. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. Arch Intern Med. 1993;153:1557-1562.
14. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med. 2003;139:893-900.
15. Dalen JE. Pulmonary embolism: what have we learned since Virchow? Natural history, pathophysiology, and diagnosis. Chest. 2002;122:1440-1456.
16. Hoellerich VL, Wigton RS. Diagnosing pulmonary embolism using clinical findings. Arch Intern Med. 1986;146:1699-1704.
17. Williams JR, Wilcox C, Andrews GJ, Burns RR. Angiography in pulmonary embolism. Jama. 1963;184:473-476.
18. Sasahara AA, Stein M, Simon M, Littmann D. Pulmonary Angiography in the Diagnosis of Thromboembolic Disease. N Engl J Med. 1964;270:1075-1081.
19. 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;56:838-842.
20. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. Eur Heart J. 2000;21:1301-1336.
21. Wagner HN, Jr., Sabiston DC, Jr., McAfee JG, Tow D, Stern HS. Diagnosis of Massive Pulmonary Embolism in Man by Radioisotope Scanning. N Engl J Med. 1964;271:377-384.
22. Hull RD, Raskob GE, Coates G, Panju AA. Clinical validity of a normal perfusion lung scan in patients with suspected pulmonary embolism. Chest. 1990;97:23-26.

23. 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;83:416-420.

24. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med. 1998;129:997-1005.

25. 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;161:92-97.

26. Chagnon I, Bounameaux H, Aujesky D, et al. Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism. Am J Med. 2002;113:269-275.

27. 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;140:589-602.

28. van Belle A, 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;295:172-179.

29. Perrier A, Bounameaux H, Morabia A, et al. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. Arch Intern Med. 1996;156:531-536.

30. van Beek EJ, van den Ende B, Berckmans RJ, et al. A comparative analysis of D-dimer assays in patients with clinically suspected pulmonary embolism. Thromb Haemost. 1993;70:408-413.

31. Bounameaux H, Cirafici P, de Moerloose P, et al. Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. Lancet. 1991;337:196-200.

32. van Beek EJ, Schenk BE, Michel BC, et al. The role of plasma D-dimers concentration in the exclusion of pulmonary embolism. Br J Haematol. 1996;92:725-732.

33. 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;135:98-107.

34. Perrier A, Roy PM, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med. 2005;352:1760-1768.

35. Ten Wolde M, Hagen PJ, Macgillavry MR, et al. Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism; results of a management study. J Thromb Haemost. 2004;2:1110-1117.

36. van Strijen MJ, de Monye W, Schiereck J, et al. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. Ann Intern Med. 2003;138:307-314.

37. Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet. 2002;360:1914-1920.

38. Goodman LR, Curtin JJ, Mewissen MW, et al. Detection of pulmonary embolism in patients with unresolved clinical and scintigraphic diagnosis: helical CT versus angiography. AJR Am J Roentgenol. 1995;164:1369-1374.

39. Drucker EA, Rivitz SM, Shepard JA, et al. Acute pulmonary embolism: assessment of helical CT for diagnosis. Radiology. 1998;209:235-241.

Chapter 2

DIAGNOSTIC STRATEGIES FOR EXCLUDING PULMONARY EMBOLISM IN CLINICAL OUTCOME STUDIES

A Systematic Review

Marieke J.H.A. Kruip, Monique G.L. Leclercq,
Cees van der Heul, Martin H. Prins, Harry R. Büller

Annals of Internal Medicine 2003;138:941-951

ABSTRACT

Background: Pulmonary embolism is a common clinical disorder that is associated with high morbidity and mortality if untreated. It is important to confirm or rule out the diagnosis in patients with clinical suspicion of the disease.

Purpose: To evaluate various diagnostic strategies for excluding pulmonary embolism.

Data Sources: MEDLINE (1966 to February 2003), EMBASE, and DARE; study investigators; and reference lists.

Study Selection: Prospective clinical outcome studies.

Data Extraction: The researchers recorded the frequency of symptomatic venous thromboembolism over 3 months of follow-up in patients in whom pulmonary embolism had been excluded according to various strategies. Strategies were divided into three categories according to the number of rounds of diagnostic tests needed to exclude pulmonary embolism.

Data Synthesis: 25 studies involving more than 7000 patients were included. In all referred patients, two strategies—normal results on pulmonary angiography or lung scintigraphy and normal D-dimer levels combined with low clinical probability—safely excluded pulmonary embolism (failure rates 5 3%). In the second round of diagnostic tests, in patients who had had a nondiagnostic lung scan, both pulmonary angiography and serial leg testing for venous thrombosis were accurate and safe. When D-dimer testing combined with clinical probability was inconclusive, a normal perfusion lung scan safely excluded pulmonary embolism. Accumulating evidence shows that normal results on spiral computed tomography may also safely exclude the disease.

Conclusions: Many diagnostic strategies to exclude pulmonary embolism have been evaluated in consecutive patients. Interest is likely to increase in a simple, fast strategy, starting with a normal perfusion lung scan or a combination of normal D-dimer levels and low clinical probability. After the initial round of testing, a reliable diagnostic method, such as angiography or lung scintigraphy, is warranted.

INTRODUCTION

Pulmonary embolism is a common clinical disorder that is associated with high morbidity and mortality if untreated. In the only randomized study comparing anticoagulant therapy with no treatment in patients with pulmonary embolism, 26% of untreated patients had a fatal embolic event and another 26% developed nonfatal recurrent emboli[1]. With a course of anticoagulant treatment, the recurrence rate of thromboembolic events decreases to approximately 2% to 9% over 3 to 6 months[2, 3]. However, anticoagulation always carries a risk for bleeding (annual rate of major bleeding, 7%)[4, 5]. To avoid unnecessary anticoagulant therapy, it is therefore important to rapidly confirm or exclude pulmonary embolism in patients who present with suspicion of the disorder.

Diagnosing or excluding pulmonary embolism on the basis of clinical manifestations alone is difficult because such manifestations are nonspecific[6]. Approximately 25% of patients with suspected pulmonary embolism have the disease confirmed by objective testing[7-9]. The goal of the first diagnostic strategies introduced was to confirm rather than exclude the presence of pulmonary emboli. The more recently evaluated diagnostic approaches have focused on identifying patients who probably do not have pulmonary embolism and therefore do not require anticoagulant therapy. Various invasive and noninvasive diagnostic methods have been advocated for excluding the disease.

We performed a systematic review of the literature to evaluate diagnostic strategies designed to exclude pulmonary embolism. Our objective was to investigate whether clinical outcome evaluation properly documented the safety of withholding anticoagulant treatment in patients in whom pulmonary embolism was excluded according to a given diagnostic strategy. We assessed the accuracy of the various diagnostic strategies by examining the number of symptomatic thromboembolic events (deep venous thrombosis or pulmonary embolism) that occurred without anticoagulant treatment during a follow-up period of at least 3 months. Studies were grouped according to the number of rounds of diagnostic testing performed before pulmonary embolism was ruled out.

METHODS

Study Selection

We attempted to identify all published clinical studies that evaluated the outcome of diagnostic strategies for excluding pulmonary embolism in consecutive patients who presented with clinical suspicion of the disease. We adhered to the criteria for systematic review outlined by McAlister and colleagues[10, 11]. We conducted a comprehensive search of English-language literature on MEDLINE (1966 to February 2003), EMBASE, and DARE using the Medical Subject Headings pulmonary embolism and diagnosing, diagnosis, pulmonary angiography, ventilation–perfusion lung scan, compression ultrasonography, contrast venography, impedance plethysmography, D-dimer, clinical probability, computerized tomography, and magnetic resonance angiography. We also included published abstracts that provided enough details for analysis. In addition, we contacted investigators and conducted a manual search by reviewing the reference lists of original and review articles. Duplicate reports were excluded.

We used predefined methodologic criteria to select studies. To be included, a study had to 1) be prospective and involve consecutive patients; 2) define a priori the diagnostic strategy used to exclude or confirm the diagnosis of pulmonary embolism; 3) withhold anticoagulant treatment when pulmonary embolism was excluded; 4) provide a detailed description of the method of follow-up; 5) have a minimum follow-up of 3 months, with fewer than 10% of patients lost during follow-up; and 6) provide detailed descriptions of diagnostic management in patients with recurrent symptoms of venous thromboembolism.

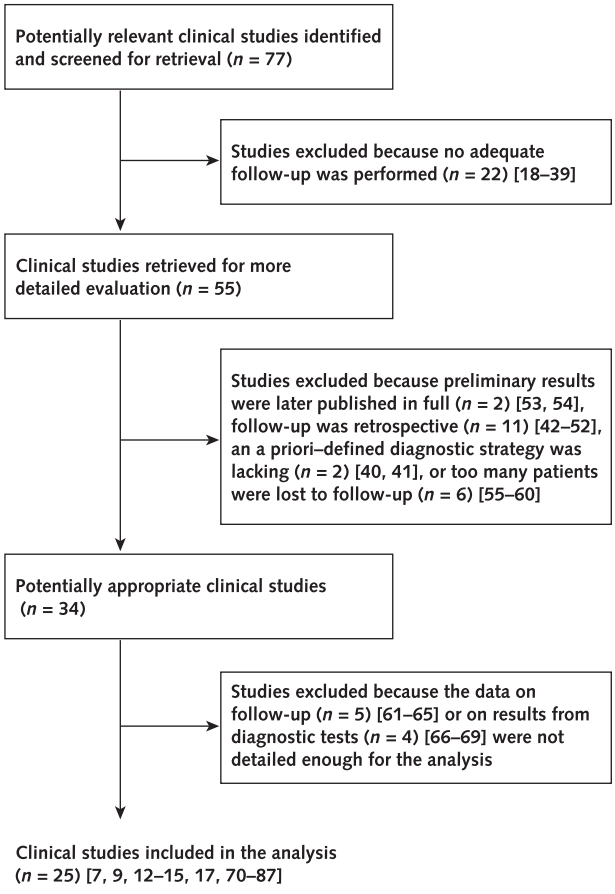
Data Extraction

One investigator abstracted data on study size, setting, patient sampling and characteristics, and prevalence of pulmonary embolism. Three investigators independently extracted data on the diagnostic strategy and tests used, the number of patients who had negative test results and therefore did not receive anticoagulant treatment, the number of symptomatic thromboembolic events confirmed by objective testing in patients without pulmonary embolism and without anticoagulant treatment, and duration and method of follow-up. Although some studies had a longer follow-up, we limited our analysis to the first 3 months after pulmonary embolism was excluded. We used the original study authors' interpretations of the different test outcomes for our analysis. Investigator disagreements were resolved by consensus.

Statistical Analysis

We defined the failure rate as the frequency with which symptomatic venous thromboembolic events were confirmed by objective testing during a 3-month follow-up period in patients who had had negative results on diagnostic tests for pulmonary embolism. The upper 95% confidence limit (CL) of the failure rate was estimated. For studies with similar diagnostic strategies, we assessed heterogeneity by using the Fisher exact test (StatXact, version 3.0, Cytel Corp., Cambridge, Massachusetts). Pooled and weighted estimates of the failure rate and their upper 95% CLs were calculated by using CIA software, version 1.0 (Confidence Interval Analysis, University of Southampton, Southampton, United Kingdom). We considered a diagnostic strategy to be safe if the upper 95% CL of the observed rate of confirmed symptomatic episodes of venous thromboembolism did not exceed 3% during the 3-month follow-up[12-17]

FIGURE. Study selection.



Numbers in square brackets are reference numbers.

TABLE 1. Main Characteristics of the Included Studies*

Study, Year (Reference)	Setting	Patient Characteristics	Pretest Probability of Pulmonary Embolism	Prevalence of Pulmonary Embolism, %	Diagnostic Strategy	Reference Standard for Failure Rate
Hull et al., 1983 (9)	Multicenter thromboembolism service (4 centers)	Consecutive referred patients	Intermediate	49	PA, venography	Clinical outcome, IPG† (after 3, 12 months)
Hull et al., 1990 (70)	Hospital thromboembolism service	Consecutive inpatients and outpatients	Very low	–	–	Clinical outcome, IPG (at 3 months)
PIOPED, 1990 (7)	Multicenter (6 centers)	Consecutive inpatients and outpatients	Low	33	PA	Clinical outcome
Kruit et al., 1991 (71)	Hospital	Consecutive patients	Low	37	Lung scan, venography, serial IPG	Serial IPG (1, 3, 6, 12 months) and lung scan (3 months), clinical outcome
Ginsberg et al., 1993 (72)	Hospital thromboembolism service	Consecutive referred patients	Low	19	Lung scan or PA, IPG, venography	Clinical outcome
Hull et al., 1994 (12)	Hospital thromboembolism service	Consecutive referred patients	Low	15	Lung scan, IPG, serial IPG†	Clinical outcome, IPG (3 months)
van Beek et al., 1995 (75)	Multicenter thromboembolism unit (2 centers)	Consecutive inpatients and outpatients	Very low	–	–	Clinical outcome
Henry et al., 1995 (74)	Multicenter (6 centers)	Consecutive inpatients and outpatients	Very low	–	–	Clinical outcome
van Beek et al., 1996 (80)	Multicenter (2 centers)	Consecutive patients	Low	27	Lung scan and PA	Clinical outcome
Perrier et al., 1996 (15)	University hospital	Consecutive outpatients	Low	35	Lung scan, clinical probability, DD (Asserachrom D-di‡), CUS and PA	Clinical outcome
van Beek et al., 1997 (73)	Multicenter (2 centers)	Consecutive inpatients and outpatients	Low	39	Lung scan, PA	Clinical outcome
Ferretti et al., 1997 (76)	University hospital	Consecutive inpatients and outpatients	Moderate	24	Helical CT	Clinical outcome alone (44%) or clinical examination, CUS, lung scan at 3 months
Wells et al., 1998 (13)	Multicenter (5 tertiary care hospitals)	Consecutive inpatients and outpatients	Low	18	Clinical probability, lung scan, CUS, venography, PA	Clinical outcome
Perrier et al., 1999 (14)	Multicenter (2 centers)	Consecutive outpatients	Low	24	DD (VIDAS§), CUS, lung scan, clinical probability, PA	Clinical outcome
Miron et al., 1999 (87)	University hospital	Consecutive inpatients	Moderate	36	Lung scan, clinical probability, DD (VIDAS§), CUS, PA	Clinical outcome
de Groot et al., 1999 (77)	Hospital	Consecutive inpatients and outpatients	Low	24	Lung scan, DD (SimpliRED‖), CUS, PA	Clinical outcome
Bernier et al., 2001 (85)	Hospital	Outpatients	Low	10¶	DD (VIDAS§)	Clinical outcome
Anderson et al., 2001 (84)	Multicenter (3 centers)	Outpatients	Low	17	Clinical probability, DD (agglutination assay), spiral CT, CUS	Clinical outcome
ten Wolde et al., 2001 (81)	Multicenter (3 centers)	Consecutive inpatients and outpatients	Low	19	Clinical probability, DD (Tinaquant**), lung scan, serial CUS	Clinical outcome
Perrier et al., 2001 (79)	University hospital	Emergency patients	Low	39	DD (VIDAS§), CUS, lung scan, clinical probability, PA	Clinical outcome
Miniati et al., 2001 (86)	Hospital	Consecutive patients	Low	39	Lung scan, PA	Clinical outcome
Wells et al., 2001 (78)	Multicenter (4 tertiary care hospitals)	Consecutive outpatients	Low	10	Clinical probability, DD (SimpliRED‖), lung scan, CUS, PA	Clinical outcome
Kruip et al., 2002 (83)	Hospital	Consecutive inpatients and outpatients	Low	22	Clinical probability, DD (VIDAS§), CUS, PA	Clinical outcome

Study, Year (Reference)	Setting	Patient Characteristics	Pretest Probability of Pulmonary Embolism	Prevalence of Pulmonary Embolism, %	Diagnostic Strategy	Reference Standard for Failure Rate
Leclercq et al., 2003 (82)	Hospital	Consecutive inpatients and outpatients	Low	29	Clinical probability, DD (Tinaquant**), lung scan, CUS, PA	Clinical outcome
Musset et al., 2002 (17)	Multicenter (14 centers)	Consecutive inpatients and outpatients	Low	35	Spiral CT and CUS, clinical probability, lung scan, PA	Clinical outcome

* CT = computed tomography; CUS = compression ultrasonography; DD = D-dimer concentration; IPG = impedance plethysmography; PA = pulmonary angiography; PE = pulmonary embolism; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis.
† Performed only in patients with adequate cardiorespiratory reserve.
‡ Diagnostica Stago, Asnières, France.
§ bioMérieux, Inc., Marcy L'Etoile, France.
‖ Agen Biochemical, Ltd., Brisbane, Australia.
¶ In patients who underwent PA to test for DVT.
** Roche Diagnostics, Almere, the Netherlands.

RESULTS

We identified 77 studies. Of these, 52 were excluded because they did not meet the predefined selection criteria [18-69] (Figure). Therefore, 25 studies including more than 7000 patients with clinical suspicion of pulmonary embolism in whom the diagnosis was ruled out by a particular strategy [7, 9, 12-15, 17, 70-87] met all selection criteria and were available for our analysis. We divided the diagnostic strategies into tests done in all referred patients, tests performed after a first diagnostic round, and tests performed in patients with nondiagnostic results after two diagnostic rounds. Among the similar diagnostic strategies, no heterogeneity in the incidence of venous thromboembolism was observed. Table 1 lists the main characteristics of each study.

Diagnostic Strategies for Excluding Pulmonary Embolism in All Referred Patients

In 19 studies involving 4096 patients, several diagnostic strategies were evaluated in consecutive patients presenting with suspected pulmonary embolism (Table 2).

STRATEGIES INVOLVING PULMONARY ANGIOGRAPHY

In one multicenter study[7], 755 of 931 inpatients and outpatients (81%) underwent pulmonary angiography. Of these, 480 had normal test results and did not receive anticoagulant treatment. During follow-up, 4 patients died of pulmonary embolism, all within the first week (failure rate, 0.8% [upper 95% CL, 2.1%])[7].

STRATEGIES INVOLVING LUNG SCINTIGRAPHY

Seven studies evaluated the outcome of excluding pulmonary embolism by using normal results on perfusion lung scintigraphy in consecutive patients [15, 71, 73, 75, 77, 86, 87]. These studies were similar in prevalence of pulmonary embolism and patient characteristics at study entry, except for the study by Miron and associates [87], which included only inpatients. Most observed failure rates were low during 3-month follow-up, and the combined failure rate showed that a normal lung scan seemed to accurately exclude pulmonary embolism (failure rate, 0.9% [upper 95% CL, 2.3%]).

In three studies, pulmonary embolism was excluded by a normal perfusion lung scan combined with normal results of bilateral leg testing (compression ultrasonography [13] or impedance plethysmography[12, 70]) performed on the same day. Patient characteristics in these studies were similar to those in the studies that examined lung scintigraphy alone. Adding a single leg test to a normal perfusion lung scan did not materially improve the accuracy of a normal perfusion scan alone [12, 13, 70]. Another approach studied involved using a nondiagnostic perfusion lung scan in patients with low clinical probability or with normal D-dimer levels and moderate clinical probability. Perrier and coworkers[15] evaluated these strategies in 48 and 53 patients, respectively, and observed no thromboembolic complications during follow-up (upper 95% CL, 7.4% and 6.7%, respectively).

STRATEGIES USING ONLY D-DIMER TESTS OR A COMBINATION OF D-DIMER TESTS AND CLINICAL PROBABILITY

A normal result on a D-dimer test was used in two ways. In two studies[14, 85], a normal D-dimer level on a rapid enzyme-linked immunosorbent assay (ELISA) was the only indicator used to exclude pulmonary embolism in 201 referred patients (failure rate, 0% [upper 95% CL, 1.8%]). The assay had a sensitivity and negative predictive value of 98% to 100%[14, 56, 79, 83, 85].

In other studies, a normal D-dimer concentration was used to exclude pulmonary embolism in patients with low [78, 81, 83, 84] or low to moderate[82] clinical probability. Three methods of D-dimer testing were used: a wholeblood agglutination assay [78, 84], a rapid ELISA assay [83], and a latex-enhanced photometric immunoassay [81, 82]. In general, the two later assays have a sensitivity and negative predictive value of nearly 100%[14, 56, 79, 81-83, 85, 88]. However, these indices vary for the agglutination assays (sensitivity, 85% to 94%; negative predictive value, 96% to 98%)[89, 90]. Most studies used a standardized clinical model for clinical probability assessment[78, 82-84]. Combining low clinical probability and normal D-dimer results appeared to safely exclude pulmonary embolism in the 894 included patients; only two venous thromboembolic events occurred during follow-up (failure rate, 0.2% [upper 95% CL, 0.8%])[78, 81, 83, 84]. In the single study that excluded pulmonary embolism by using low to moderate

clinical probability and normal D-dimer levels, no venous thromboembolic events were noted (failure rate, 0% [upper 95% CL, 5.6%])[82].

STRATEGIES INVOLVING SPIRAL COMPUTED TOMOGRAPHY AND COMPRESSION ULTRASONOGRAPHY

One study excluded pulmonary embolism with normal results on spiral computed tomography (CT) and compression ultrasonography in 507 patients with low to moderate clinical probability. During follow-up, nine patients had a thromboembolic event (failure rate, 1.8% [upper 95% CL, 3.3%]). Of these, five died, possibly of pulmonary embolism or related causes. Ten patients were lost to follow-up[17].

TABLE 2. Outcome of Diagnostic Strategies for Excluding Pulmonary Embolism in All Referred Patients*

Exclusion Strategy	Study, Year (Reference)	Included Patients	VTE Complications†	Failure Rate (95% CL)
		n		%
Pulmonary angiography				
Normal results	PIOPED, 1990 (7)	480	4	0.8 (2.1)
Lung scintigraphy				
Normal results	Kruit et al., 1991 (71)	44	0	0 (8.0)
	van Beek et al., 1995 (75)	113	0	0 (3.2)
	Perrier et al., 1996 (15)	43	0	0 (8.2)
	van Beek et al., 1997 (73)	137	1	0.7 (4.0)
	de Groot et al., 1999 (77)	54	3	5.6 (15.4)
	Miron et al., 1999 (87)	16	0	0 (20.6)
	Miniati et al., 2001 (86)	34	0	0 (10.3)
	Total	441	4	0.9 (2.3)
Normal results plus normal results on leg testing‡	Hull et al., 1990 (70)	515	3	0.6 (1.7)
	Hull et al., 1994 (12)	576	4	0.7 (1.8)
	Wells et al., 1998 (13)	332	2	0.6 (2.2)
	Total	1423	9	0.6 (1.2)
Nondiagnostic results in patients with low clinical probability	Perrier et al., 1996 (15)	48	0	0 (7.4)
Nondiagnostic results in patients with normal D-dimer levels and moderate clinical probability	Perrier et al., 1996 (15)	53	0	0 (6.7)
D-Dimer testing alone or combined with clinical probability				
Normal D-dimer level	Perrier et al., 1999 (14)	159	0	0 (2.3)
	Bernier et al., 2001 (85)	42	0	0 (8.4)
	Total	201	0	0 (1.8)
Normal D-dimer level in patients with low clinical probability	Wells et al., 2001 (78)	437	1	0.2 (1.3)
	Anderson et al., 2001 (84)	306	1	0.3 (1.8)
	Kruip et al., 2002 (83)	60	0	0 (6.0)
	ten Wolde et al., 2001 (81)	91	0	0 (4.0)
	Total	894	2	0.2 (0.8)
Normal D-dimer level in patients with low to moderate clinical probability	Leclercq et al., 2002 (82)	64	0	0 (5.6)
Spiral CT and CUS				
Normal results on both in patients with low to moderate clinical probability	Musset et al., 2002 (17)	507	9	1.8 (3.3)

* CL = confidence limit; CT = computed tomography; CUS = compression ultrasonography; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; VTE = venous thromboembolic.
† Symptomatic VTE complications during the 3-month follow-up.
‡ Leg testing includes impedance plethysmography or compression ultrasonography.

TABLE 3. Outcome of Diagnostic Strategies for Excluding Pulmonary Embolism after the First Inconclusive Diagnostic Round*

Exclusion Strategy	Study, Year (Reference)	Included Patients	VTE Complications†	Failure Rate (95% CL)
		n		%
After abnormal lung scan				
Normal results on pulmonary angiography	Hull et al., 1983 (9)	44	1	2.3 (12.0)
	Henry et al., 1995 (74)	380	5	1.3 (3.1)
	Miniati et al., 2001 (86)	33	0	0 (10.6)
	Total	457	6	1.3 (2.8)
After nondiagnostic lung scan				
Normal results on pulmonary angiography	van Beek et al., 1996 (80)	105	0	0 (3.5)
Normal results on CUS and pulmonary angiography in patients with elevated D-dimer levels and moderate clinical probability	Perrier et al., 1996 (15)	55	1	1.8 (9.7)
Low clinical probability	Miron et al., 1999 (87)	20	0	0 (16.8)
Normal D-dimer levels in patients with low to moderate clinical probability	de Groot et al., 1999 (77)	59	1	1.7 (9.1)
Serial IPG	Kruit et al., 1991 (71)	62	0	0 (5.8)
	Ginsberg et al., 1993 (72)	90	1	1.1 (6.0)
	Hull et al., 1994 (12)	627	12	1.9 (3.3)
	Total	779	13	1.7 (2.8)
Serial CUS in patients with low to moderate clinical probability	Wells et al., 1998 (13)	665	3	0.5 (1.3)
Normal results on spiral CT and CUS in patients with low to moderate clinical probability	Ferretti et al., 1997 (76)	109	6	5.5 (11.6)
After elevated D-dimer level and normal results on CUS				
Normal or near-normal lung scan	Perrier et al., 2001 (79)	44	0	0 (8.0)
Nondiagnostic lung scan in patients with low clinical probability	Perrier et al., 2001 (79)	79	0	0 (4.6)
Lung scan normal or near-normal, or nondiagnostic lung scan in patients with low clinical probability	Perrier et al., 1999 (14)	144	2	1.4 (4.9)
After elevated D-dimer level and low clinical probability or moderate to high clinical probability				
Normal lung scan	Wells et al., 2001 (78)	183	0	0 (2.0)
	ten Wolde et al., 2001 (81)	160	0	0 (2.3)
	Total	343	0	0 (1.1)
Normal results on CUS and pulmonary angiography	Kruip et al., 2002 (83)	122	1	0.8 (4.5)
Normal results on spiral CT and CUS	Anderson et al., 2001 (84)	287	0	0 (1.3)
After elevated D-dimer level and low to moderate clinical probability or high clinical probability				
Normal lung scan	Leclercq et al., 2002 (82)	31	0	0 (11.2)
After CT and CUS				
Negative results on both tests in patients with high clinical probability, normal lung scan, normal results on PA, or both	Musset et al., 2002 (17)	70	0	0 (5.1)
Inconclusive results on both tests in patients with normal lung scan, normal results on PA, or both‡	Musset et al., 2002 (17)	84	0	0 (4.3)

* CL = confidence limit; CT = computed tomography; CUS = compression ultrasonography; IPG = impedance plethysmography; VTE = venous thromboembolic.
† Symptomatic VTE complications during the 3-month follow-up.
‡ Inconclusive results were nondiagnostic results on CT and normal results on CUS, normal results on CT and nondiagnostic results on CUS, or subsegmental pulmonary embolism on CT and normal results on CUS.

Diagnostic Strategies after the First Diagnostic Round

Twenty studies involving 3376 patients (Table 3) investigated different strategies when a first diagnostic test or tests did not exclude or confirm the diagnosis of pulmonary embolism. The study samples tested in this second round may have varied with respect to clinical characteristics and likelihood of disease, depending on the first tests used.

STRATEGIES AFTER AN ABNORMAL OR NONDIAGNOSTIC LUNG SCAN

After an abnormal or nondiagnostic lung scan, four diagnostic strategies were studied: pulmonary angiography, D-dimer testing and clinical probability assessment, serial leg testing, and spiral CT. Pulmonary angiography was used as the sole test in four studies[9, 74, 80, 86]. In three of the four[9, 74, 86], pulmonary angiography was performed in 457 consecutive inpatients and outpatients with suspected pulmonary embolism after an abnormal lung scan[9, 74, 86]. In the remaining study [80], pulmonary angiography was performed in 105 patients after a nondiagnostic lung scan. During follow-up, 6 thromboembolic events[9, 74, 86] and 0 thromboembolic events [80] were observed, with respective failure rates of 1.3% (upper 95% CL, 2.8%) and 0% (upper 95% CL, 3.5%). Another study [15] used pulmonary angiography in combination with compression ultrasonography in 55 outpatients with elevated D-dimer levels and moderate clinical probability. One nonfatal venous thromboembolic event occurred during follow-up (failure rate, 1.8% [upper 95% CL, 9.7%]) [15]. Two studies used clinical probability alone or in combination with normal D-dimer levels to exclude pulmonary embolism after a nondiagnostic lung scan [77, 87]. Of these studies, one [87] was performed in hospitalized patients; both studies involved small numbers of patients.

Four studies used serial leg testing (impedance plethysmography [12, 71, 72] or compression ultrasonography [13]) over approximately 10 days to exclude pulmonary embolism after a nondiagnostic lung scan. Hull and colleagues [9] also performed serial impedance plethysmography but only in patients with adequate cardiorespiratory reserve. The three studies that used serial impedance plethysmography in 779 referred patients had a failure rate of 1.7% (upper 95% CL, 2.8%) [12, 71, 72]. Wells and associates [13] included only patients with low to moderate clinical probability as assessed by a standardized clinical model. Of the 665 inpatients and outpatients with normal results on serial compression ultrasonography, 3 had a thromboembolic event during follow-up (failure rate, 0.5% [upper 95% CL, 1.3%]).

Finally, one study used spiral CT in combination with normal results on compression ultrasonography to exclude pulmonary embolism in 109 inpatients and outpatients with low to moderate clinical probability after a nondiagnostic lung scan [76]. The failure rate was 5.5% (upper 95% CL, 11.6%).

STRATEGIES AFTER ELEVATED D-DIMER LEVEL IN COMBINATION WITH NORMAL RESULTS ON COMPRESSION ULTRASONOGRAPHY OR CLINICAL PROBABILITY ASSESSMENT

After elevated D-dimer levels were detected, most diagnostic strategies continued with lung scintigraphy, sometimes in combination with clinical probability assessment or compression ultrasonography (Table 3) [14, 78, 79, 81-84]. The subgroups were mostly moderate in size and were tested by using strategies that had been previously examined in only a single study.

Consequently, the upper 95% CLs of the failure rates clearly exceeded 3%. In two studies[78, 81], a normal lung scan excluded pulmonary embolism in 343 patients with moderate to high clinical probability or with low clinical probability and elevated D-dimer levels. During follow-up, no thromboembolic events were noted (failure rate, 0% [upper 95% CL, 1.1%]).

Kruip and colleagues[83] studied the combination of normal results on compression ultrasonography and pulmonary angiography in 122 inpatients and outpatients with moderate to high clinical probability or with low clinical probability and elevated D-dimer levels. This diagnostic strategy resulted in a failure rate of 0.8% (upper 95% CL, 4.5%). Anderson and coworkers [84] found that normal results on spiral CT in combination with one instance of normal results on compression ultrasonography excluded pulmonary embolism in 287 consecutive patients with moderate to high clinical probability or with elevated D-dimer levels and low clinical probability. No thromboembolic complications were noted during follow-up (failure rate, 0% [upper 95% CL, 1.3%]) [84].

STRATEGIES AFTER SPIRAL CT AND COMPRESSION ULTRASONOGRAPHY

In 95 of 1041 patients, Musset and associates[17] could not confirm or exclude the diagnosis of pulmonary embolism with spiral CT and compression ultrasonography. Lung scintigraphy, pulmonary angiography, or both were therefore performed, and results were normal in 84 patients. No thromboembolic events were observed during follow-up (failure rate, 0% [upper 95% CL, 4.3%]) [17].

Strategies after Two Diagnostic Rounds

After two diagnostic rounds, pulmonary embolism could still not be confirmed or excluded in small subgroups of the original referred cohorts (Table 4). We identified seven studies that used a third round of diagnostic tests involving six strategies [14, 77-79, 81, 82, 87]. Miron and associates [87] studied only hospitalized patients. Testing ended when patients were found to have normal results on serial compression ultrasonography and a nondiagnostic lung scan or normal results on both compression ultrasonography and pulmonary angiography. Three studies [14, 79, 87] used the same diagnostic strategy and D-dimer assay. In patients with elevated D-dimer levels, nondiagnostic lung scans, and moderate to high clinical probability, pulmonary embolism was excluded by normal results on compression ultrasonography and pulmonary angiography. Among the 130 studied patients in all three studies, one thromboembolic event occurred (failure rate, 0.8% [upper 95% CL, 4.2%])[14, 79, 87].

ten Wolde and colleagues [81] performed serial compression ultrasonography in 246 patients who had a nondiagnostic lung scan, elevated D-dimer levels, and low or moderate to high clinical probability. The observed failure rate, 2.0% (upper 95% CL, 4.7%), appears some what higher than those in other studies that used serial leg testing [12, 13, 71, 72, 81]. However, this may be the result of chance.

TABLE 4. Outcome of the Diagnostic Strategies after Two Diagnostic Rounds in Patients with Suspected Pulmonary Embolism*

Exclusion Strategy	Study, Year (Reference)	Included Patients	VTE Complications†	Failure Rate (95% CL)
		n		%
Normal results on CUS and pulmonary angiography in patients with elevated D-dimer levels, nondiagnostic lung scans, and moderate to high clinical probability	Miron et al., 1999 (87)	35	0	0 (10.0)
	Perrier et al., 1999 (14)	37	1	2.7 (14.2)
	Perrier et al., 2001 (79)	58	0	0 (6.2)
	Total	130	1	0.8 (4.2)
Normal results on CUS in patients with elevated D-dimer levels, low clinical probability, nondiagnostic lung scans	Wells et al., 2001 (78)	41	1	2.4 (12.9)
Normal results on CUS in patients with normal D-dimer levels, moderate clinical probability, and nondiagnostic lung scans	Wells et al., 2001 (78)	60	0	0 (6.0)
Normal results on serial CUS in patients with elevated D-dimer levels, low clinical probability or moderate to high clinical probability, and nondiagnostic lung scans	ten Wolde et al., 2001 (81)	246	5	2.0 (4.7)
Normal results on CUS and pulmonary angiography in patients with elevated D-dimer levels, low to moderate clinical probability or high clinical probability, and nondiagnostic lung scans	Leclercq et al., 2002 (82)	38	0	0 (9.3)
Normal results on CUS and pulmonary angiography in angiography in patients with nondiagnostic lung scans and elevated D-dimer levels	de Groot et al., 1999 (77)	40	0	0 (8.8)

* CL = confidence limit; CUS = compression ultrasonography; VTE = venous thromboembolic.
† Symptomatic VTE complications during the 3-month follow-up.

TABLE 5. Summary Table of the Diagnostic Strategies for Excluding Pulmonary Embolism with an Upper 95% Confidence Limit of 3% or Less for 3-Month Thromboembolic Risk*

Variable	3-Month Risk for VTE Complications (Upper 95% CL)
Diagnostic strategies for excluding pulmonary embolism in all referred patients	
Normal results on PA	0.8 (2.1)
Normal lung scan	0.9 (2.3)
Normal lung scan and normal leg testing results	0.6 (1.2)
Normal D-dimer level	0.0 (1.8)
Normal D-dimer level and low clinical probability	0.2 (0.8)
Diagnostic strategies for excluding pulmonary embolism after the first diagnostic round	
Abnormal lung scan plus normal results on PA	1.3 (2.8)
Nondiagnostic lung scan plus normal results on serial IPG	1.7 (2.8)
Nondiagnostic lung scan, normal results on serial CUS, and low to moderate clinical probability	0.5 (1.3)
Moderate to high clinical probability or elevated D-dimer level and low clinical probability plus normal lung scan	0.0 (1.1)
Moderate to high clinical probability or elevated D-dimer level and low clinical probability plus normal results on spiral CT and CUS	0.0 (1.3)

* CL = confidence limit; CT = computed tomography; CUS = compression ultrasonography; IPG = impedance plethysmography; PA = pulmonary angiography; VTE = venous thromboembolism.

DISCUSSION

This systematic review of diagnostic strategies to exclude pulmonary embolism in patients with clinical suspicion of the disease allows several interesting inferences. The first concerns strategies performed in all referred patients. In addition to the accepted methods for excluding pulmonary embolism (that is, normal pulmonary angiogram or perfusion lung scan), an alternative strategy emerged: normal D-dimer levels alone or in combination with low clinical probability. A normal D-dimer result as the sole basis for excluding pulmonary embolism has been evaluated in only 201 patients and with only one type of assay, but the upper 95% CL of the failure rate compares favourably with that of a normal pulmonary angiogram or perfusion lung scan and is below our arbitrarily chosen upper 95% CL of 3% [7, 14, 15, 73, 75, 77, 85]. The combination of normal D-dimer levels and low clinical probability, a strategy probably more applicable to clinical practice, has been evaluated more extensively, with three types of D-dimer assay. Our analysis indicated that the combination of low clinical probability and normal D-dimer levels is accurate regardless of the D-dimer assay used [78, 81, 83, 84]. One moderately sized study evaluated the combination of low to moderate clinical probability and normal D-dimer levels [82]. Although this strategy can exclude pulmonary embolism in more patients, its results require confirmation. The use of a D-dimer test in combination with clinical probability assessment is obviously rapid, more convenient for the patient, and probably cost-effective compared with the current accepted diagnostic methods.

After the initial diagnostic round, we found roughly two main approaches to continuing the diagnostic process. The first approach encompassed strategies after initial abnormal or nondiagnostic results on lung scintigraphy while the second included diagnostic strategies for patients in whom pulmonary embolism was not excluded by D-dimer testing combined with clinical probability. Regarding the first approach, we found, as expected, good evidence for the safety of withholding anticoagulant treatment after a normal pulmonary angiogram [9, 74, 80, 86]. Other strategies after a nondiagnostic lung scan evaluated serial noninvasive testing of the deep leg veins. Although the data on serial compression ultrasonography appear especially convincing, they were obtained from only one large study in 665 patients with low to moderate clinical probability [13]. Compression ultrasonography is attractive because it is widely available and easy to perform; however, it requires patients to make several visits to the hospital. With respect to the second approach (after D-dimer testing and clinical probability estimate), a normal perfusion lung scan is still a useful and safe strategy to exclude pulmonary embolism [14, 78, 79, 81, 82].

To date, only three studies have evaluated the role of spiral CT imaging in proper clinical outcome studies. We found that in one study, which examined patients with low to moderate

clinical probability after a nondiagnostic lung scan and normal results on compression ultrasonography, normal results on helical CT were associated with an unacceptably high failure rate [76]. This is probably because subsegmental thrombi were not detected. However, in the second [84] and third [17] studies, the failure rates were lower. The difference between the first and last two studies can be explained in part by improved resolution of the more modern CT machines. More data are needed to study the safety of excluding pulmonary embolism with normal results on spiral CT. Many strategies have been evaluated for screening after two diagnostic rounds. However, no conclusions can be made about which strategy is best because most of the relevant studies have been modest in size. The results of these studies are summarized in Table 4.

Most of the patients in studies we examined were outpatients. One study was performed only in inpatients, six studies were performed only in outpatients, and the remaining studies included both types of patients but predominantly outpatients. Whether the diagnostic strategies studied can be used for inpatients with the same results and failure rates requires further testing.

Our analysis has potential limitations. First, we accepted the interpretations of the various test outcomes as reported by the study authors. This may have resulted in varied failure rates for the same strategy. Nevertheless, the pooled estimates, particularly those for the strategies examined in several studies, appear to be robust. A second potential limitation is the risk for spectrum bias. However, the range of the overall prevalences of pulmonary embolism, an indicator of the case mix of the included studies, was relatively narrow. Therefore, we do not believe that spectrum bias influenced our conclusions. Third, the a priori likelihood of disease in patients with suspected pulmonary embolism is known to differ according to referral pattern and clinical setting, which may vary among hospitals, regions, and countries. For that reason, it is wise to advocate a strategy that has been evaluated in different settings with similar results. Fourth, our arbitrarily chosen boundaries of 3% for the upper 95% CL of the failure rate and 90% for the minimal completeness of follow-up can be criticized. However, we defined these criteria a priori to maximize the methodologic quality of the included studies. Finally, since the studies we examined did not directly compare different diagnostic strategies, inferences about the relative safety of one strategy compared with another should be made with caution.

Overall, many diagnostic strategies to exclude pulmonary embolism have been prospectively evaluated in consecutive patients. The diagnostic strategies with a failure rate of 3% or less (that is, a 3-month thromboembolic risk of 3%) are summarized in Table 5. We expect that clinicians will be increasingly interested in working with a simple strategy that can be performed quickly in every clinical setting. The first goal of this strategy will be to exclude pulmonary embolism safely in as many patients as possible. This can be

done by using either normal D-dimer levels in patients who have low clinical probability or a normal perfusion lung scan. The next goal will be to develop a reliable, simple method to confirm the diagnosis of pulmonary embolism. Our analysis, however, was not designed to identify safe methods to confirm the presence of pulmonary emboli. The most accurate tests for excluding pulmonary embolism after the first round of diagnostic tests remains a normal pulmonary angiogram, a normal perfusion lung scan, or normal results on serial leg testing in patients with a nondiagnostic lung scan and low to moderate clinical probability. If spiral CT is indeed shown to be an accurate method, the diagnostic approach may be further simplified. However, the choice of a diagnostic strategy should depend not only on the strategy's accuracy but also on the local facilities and expertise required for its use.

REFERENCES

1. Barrit DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. Lancet 1960; 1:1309-12.
2. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. Arch Intern Med 2000 Dec 11-25; 160(22):3431-6.
3. Pinede L, Cucherat M, Duhaut P, Ninet J, Boissel JP. Optimal duration of anticoagulant therapy after an episode of venous thromboembolism. Blood Coagul Fibrinolysis 2000 Dec; 11(8):701-7.
4. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. Arch Intern Med 1993; 153(13):1557-62.
5. Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. Chest 1995; 108(4 Suppl):276S-290S.
6. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 1998; 129(12):1044-9.
7. 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):2753-9.
8. Stein PD, Hull RD, Saltzman HA, Pineo G. Strategy for diagnosis of patients with suspected acute pulmonary embolism. Chest 1993; 103(5):1553-9.
9. Hull RD, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. Ann Intern Med 1983; 98(6):891-9.
10. McAlister FA, Clark HD, van Walraven C, Straus SE, Lawson FM, Moher D, et al. The medical review article revisited: has the science improved? Ann Intern Med 1999; 131(12):947-51.
11. McAlister FA, Straus SE, Guyatt GH, Haynes RB. Users' guides to the medical literature: XX. Integrating research evidence with the care of the individual patient. Evidence-Based Medicine Working Group.PG - 2829-36. Jama 2000 Jun 7; 283(21):2829-36.
12. Hull RD, Raskob GE, Ginsberg JS, Panju AA, Brill-Edwards P, Coates G, et al. A noninvasive strategy for the treatment of patients with suspected pulmonary embolism. Arch Intern Med 1994; 154(febr 14):289-297.
13. Wells PS, Ginsberg JS, Anderson DR, Kearon C, Gent M, Turpie AG, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998; 129(12):997-1005.
14. Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999; 353(9148):190-5.
15. Perrier A, Bounameaux H, Morabia A, de Moerloose P, Slosman D, Didier D, et al. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. Arch Intern Med 1996; 156(5):531-6.
16. Worsley DF, Palevsky HI, Alavi A. A detailed evaluation of patients with acute pulmonary embolism and low- or very-low-probability lung scan interpretations. Arch Intern Med 1994; 154(23):2737-41.
17. Musset D, Parent F, Meyer G, Maitre S, Girard P, Leroyer C, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet 1914; 360(9349):1914-20.
18. Meaney JF, Weg JG, Chenevert TL, Stafford-Johnson D, Hamilton BH, Prince MR. Diagnosis of pulmonary embolism with magnetic resonance angiography. N Engl J Med 1997; 336(20):1422-7.
19. Gupta A, Frazer CK, Ferguson JM, Kumar AB, Davis SJ, Fallon MJ, et al. Acute pulmonary embolism: diagnosis with MR angiography. Radiology 1999; 210(2):353-9.
20. Hull RD, Hirsh J, Carter CJ, Raskob GE, Gill GJ, Jay RM, et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. Chest 1985; 88(6):819-28.
21. van Rossum AB, Treurniet FE, Kieft GJ, Smith SJ, Schepers-Bok R. Role of spiral volumetric computed tomographic scanning in the assessment of patients with clinical suspicion of pulmonary embolism and an abnormal ventilation/perfusion lung scan. Thorax 1996; 51(1):23-8.

22. van Strijen MJL, de Monyé W, Kieft GJ, Pattynama PMT, Prins MH, Bloem JL, et al. Accuracy of spiral ct in the diagnosis of pulmonary embolism: a prospective multicenter cohort study of consecutive patients. Thromb Haemost 2001; 7(suppl):OC154.

23. El-Batarny HS, Othman MA, O'Shaughnessy DF. A combination of simple clinical model and advanced latex D-dimer assay can be safely used for exclusion of pulmonary embolism. Thromb Haemost 2001; 7(suppl):P738.

24. Barro C, Bosson JL, Pernod G, Hamidfar-Roy R, Blanc-Jouvan F, Carpentier P, et al. Essential role of plasma D-dimers to optimize pulmonary embolism diagnostic strategy in well-defined hospitalized patients: a prospective study. Thromb Haemost 2001; 7(suppl):P718.

25. Qanadli SD, Hajjam ME, Mesurolle B, Barre O, Bruckert F, Joseph T, et al. Pulmonary embolism detection: prospective evaluation of dual-section helical CT versus selective pulmonary arteriography in 157 patients. Radiology 2000 Nov; 217(2):447-55.

26. Ghaye B, Szapiro D, Willems V, Dondelinger RF. Combined CT venography of the lower limbs and spiral CT angiography of pulmonary arteries in acute pulmonary embolism: preliminary results of a prospective study. Jbr-Btr 2000 Oct; 83(5):271-8.

27. Mathis G, Bitschnau R, Gehmacher O, Scheier M, Kopf A, Schwarzler B, et al. Chest ultrasound in diagnosis of pulmonary embolism in comparison to helical CT. Ultraschall Med 1999; 20(2):54-9.

28. Drucker EA, Rivitz SM, Shepard JA, Boiselle PM, Trotman-Dickenson B, Welch TJ, et al. Acute pulmonary embolism: assessment of helical CT for diagnosis. Radiology 1998; 209(1):235-41.

29. Remy-Jardin M, Remy J, Deschildre F, Artaud D, Beregi JP, Hossein-Foucher C, et al. Diagnosis of pulmonary embolism with spiral CT: comparison with pulmonary angiography and scintigraphy. Radiology 1996; 200(3):699-706.

30. Pruszczyk P, Torbicki A, Pacho R, Chlebus M, Kuch-Wocial A, Pruszynski B, et al. Noninvasive diagnosis of suspected severe pulmonary embolism: transesophageal echocardiography vs spiral CT. Chest 1997; 112(3):722-8.

31. Biello DR, Mattar AG, McKnight RC, Siegel BA. Ventilation-perfusion studies in suspected pulmonary embolism. AJR Am J Roentgenol 1979; 133(6):1033-7.

32. Teigen CL, Maus TP, Sheedy PF, 2nd, Johnson CM, Stanson AW, Welch TJ. Pulmonary embolism: diagnosis with electron-beam CT. Radiology 1993; 188(3):839-45.

33. Rodger MA, Jones G, Rasuli P, Raymond F, Djunaedi H, Bredeson CN, et al. Steady-state end-tidal alveolar dead space fraction and D-dimer: bedside tests to exclude pulmonary embolism. Chest 2001 Jul; 120(1):115-9.

34. Goodman LR, Curtin JJ, Mewissen MW, Foley WD, Lipchik RJ, Crain MR, et al. Detection of pulmonary embolism in patients with unresolved clinical and scintigraphic diagnosis: helical CT versus angiography. AJR Am J Roentgenol 1995; 164(6):1369-74.

35. Teigen CL, Maus TP, Sheedy PF, 2nd, Stanson AW, Johnson CM, Breen JF, et al. Pulmonary embolism: diagnosis with contrast-enhanced electron-beam CT and comparison with pulmonary angiography. Radiology 1995; 194(2):313-9.

36. McNeil BJ. A diagnostic strategy using ventilation-perfusion studies in patients suspect for pulmonary embolism. J Nucl Med 1976; 17(7):613-6.

37. Schoepf UJ, Holzknecht N, Helmberger TK, Crispin A, Hong C, Becker CR, et al. Subsegmental pulmonary emboli: improved detection with thin-collimation multi-detector row spiral CT. Radiology 2002 Feb; 222(2):483-90.

38. Burkill GJ, Bell JR, Chinn RJ, Healy JC, Costello C, Acton L, et al. The use of a D-dimer assay in patients undergoing CT pulmonary angiography for suspected pulmonary embolus. Clin Radiol 2002 Jan; 57(1):41-6.

39. Wallis JW, Kruip M, de Jongh-Leuvenink J, Buller HR. A comparative study of two rapid D-dimer tests for the exclusion of pulmonary embolism in symptomatic patients. Thromb Haemost 2000 Nov; 84(5):925.

40. Kim KI, Muller NL, Mayo JR. Clinically suspected pulmonary embolism: utility of spiral CT. Radiology 1999; 210(3):693-7.

41. Ost D, Rozenshtein A, Saffran L, Snider A. The negative predictive value of spiral computed tomography for the diagnosis of pulmonary embolism in patients with nondiagnostic ventilation-perfusion scans. Am J Med 2001 Jan; 110(1):16-21.

42. Novelline RA, Baltarowich OH, Athanasoulis CA, Waltman AC, Greenfield AJ, McKusick KA. The clinical course of patients with suspected pulmonary embolism and a negative pulmonary arteriogram. Radiology 1978; 126(3):561-7.

43. Fischer KC, McNeil BJ. The indeterminate lung scan: its characteristics and its association with pulmonary embolism. Eur J Nucl Med 1979; 4(1):49-53.

44. Kipper MS, Moser KM, Kortman KE, Ashburn WL. Longterm follow-up of patients with suspected pulmonary embolism and a normal lung scan. Perfusion scans in embolic suspects. Chest 1982; 82(4):411-5.

45. Spies WG, Burstein SP, Dillehay GL, Vogelzang RL, Spies SM. Ventilation-perfusion scintigraphy in suspected pulmonary embolism: correlation with pulmonary angiography and refinement of criteria for interpretation. Radiology 1986; 159(2):383-90.

46. McBride K, La Morte WW, Menzoian JO. Can ventilation-perfusion scans accurately diagnose acute pulmonary embolism? Arch Surg 1986; 121(7):754-7.

47. Kahn D, Bushnell DL, Dean R, Perlman SB. Clinical outcome of patients with a 'low probability' of pulmonary embolism on ventilation-perfusion lung scan. Arch Intern Med 1989; 149(2):377-9.

48. van Rooij WJ, den Heeten GJ, Sluzewski M. Pulmonary embolism: diagnosis in 211 patients with use of selective pulmonary digital subtraction angiography with a flow-directed catheter. Radiology 1995; 195(3):793-7.

49. van Rossum AB, Pattynama PM, Ton ER, Treurniet FE, Arndt JW, van Eck B, et al. Pulmonary embolism: validation of spiral CT angiography in 149 patients. Radiology 1996; 201(2):467-70.

50. Oser RF, Zuckerman DA, Gutierrez FR, Brink JA. Anatomic distribution of pulmonary emboli at pulmonary angiography: implications for cross-sectional imaging. Radiology 1996; 199(1):31-5.

51. Lomis NN, Yoon HC, Moran AG, Miller FJ. Clinical outcomes of patients after a negative spiral CT pulmonary arteriogram in the evaluation of acute pulmonary embolism. J Vasc Interv Radiol 1999; 10(6):707-12.

52. Palud L, Laurent M, Guéret P, Langella B, Meunier C, Pommereuil M, et al. D-dimers and diagnostic strategy for acute pulmonary embolism. Thromb Haemost 2001; 7(suppl):CD3530.

53. Hull RD, Raskob GE, Coates G, Panju AA, Gill GJ. A new noninvasive management strategy for patients with suspected pulmonary embolism. Arch Intern Med 1989; 149(11):2549-55.

54. Invasive and noninvasive diagnosis of pulmonary embolism. Preliminary results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Chest 1995; 107(1 Suppl):33S-38S.

55. Gray HW, McKillop JH, Bessent RG, Fogelman I, Smith ML, Moran F. Lung scanning for pulmonary embolism: clinical and pulmonary angiographic correlations. Q J Med 1990; 77(283):1135-50.

56. de Moerloose P, Desmarais S, Bounameaux H, Reber G, Perrier A, Dupuy G, et al. Contribution of a new, rapid, individual and quantitative automated D- dimer ELISA to exclude pulmonary embolism. Thromb Haemost 1996; 75(1):11-3.

57. Miniati M, Pistolesi M, Marini C, Di Ricco G, Formichi B, Prediletto R, et al. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Am J Respir Crit Care Med 1996; 154(5):1387-93.

58. Mayo JR, Remy-Jardin M, Muller NL, Remy J, Worsley DF, Hossein-Foucher C, et al. Pulmonary embolism: prospective comparison of spiral CT with ventilation-perfusion scintigraphy. Radiology 1997; 205(2):447-52.

59. Goodman LR, Lipchik RJ, Kuzo RS, Liu Y, McAuliffe TL, DJ OB. Subsequent pulmonary embolism: risk after a negative helical CT pulmonary angiogram--prospective comparison with scintigraphy. Radiology 2000 May; 215(2):535-42.

60. Lorut C, Ghossains M, Horellou MH, Achkar A, Fretault J, Laaban JP. A noninvasive diagnostic strategy including spiral computed tomography in patients with suspected pulmonary embolism. Am J Respir Crit Care Med 2000 Oct; 162(4 Pt 1):1413-8.

61. Garg K, Welsh CH, Feyerabend AJ, Subber SW, Russ PD, Johnston RJ, et al. Pulmonary embolism: diagnosis with spiral CT and ventilation-perfusion scanning--correlation with pulmonary angiographic results or clinical outcome. Radiology 1998; 208(1):201-8.

62. Barghouth G, Yersin B, Boubaker A, Doenz F, Schnyder P, Delaloye AB. Combination of clinical and V/Q scan assessment for the diagnosis of pulmonary embolism: a 2-year outcome prospective study. Eur J Nucl Med 2000 Sep; 27(9):1280-5.

63. Kline JA, Israel EG, Michelson EA, BJ ON, Plewa MC, Portelli DC. Diagnostic accuracy of a bedside D-dimer assay and alveolar dead-space measurement for rapid exclusion of pulmonary embolism: a multicenter study. Jama 2001 Feb 14; 285(6):761-8.

64. Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Buller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. Ann Intern Med 1997; 126(10):775-81.

65. Cross JJ, Kemp PM, Walsh CG, Flower CD, Dixon AK. A randomized trial of spiral CT and ventilation perfusion scintigraphy for the diagnosis of pulmonary embolism. Clin Radiol 1998; 53(3):177-82.

66. 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 Feb; 39(2):144-52.

67. Siragusa S, Anastasio R, Falaschi F, Porta C, Guarnone R, Bressan MA. Diagnostic accuracy of standardised clinical probability alone or in combination with D-dimer for excluding acute venous thromboembolism (VTE) at the emergency wards. Thromb Haemost 2001; 7(suppl):P1425.

68. Stein PD, Athanasoulis C, Alavi A, Greenspan RH, Hales CA, Saltzman HA, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation 1992; 85(2):462-8.

69. Cheely R, McCartney WH, Perry JR, Delany DJ, Bustad L, Wynia VH, et al. The role of noninvasive tests versus pulmonary angiography in the diagnosis of pulmonary embolism. Am J Med 1981; 70(1):17-22.

70. Hull RD, Raskob GE, Coates G, Panju AA. Clinical validity of a normal perfusion lung scan in patients with suspected pulmonary embolism. Chest 1990; 97:23-26.

71. Kruit WHJ, de Boer AC, Sing AK, van Roon F. The significance of venography in the management of patients with clinically suspected pulmonary embolism. J Intern Med 1991; 230:333-39.

72. Ginsberg JS, Brill-Edwards PA, Demers C, Donovan D, Panju A. D-dimer in patients with clinically suspected pulmonary embolism. Chest 1993; 104(6):1679-84.

73. van Beek EJR, Kuyer PMM, Büller HR, Brandjes DPM, Bossuyt PMM, ten Cate JW. The clinical course of patients with suspected pulmonary embolism. Arch Intern Med 1997; 157:2593-98.

74. Henry JW, Relyea B, Stein PD. Continuing risk of thromboemboli among patients with normal pulmonary angiograms. Chest 1995; 107:1375-78.

75. van Beek EJR, Kuyer PMM, Schenk BE, Brandjes DPM, ten Cate JW, Büller HR. A normal perfusion lung scna in patients with clinically suspected pulmonary embolism. Frequency and clinical validity. Chest 1995; 108:170-73.

76. Ferretti GR, Bosson J-L, Buffaz P-D, Ayanian D, Pison C, Blanc F, et al. Acute pulmonary embolism: Role of helical CT in 164 patients with intermediate probability at ventilation-perfusion scintigraphy and normal results at duplex US of the legs. Radiology 1997; 205:453-458.

77. de Groot MR, van Marwijk Kooy M, Pouwels JG, Engelage AH, Kuipers BF, Buller HR. The use of a rapid D-dimer blood test in the diagnostic work-up for pulmonary embolism: a management study. Thromb Haemost 1999; 82(6):1588-92.

78. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, 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; 135:98-107.

79. Perrier A, Howarth N, Didier D, Loubeyre P, Unger P-F, de Moerloose P, et al. Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. Ann Intern Med 2001; 135:88-97.

80. van Beek EJR, Reekers JA, Batchelor DA, Brandjes DPM, Büller HR. Feasibility, safety and clinical utility of angiography in patients with suspected pulmonary embolism. Eur. Radiol. 1996; 6:415-419.

81. ten Wolde M, Hagen PJ, Mac Gillavry MR, Pollen IJ, Koopman MMW, Postmus PE, et al. Non-invasive diagnostic work-up of patients with suspected pulmonary embolims: preliminary results of a management study. Thromb Haemost 2001; 7(suppl):OC153.

82. Leclercq MG, Lutisan JG, Van Marwijk Kooy M, Kuipers BF, Oostdijk AH, Van Der Leur JJ, et al. Ruling out clinically suspected pulmonary embolism by assessment of clinical probability and D-dimer levels: a management study. Thromb Haemost 2003 Jan; 89(1):97-103.

83. 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 Jul 22; 162(14):1631-5.

84. Anderson DR, Wells PS, Kovacs M, Dennie C, Kovacs G, Stiell I, et al. Use of spiral computerized tomography (ct) to exclude the diagnosis of pulmonary embolism in the emergency department. Thromb Haemost 2001; 7(suppl): OC156.

85. Bernier M, Miron MJ, Desmarais S, Bérubé C. Use of the D-dimer measurement as first step in the diagnosis deep vein thrombosis (DVT) and pulmonary embolism (PE) in an emergency department. Thromb Haemost 2001; 7(suppl):P754.

86. Miniati M, Monti S, Pratali L, Di Ricco G, Marini C, Formichi B, et al. Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. Am J Med 2001 May; 110(7):528-35.

87. Miron MJ, Perrier A, Bounameaux H, de Moerloose P, Slosman DO, Didier D, et al. A. Contribution of noninvasive evaluation to the diagnosis of pulmonary embolism in hospitalized patients. Eur Respir J 1999; 13(6):1365-70.

88. Knecht MF, Heinrich F. Clinical evaluation of an immunoturbidimetric D-dimer assay in the diagnostic procedure of deep vein thrombosis and pulmonary embolism. Thromb Res 1997; 88(5):413-7.

89. Janssen MC, Wollersheim H, Verbruggen B, Novakova IR. Rapid D-dimer assays to exclude deep venous thrombosis and pulmonary embolism: current status and new developments. Semin Thromb Hemost 1998; 24(4):393-400.

90. Perrier A, Bounameaux H. Diagnosis of pulmonary embolism in outpatients by sequential noninvasive tools. Semin Thromb Hemost 2001; 27(1):25-32.

Chapter 3

THE USE OF A CLINICAL DECISION RULE IN COMBINATION WITH D-DIMER CONCENTRATION IN THE DIAGNOSTIC WORK UP OF PATIENTS WITH SUSPECTED PULMONARY EMBOLISM;

a prospective management study

Marieke J.H.A. Kruip, Marjan J. Slob, Joost H.E.M. Schijen,
Cees van der Heul, Harry R. Büller

Archives of Internal Medicine 2002;162:1631-1635

ABSTRACT

Background We designed a diagnostic strategy, based on clinical probability and D-dimer concentration to select patients who are unlikely to have pulmonary embolism (PE), before further diagnostic workup was performed. The utility and safety of this strategy were evaluated in a prospective management study.

Methods Consecutive patients with suspected PE had D-dimer testing and clinical probability assessment with a clinical decision rule. Patients with a low probability and a normal D-dimer concentration (< 500 ng/ml) were considered not to have PE, and further diagnostic testing and anticoagulant therapy were withheld. In patients with a low probability and elevated D-dimer level or with a moderate or high probability, bilateral compression ultrasonography of the legs was performed. If deep venous thrombosis was detected, venous thromboembolism was diagnosed If compression ultrasonography was normal pulmonary angiography was performed. All patients were followed up for 3 months.

Results Of the 234 consecutive patients, 26% had the combination of a low probability and normal D-dimer level. During the follow up period, none of these patients died and 3 patients had recurrent complaints of PE. In these 3 patients, PE was excluded by objective testing. The 3-month thromboembolic risk was therefore 0% (95% confidence interval, 0-6%). The prevalence of PE in the entire population was 22%.

Conclusions The combination of a low clinical probability and a normal D-dimer concentration appears to be a safe method to exclude pulmonary embolism, with a high clinical utility, and is readily accepted by clinicians.

INTRODUCTION

Diagnosing or excluding pulmonary embolism (PE) is difficult because the clinical manifestations are nonspecific[1]. Less than 30% of patients presenting with signs and symptoms suggestive of PE actually have the disease confirmed by objective testing[2-4]. As a result, the diagnostic approach has gradually changed from trying to confirm PE to also identifying the large proportion of patients who do not have the disease. Several methods have recently been advocated for excluding PE.

Clinical assessment has been used to stratify patients with suspected PE into low, moderate or high clinical probability categories. Studies have been performed with the use of clinical judgement, as well as a structured algorithm, to achieve this stratification. However, in 3 to 28% of patients with a low clinical probability, PE was subsequently confirmed to be present [2,5-10]. These figures are too high to safely exclude PE in symptomatic patients on the basis of clinical probability assessment alone.

The finding of a normal plasma concentration of D-dimer, the degradation product of cross-linked fibrin, was shown to be able to exclude PE accurately in most patients presenting with clinical suspicion. The sensitivity and negative predictive value vary depending on the type of D-dimer assay, but with the current rapid tests, both are usually high (90-100%, and 94-100%, respectively) [6,11-17]. To safely exclude PE, the sensitivity should approach 100%. This is important because for every 2% decrease in sensitivity, 1 per 1000 evaluated patients will die of recurrent PE, as a result of inappropriately withholding anticoagulant therapy[18]. Most D-dimer assays do not have a sufficiently high sensitivity to be safely used and accepted by clinicians as the only method to exclude PE.

Hence, the combination of clinical assessment and D-dimer concentration may be well suited to differentiate between patients who will probably have PE and those who will not have this disease. Findings in recent studies in patients with suspected venous thromboembolism (VTE) support this assumption [6,7,19]. The aim of the present study was to evaluate the utility and safety of a novel strategy in excluding PE in patients with a low clinical probability, according to a validated clinical decision rule[7], and a normal D-dimer concentration. In these patients no further diagnostic investigations were performed and anticoagulant therapy was withheld. In the remaining patients we used compression ultrasonography (CUS), followed by pulmonary angiography if results were normal.

PATIENTS AND METHODS

Patients

Consecutive inpatients and outpatients older than 16 years, with clinically suspected PE seen at St. Elisabeth Hospital, Tilburg, the Netherlands, were prospectively included in the study between January 1, 1998, and May 31, 2000. The protocol was approved by the local ethics committees, and written informed consent was obtained from all patients.

Study design and diagnostic studies

The clinical decision rule (CDR) was completed and the patients were stratified into low, moderate or high clinical probability categories of PE. The CDR consists, as described elsewhere[7], of risk factors for PE, signs and symptoms from history and physical examination, chest radiography, oxygen saturation tests, and electrocardiography, as well as the likelihood for an alternative diagnosis for the patient's symptoms. The CDR was applied by a group of at least 10 attending physicians, who all received extensive instructions about how to use the rule before to the start of the study. The plasma D-dimer concentration was then measured with a quantitative raid enzyme-linked immunosorbent D-dimer assay (Vidas DD; bioMérieux, Paris, France). The concentration was expressed in nanograms per milliliter of fibrinogen equivalent units. The cut-off value, according to the manufacturer's instructions, was 500 ng/mL. All measurements were carried out in duplicate by a technician, who was unaware of the outcome of the CDR and the patient's history.

Patients with a low probability of PE and a normal D-dimer test result (< 500 ng/ml) did not undergo further diagnostic procedures and anticoagulant treatment was withheld. They were instructed to return to the thrombosis unit immediately when signs or symptoms of PE or deep venous thrombosis (DVT) recurred and appropriate objective testing (CUS, lung scanning or pulmonary angiography) was performed to confirm or refute the diagnosis.

In patients with a low probability of PE and elevated D-dimer concentration, or moderate or high clinical probability, first bilateral CUS of the legs was performed, within 24 hours. The femoral vein was visualised in the supine position in its full length and the popliteal vein was investigated in the prone position to the trifurcation. Visualisation of a clot, i.e. not being able to compress the vein and lack of flow, was considered as abnormal and to indicate the presence of DVT.

When a DVT was present VTE was diagnosed and treatment with anticoagulants was initiated. If CUS was normal, selective pulmonary digital substraction angiography was performed, within 48 hours after initial presentation. A 7F Swan-Ganz flow-directed pulmonary angiography true-size catheter was positioned into a main pulmonary artery and selectively in the lobar arteries of both lungs. Subselective magnification series were obtained of lower, middle and upper portions of both lungs with the catheter in lobar and segmental branches. Anteroposterior projections were obtained routinely; different projections and/or selective series were obtained if the initial images were not conclusive. Bilateral pulmonary angiography was performed in all patients. The following criteria were considered diagnostic of PE: a constant intraluminal filling defect or a persistent acute cut-off sign of an arterial pulmonary branch seen on more than 1 projection. In case of doubt a second experienced radiologist was asked for his opinion and the diagnosis was made by means of consensus; if necessary, additional superselective series were performed.

3-month follow-up

All patients were re-evaluated by the study coordinator (M.J.H.A.K.) 1 week and 1 and 3 months after inclusion at the outpatient clinic or interviewed by phone. Suspected venous thrombotic events (PE or DVT) were investigated by appropriate objective diagnostic methods, within 48 hours of presentation. When a patient was readmitted to the hospital for any cause, the charts were reviewed. Venous thromboembolic events, as well as causes of dead, were recorded and adjudicated independently.

RESULTS

During the investigation period, 251 consecutive patients with clinically suspected PE were studied. Seventeen patients (7%) were excluded because of refusal or inability to give consent (5 patients), contraindications to pulmonary angiography (2 patients) and absence of D-dimer measurements because of logistic problems (10 patients).

Thus, the study population available for analysis consisted of 234 patients. The mean age of this cohort was 51 years (SD, 17 years) and the prevalence of VTE was 22%. Of the total population 83% presented as outpatients and 11% had a history of previous VTE (Table). The 3-month follow-up period was completed in all patients.

Low clinical probability and normal D-dimer concentration

The Figure summarizes the results of the evaluated diagnostic strategy. The clinical probability of PE, according to the CDR, was low in 120 (51%), moderate in 74 patients (32%) and high in 40 patients (17%). Of the patients with a low clinical probability, 60 had a normal D-dimer concentration, so no further diagnostic procedures were performed and the patients did not receive anticoagulant therapy. This subgroup represents 26% of the original study cohort. Fifty-six of these presented as outpatients. Thus, in 4 (10%) of the 40 already hospitalised patients and in 56 (29%) of the 194 outpatients, PE was excluded by this diagnostic strategy. During the 3-month follow-up period none of the patients with a low clinical probability and a normal D-dimer concentration died, and 3 returned with new complaints of PE (3, 14 and 16 days after initial presentation). In all these 3 patients PE was excluded (by normal pulmonary angiography in 2 normal perfusion scan results in 1). Hence, the subsequent rate of VTE in this patient group during follow up was 0% (95% confidence interval [CI], 0-6%).

Patients with other test outcomes

Of the 174 patients with either a low clinical probability of PE but elevated D-dimer concentration or a moderate or high clinical probability, 27 had a DVT detected by bilateral CUS. This subgroup with confirmed VTE by CUS represents 12% of the original study cohort. In the patients with a normal CUS (n=147) pulmonary angiography was performed. PE was present in 25 patients. Thus, a total of 52 patients had documented VTE; hence the overall prevalence was 22%. Of the 122 patients with a normal pulmonary angiography, 1 presented with suspected PE 10 days after the initial pulmonary angiogram. Pulmonary angiography was again performed and showed PE. Hence, the subsequent rate of VTE in patients with normal pulmonary angiograms was 0.8% (95% CI, 0.02-4.5%). During the 3-month follow-up period of these 122 patients, a total of 4 patients died. The causes of death were cancer in 3 and progressive chronic obstructive pulmonary disease in 1.

Additional observations

In the present study, only patients with a low clinical probability of PE in combination with a normal D-dimer concentration were considered not to have PE. If we had added the patients with a moderate clinical probability and a normal D-dimer concentration to this group, a total of 85 (36%) of the presenting cohort would have been spared further diagnostic procedures and anticoagulant therapy. One of these 85 patients had PE involving the segmental arteries, confirmed by pulmonary angiography (failure rate 1.2%; 95% CI, 0.03-6.4%). This patient was a 40 year old women, who recently had a neurosurgical operation (9 days before presentation) and who presented with complaints of dyspnea of 3 days' duration. The remaining 149 patients,

i.e. with a low or moderate clinical probability and elevated D-dimer concentration or with a high clinical probability, would have undergone further diagnostic procedures, which would have revealed PE in approximately one third (51 patients).

The D-dimer concentration was measured in all patients. The result was normal in 100 patients (43%) of the presenting population. One of these 100 patients actually had PE in segmental arteries at pulmonary angiography (same patient as described above). The D-dimer concentration of this patient was 480 ng/ml. The sensitivity of the D-dimer assay was 98% (95% CI, 90-100%) and the negative predictive value 99% (95% CI, 95-100%).

DISCUSSION

The primary finding of this study is that the combination of a low clinical probability of PE a normal D-dimer concentration is able to exclude the disease safely in a substantial proportion (26%) of patients presenting with suspected PE. This new strategy was introduced in a large teaching hospital that previously used lung scanning and pulmonary angiography and was well accepted by the clinicians (physicians, internists, pulmonologists, and surgeons) involved in the diagnostic work up of such patients.

Furthermore, the present study confirms that the combination of CUS and pulmonary angiography is a feasible, effective, and safe subsequent diagnostic strategy. Performing CUS of the deep leg veins in patients with a moderate or high clinical probability or a low clinical probability and elevated D-dimer levels (n=174) was worthwhile: 16% had DVT detected by ultrasonography and anticoagulant treatment was initiated. Taken together, the use of the clinical probability assessment, D-dimer assay and CUS, all non-invasive methods, was able to confirm or refute the diagnosis in 37% of the patients of the original study cohort. Pulmonary angiography was performed without any complication, confirming earlier observations[20], although in one patient the initial pulmonary embolism was most likely missed. The outcome with respect to subsequent episodes of symptomatic VTE during the 3-month follow up in patients with a low clinical probability and a normal D-dimer concentration (failure rate 0%; 95%CI, 0-6%) compared favourable with that of patients with normal pulmonary angiograms (failure rate 0.8%; 95%CI, 0.02-4.5%) and is in agreement with studies using normal perfusion scans results or serial ultrasound scan results to exclude VTE [4,6,7,19,21].

Only a limited number of prospective management studies with D-dimer, CDR, or a combination of both are available [6,7,19,21]. Our observations of the combination of CDR and D-dimer are comparable to the findings of these studies. However, de Groot et al[19] and Perrier et al[6] used

the combination only in patients with a nondiagnostic perfusion-ventilation lung scan result, whereas in the present study the combination was used as the first step in the diagnostic workup. Therefore, a larger proportion of our study cohort, approximately one quarter, was spared radiologic or nuclear investigations compared with these studies.

In a recent study by Perrier and colleagues[21], D-dimer measurements were used as the first test in the diagnostic work up of 444 outpatients with suspected PE. A total of 159 patients (36%) had normal D-dimer concentrations, and this method was used as the sole test to exclude VTE (subsequent failure rate was 0%; 95% CI, 0-2.3%). If we had adopted a similar strategy, while we used exactly the same D-dimer assay, we would have missed 1 patient with significant PE, although our findings are still consisted with the CIs of that study. It should be noted that we studied both inpatients and outpatients and that combining clinical assessment and D-dimer testing was readily accepted by the specialists who see patients with suspected PE.

Several studies using CUS and pulmonary angiography in patients with suspected PE have been published. An abnormal venous ultrasonogram is found in 5% to 12% of patients with a nondiagnostic lung scan result [6,7,22-25]. In a meta-analysis by van Rossum et al[25], the prevalence of DVT in patients with clinically suspected PE was approximately 18%, and in patients with proven PE 36% to 45% (range, 10%-93%). Our observations with respect to the proportion of patients with abnormal CUS are comparable to the findings in patients with a high-probability lung scan result but are higher than the proportion of patients with a nondiagnostic lung scan result[6,7,22-25]. Investigations that assessed the validity and safety of pulmonary angiography found that this method may be falsely negative in approximately 1% and that the morbidity and mortality rates associated with the test itself are very low (0.4% (95% CI, 0.09-1.25%) and 0% (95% CI, 0.0-0.53%), respectively), as was seen in the present study [2,20,26].

Some aspects of our study warrant comment. Although we studied a consecutive series of patients with suspected PE seen in a large teaching hospital, the total number of patients included is moderate. In particular, in the subgroup of patients with a low clinical probability of PE and a normal D-dimer concentration, there remains some uncertainty about the safety of withholding further diagnostic testing and anticoagulant treatment, since the upper limit of the 95% CIl of the 3-month thromboembolic risk was 6%. Similar outcome studies using other strategies to exclude VTE usually had an upper limit of 4% [6,21,27-29]. However, there is a wealth of evidence that D-dimer assays based on enzyme-linked immunosorbent assays are effective in excluding significant VTE. Therefore, it seems reasonable to conclude that a normal D-dimer concentration combined with a low clinical probability of PE is safe. Further studies are required to include patients with a moderate clinical probability.

We did not include perfusion-ventilation lung scanning in the present strategy. This is mainly because of the limited availability of, in particular, ventilation scanning and the often nondiagnostic test results. The strategy used in this study eliminates the need for nuclear medicine facilities, which may be relevant for those institutes without such services.

We conclude that the combination of a low clinical probability of PE, assessed by a CDR, and a normal D-dimer concentration contributes to the increasing body of evidence that this is a rapid and cost-effective method to exclude PE safely, and that this strategy is readily accepted. The combination of CUS and pulmonary angiography remains a valid and effective approach for patients with suspected PE.

Acknowledgements

We thank all physicians of the Internal Medicine, Pulmonology, and Radiology departments for participating in the study and treating the patients by the diagnostic strategy. We thank J. de Jongh-Leuvenink, and the technicians of the clinical chemical laboratory for performing the D-dimer assay.

REFERENCES

1. Kearon C, Hirsh J. The diagnosis of pulmonary embolism. Haemostasis 1995;25(1-2):72-87.
2. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA 1990;263(20):2753-9.
3. Stein PD, Hull RD, Saltzman HA, Pineo G. Strategy for diagnosis of patients with suspected acute pulmonary embolism. Chest 1993;103(5):1553-9.
4. Hull RD, Hirsh J, Carter CJ, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. Ann Intern Med 1983;98(6):891-9.
5. Ginsberg JS, Wells PS, Kearon C, et al. Sensitivity and specificity of a rapid whole-blood assay for D-dimer in the diagnosis of pulmonary embolism. Ann Intern Med 1998;129(12):1006-11.
6. Perrier A, Bounameaux H, Morabia A, et al. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. Arch Intern Med 1996;156(5):531-6.
7. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998;129(12):997-1005.
8. Hull RD, Hirsh J, Carter CJ, et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. Chest 1985;88(6):819-28.
9. Huisman MV. Recurrent venous thromboembolism: diagnosis and management. Curr Opin Pulm Med 2000 Jul;6(4):330-4.
10. Sanson BJ, Lijmer JG, Mac Gillavry MR, Turkstra F, Prins MH, Büller HR, for the ANTELOPE-Study Group. Comparison of a clinical probability estimate and two clinical models in patients with suspected pulmonary embolism. Thromb Haemost 2000 Feb;83(2):199-203.
11. van Beek EJ, van den Ende B, Berckmans RJ, et al. A comparative analysis of D-dimer assays in patients with clinically suspected pulmonary embolism. Thromb Haemost 1993;70(3):408-13.
12. Ginsberg JS, Wells PS, Brill-Edwards P, et al. Application of a novel and rapid whole blood assay for D-dimer in patients with clinically suspected pulmonary embolism. Thromb Haemost 1995;73(1):35-8.
13. Turkstra F, van Beek EJ, ten Cate JW, Büller HR. Reliable rapid blood test for the exclusion of venous thromboembolism in symptomatic outpatients. Thromb Haemost 1996;76(1):9-11.
14. Bounameaux H, Cirafici P, de Moerloose P, et al. Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. Lancet 1991;337(8735):196-200.
15. Demers C, Ginsberg JS, Johnston M, Brill-Edwards P, Panju A. D-dimer and thrombin-antithrombin III complexes in patients with clinically suspected pulmonary embolism. Thromb Haemost 1992;67(4):408-12.
16. Sijens PE, van Ingen HE, van Beek EJ, Berghout A, Oudkerk M. Rapid ELISA assay for plasma D-dimer in the diagnosis of segmental and subsegmental pulmonary embolism. A comparison with pulmonary angiography. Thromb Haemost 2000 Aug;84(2):156-9.
17. de Moerloose P, Desmarais S, Bounameaux H, et al. Contribution of a new, rapid, individual and quantitative automated D- dimer ELISA to exclude pulmonary embolism. Thromb Haemost 1996;75(1):11-3.
18. van Beek EJ, Schenk BE, Michel BC, et al. The role of plasma D-dimers concentration in the exclusion of pulmonary embolism [published erratum appears in Br J Haematol 1996 Oct;95(1):218]. Br J Haematol 1996;92(3):725-32.
19. de Groot MR, van Marwijk Kooy M, Pouwels JG, Engelage AH, Kuipers BF, Büller HR. The use of a rapid D-dimer blood test in the diagnostic work-up for pulmonary embolism: a management study. Thromb Haemost 1999;82(6):1588-92.
20. Wallis JW, van Beek EJ, Reekers JA, van Rooij WJ, Oudkerk M. [Reserve concerning pulmonary angiography in pulmonary embolism is not justified]. Ned Tijdschr Geneeskd 1997;141(12):578-81.

21. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999;353(9148):190-5.

22. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 1998;129(12):1044-9.

23. Hull RD, Raskob GE, Ginsberg JS, et al. A noninvasive strategy for the treatment of patients with suspected pulmonary embolism. Arch Intern Med 1994;154(febr 14):289-297.

24. Turkstra F, Kuijer PM, van Beek EJ, Brandjes DP, ten Cate JW, Büller HR. Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. Ann Intern Med 1997;126(10):775-81.

25. van Rossum AB, van Houwelingen HC, Kieft GJ, Pattynama PM. Prevalence of deep vein thrombosis in suspected and proven pulmonary embolism: a meta-analysis. Br J Radiol 1998;71(852):1260-5.

26. Stein PD, Athanasoulis C, Alavi A, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation 1992;85(2):462-8.

27. 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):492-6.

28. Huisman MV, Büller HR, ten Cate JW, Heijermans HS, van der Laan J, van Maanen DJ. Management of clinically suspected acute venous thrombosis in outpatients with serial impedance plethysmography in a community hospital setting. Arch Intern Med 1989;149(3):511-3.

29. Worsley DF, Palevsky HI, Alavi A. A detailed evaluation of patients with acute pulmonary embolism and low- or very-low-probability lung scan interpretations. Arch Intern Med 1994;154(23):2737-41.

Chapter 4

EFFECTIVENESS OF MANAGING SUSPECTED PULMONARY EMBOLISM USING AN ALGORITHM COMBINING CLINICAL PROBABILITY, D-DIMER TESTING, AND COMPUTED TOMOGRAPHY

Writing Group for the Christopher Study Investigators

JAMA 2006;295:172-179.

ABSTRACT

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

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

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

Interventions Patients were categorized as "pulmonary embolism unlikely" or "pulmonary embolism likely" using a dichotomized version of the Wells clinical decision rule. Patients classified as unlikely had D-dimer testing, and pulmonary embolism was considered excluded if the D-dimer test result was normal. All other patients underwent CT, and pulmonary embolism was considered present or excluded based on the results. Anticoagulants were withheld from patients classified as excluded, and all patients were followed up for 3 months.

Main Outcome Measure Symptomatic or fatal venous thromboembolism (VTE) during 3-month follow-up.

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

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

INTRODUCTION

The main challenge in the diagnostic workup of patients with clinically suspected pulmonary embolism is to accurately and rapidly distinguish the approximately 25% of patients who have the disease and require anticoagulant treatment from the 75% who do not [1,2]. A number of new approaches have improved the diagnostic process for pulmonary embolism. The first is the combination of a clinical decision rule such as the Wells score,[3] which categorizes patients as low, intermediate, or high clinical probability of pulmonary embolism, with a D-dimer test. Several management studies have shown that pulmonary embolism can be safely ruled out without the need for additional imaging in patients with low clinical probability and a normal D-dimer test result, occurring in 20% to 40% of patients [3-5]. In these studies, 3 categories of likelihood were used. However, a retrospective analysis suggested that the clinical utility of the Wells score could be further increased by using 2 instead of 3 categories of clinical probability, dichotomizing patients as either likely or unlikely to have had a pulmonary embolism,[3] but no large prospective studies evaluating this dichotomization have been carried out.

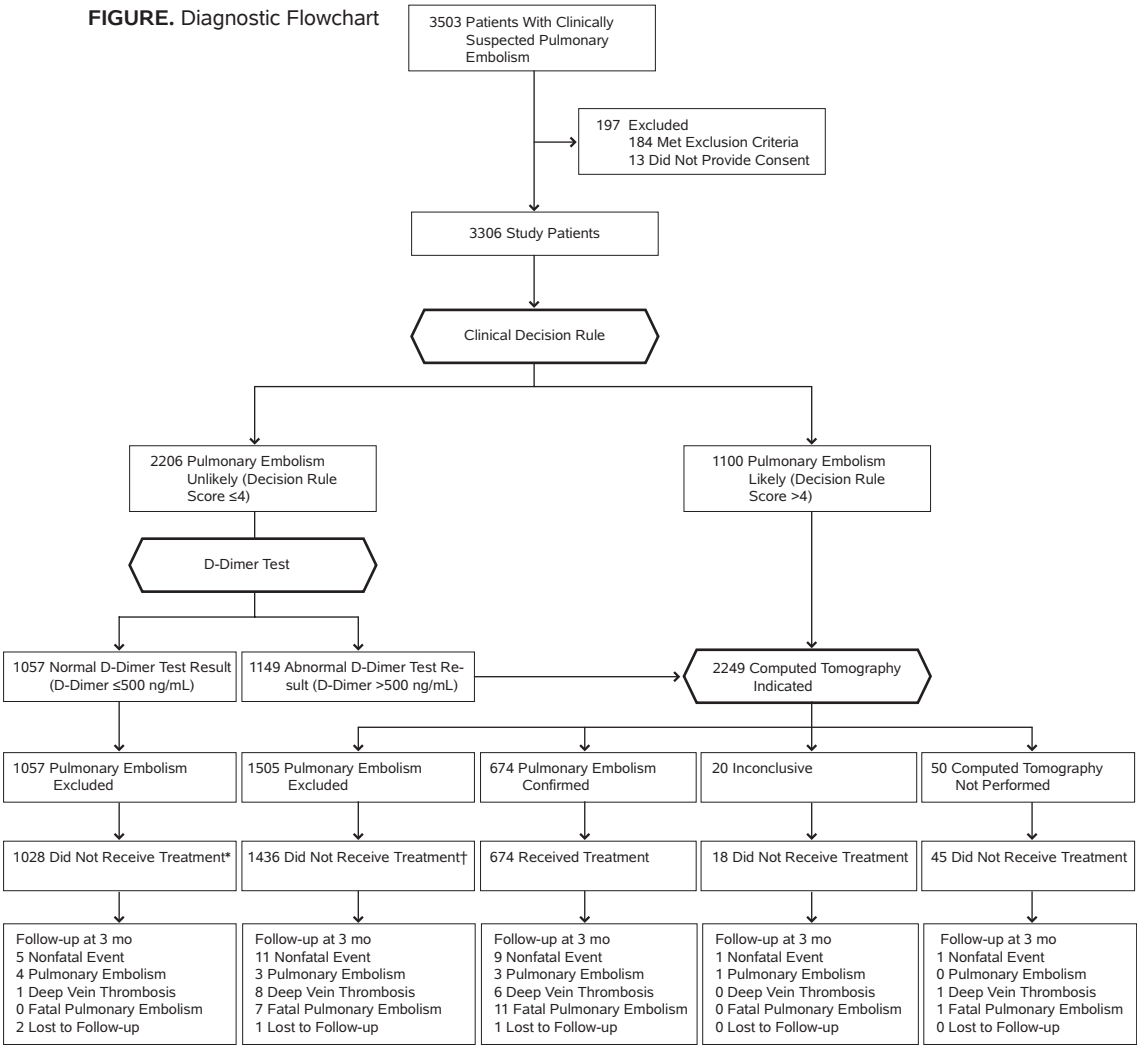
Another advancement is computed tomography (CT), which has emerged as a prominent imaging technique for the exclusion or confirmation of pulmonary embolism, as well as the detection of alternative diagnoses [6-10]. However, a critical missing piece of information has been whether it is safe to withhold anticoagulation treatment after a CT that is negative for pulmonary embolism[11,12]. In a recent study, [13] recurrent venous thromboembolism (VTE) occurred in 1.7% of patients who initially had a low or intermediate probability for pulmonary embolism using the Geneva score, [14] an abnormal D-dimer test result, normal bilateral compression ultrasound (CUS) of the leg veins, and a normal multidetector-row CT scan. In that study, all patients with high probability for pulmonary embolism had to undergo pulmonary angiography after normal CT and normal CUS. A more efficient strategy would consist of an algorithm with a dichotomized decision rule, D-dimer testing, and CT, in which pulmonary embolism is considered excluded in patients with an unlikely clinical probability score and a normal D-dimer test result, while CT is used in all other patients as the sole imaging method to make management decisions. Therefore, we performed a prospective study in a large cohort of consecutive patients with clinically suspected pulmonary embolism to evaluate the effectiveness of this novel management strategy.

METHODS

Study Design

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

FIGURE. Diagnostic Flowchart



*Excludes 29 patients treated with anticoagulant therapy for reasons other than venous thromboembolism.
†Excludes 69 patients treated with anticoagulant therapy for reasons other than venous thromboembolism.

Patients

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

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

TABLE 1. Clinical Decision Rule*

Variable	points
Clinical signs and symptoms of deep vein thrombosis (minimum of leg swelling and pain with palpation of the deep veins)	3
Alternative diagnosis less likely than pulmonary embolism	3
Heart rate > 100/min	1.5
Immobilization (> 3 days) or surgery in previous 4 weeks	1.5
Previous pulmonary embolism or deep vein thrombosis	1.5
Hemoptysis	1.0
Malignancy (receiving treatment, treated in the last 6 months or palliative)	1.0

* clinical probability of pulmonary embolism unlikely: 4 or less points; clinical probability of pulmonary embolism likely: more than 4 points. Source: Wells et al. [3]

Clinical Decision Rule and D-Dimer Assay

Patients with clinically suspected pulmonary embolism were evaluated by an attending physician using a validated clinical decision rule (table 1)[3] Pulmonary embolism was classified as “unlikely” with a clinical decision rule score of 4 or less points, and “likely” with a score of more than 4 points. This cut-off was chosen because it has been shown to give an acceptable

VTE diagnostic failure rate of 1.7% to 2.2% in combination with a normal D-dimer test result.3 An estimated 300 attending physicians in the participating hospitals used the clinical decision rule with the study participants.

In patients with a clinical decision rule indicating pulmonary embolism unlikely, a D-dimer concentration was measured, using either the VIDAS D-dimer assay (Biomerieux, Marcy L'Etoile, France) or the Tinaquant assay (Roche Diagnostica, Mannheim, Germany). A D-dimer concentration of 500 ng/mL or less was defined as nor-mal. In patients with pulmonary embolism unlikely and a normal D-dimer test result, the diagnosis of pulmonary embolism was considered excluded and anticoagulant treatment was withheld. Those patients who had a combination of clinical decision rule indicating pulmonary embolism unlikely with an abnormal D-dimer test result, or who had a clinical decision rule indicating pulmonary embolism likely, underwent CT.

Radiological Evaluation

Computed tomography was performed using either single-detector row or multidetector-row systems. Patients were examined during suspended inspiration. The single-detector row CT parameters were 3-mm slice thickness with a 2-mm reconstruction interval at 120 kV/140 mAs, 120 to 140 mL of nonionic contrast material containing 350 mg of iodine per mL with an injection speed of 3.0 mL/s and an injection delay of 16 seconds. Multidetector-row CT parameters were 1.25-mm slice thickness with a 1.2-mm reconstruction interval at 120 kV/120 mAs, 80 to 100 mL of nonionic contrast material containing 350 mg of iodine per mL with an injection speed of 4.0 mL/s and bolus tracking in the common pulmonary artery to get optimal contrast opacification of the pulmonary arteries.

The pulmonary arteries were evaluated up to and including the subsegmental vessels from the level of the aortic arch to the lowest hemidiaphragm. Pulmonary embolism was diagnosed if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least 2 adjacent slices. These patients received low-molecular-weight heparin or unfractionated heparin, followed by vitamin K antagonists, according to local practice. In patients without pulmonary embolism, the presence or absence of an alternative diagnosis was recorded and anticoagulant treatment was withheld. The CT was considered inconclusive if the images could not be interpreted because of motion artifacts due to movements of the patient or the heart or if there was insufficient contrast enhancement of the pulmonary arteries. The management of patients in whom the CT could not be performed or who had an inconclusive CT scan was left to the discretion of the attending physician.

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

Outcome Measures

The primary outcome of the study was the incidence of symptomatic VTE events during 3 months of follow-up, defined as fatal pulmonary embolism, nonfatal pulmonary embolism, or deep vein thrombosis (DVT). An independent adjudication committee, whose members were unaware of the patient's allocation within the diagnostic algorithm, evaluated all suspected VTE and deaths. A diagnosis of pulmonary embolism or DVT was based on a priori defined and generally accepted criteria 15. Deaths were classified as caused by pulmonary embolism in case of confirmation by autopsy, in case of an objective test positive for pulmonary embolism prior to death, or if pulmonary embolism could not be confidently excluded as the cause of death.

Follow-up consisted of a scheduled outpatient visit or telephone interview at 3 months. Patients were additionally instructed to contact the study center or their general practitioner immediately in the event of symptoms suggestive of DVT or pulmonary embolism. At each visit, information was obtained on complaints suggestive of VTE, including acute onset of dyspnea, acute worsening of existing dyspnea, acute onset of chest pain, unilateral leg swelling and leg pain, as well as interval initiation of anticoagulants. In case of clinically suspected DVT or pulmonary embolism, objective diagnostic tests were required, in- cluding CUS for suspected DVT, and ventilation-perfusion scintigraphy or CT for suspected pulmonary embolism. In case of death, information was obtained from the general practitioner, from the hospital records, or from autopsy.

Statistical Analysis

The 2 primary analyses were incidence of symptomatic VTE during follow-up, confirmed by objective testing, in (1) the group of patients in whom anticoagulant treatment was withheld based on a classification of pulmonary embolism unlikely by clinical decision rule and a normal D-dimer test result, and (2) the group of patients in whom anticoagulant treatment was withheld based on a CT scan that excluded pulmonary embolism. Additional analyses were performed for fatal pulmonary embolism in these groups, as well as among the patients with a normal CT scan and an alternative diagnosis on CT separately.

Sample size was based on an assumption of a 1% incidence of VTE in both patient groups[5,9] and a goal to keep the upper limit of the 95% confidence interval (CI) below 2.7%, which has been reported as the upper limit of the range of recurrent VTE after a normal angiogram [16]. We calculated that approximately 1000 patients would have to be included in each group, using a 2-sided type I error of .05 and a type II error of .20. Since we expected that approximately 30% of patients would have a classification of pulmonary embolism unlikely by clinical decision rule and a normal D-dimer test result,[5] a total study population of 3300 patients was needed.

Exact 95% CIs were calculated around the observed incidences using StatXact software, version 5 (Cytel Software Corp, Cambridge, Mass). Descriptive parameters were calculated using SPSS software, version 11.5 (SPSS Inc, Chicago, Ill). For statistical differences, the Fisher exact test was used; statistical significance was set at $P < .05$.

RESULTS

Study Patients

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

Results of Diagnostic Algorithm

Of the 3306 included patients, 2206 (66.7%) had a clinical decision rule indicating pulmonary embolism unlikely and were tested for D-dimer concentrations (Figure). The prevalence of pulmonary embolism in these patients was 12.1% (266/2206; 95% CI, 10.7%-13.5%) versus 37.1% (408/1100; 95% CI, 34.2%-40.0%) in those with a clinical decision rule indicating pulmonary embolism likely ($P<.001$). Among the 1149 patients classified as unlikely but with an abnormal D-dimer test result, the prevalence of pulmonary embolism was 23.2% (266/ 1149). D-dimer test results were normal in 1057 (32.0%) patients, and in these patients, pulmonary embolism was considered excluded. Of the 2206 patients undergoing D-dimer testing, 968 (44%) had a VIDAS D-dimer test performed; 1238 patients (56%) had a Tinaquant D-dimer test.

Of the 2249 patients with either abnormal D-dimer concentrations (n=1149) or a clinical decision rule indicating pulmonary embolism likely (n=1100), 2199 underwent CT. In the other 50 patients a CT was indicated but not performed because of lack of venous access, extreme obesity, DVT confirmed by CUS prior to CT, or a deteriorating clinical condition prior to CT. Multidetector-row CT was performed in 1939 patients and single-detector row CT in 260 patients. Computed tomography excluded pulmonary embolism in 1505 patients (45.5% of the study population). In these patients, 702 (21.2% of the study population) had additional diagnostic information visualized on CT: pneumonia (n=212), pleural effusion (n=163), malignancy (n=50), and other diagnoses (n=277). Pulmonary embolism was confirmed in 674 patients (20.4% of the study population). Computed tomography was inconclusive in 20 patients (0.9%). Hence, the diagnostic algorithm could be completed according to the protocol in 3256 patients (98.5%) and allowed a management decision in 3236 patients (97.9%).

TABLE 2. Baseline Demographic and Clinical Characteristics of Study Population (n = 3306)*

Characteristic	Value
Age, mean (SD), y	53.0 (18.4)
Female	1897 (57.4)
Outpatients	2701 (81.7)
Duration of complaints, median (IQR), d	2(1-5)
Paralysis	91(2.8)
Immobilization or recent surgery	610 (18.5)
Previous venous thromboembolism	480 (14.5)
COPD with treatment	341 (10.3)
Heart failure with treatment	243 (7.4)
Malignancy	476 (14.4)
Estrogen use, women	438 (23.1)
Clinical symptoms of deep vein thrombosis	190 (5.7)
Heart rate >100/min	867 (26.2)
Hemoptysis	176 (5.3)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
*Data are presented as number and percentage unless otherwise indicated.

Patients With Pulmonary Embolism Unlikely and Normal D-Dimer Test Result

Of the 1057 patients with the combination of a clinical decision rule indicating pulmonary embolism unlikely and a normal D-dimer test result, 29 patients (2.7%) were treated with oral anticoagulants during follow-up for various reasons other than VTE. Three of the 1028 remaining patients returned with symptomatic VTE events (2 nonfatal pulmonary embolism, 1 DVT) during the 3-month follow-up. In 25 patients, the protocol was violated and a CT or a ventilation-perfusion scan was performed while not indicated. Pulmonary embolism was diagnosed in 2 of these 25 patients. Therefore, the incidence of VTE was 5 of 1028 (0.5% [95% CI, 0.2%- 1.1%]) (Table 3). Two patients were lost to follow-up (0.2%). In a "worst case" scenario, in which these 2 patients would have developed VTE, the incidence of VTE would have been 7 of 1028 (0.7% [95% CI, 0.3%-1.4%]). There were no fatal pulmonary embolisms. Eight (0.8%) of the 1057 patients died of other causes.

Of the study population, 605 were inpatients, and 56 of these had a decision rule indicating pulmonary embolism unlikely and a normal D-dimer test result (9.3%). No VTE was observed at follow-up in these patients (VTE rate, 0% [95% CI, 0%-6.4%]). The results for inpatients and outpatients were comparable (VTE rate, 0% [95% CI, 0%- 6.4%] vs 0.5% [95% CI, 0.2%-1.2%]). There were no significant differences between patients at academic and general hospitals.

The VIDAS D-dimer assay had a true-negative rate of 44.2% (428/968 patients) and the Tinaquant D-dimer assay had a true-negative rate of 50.8% (629/1238 patients) (P<.002). The negative predictive values for the VIDAS and Tinaquant assays were 100% (95% CI, 99.1%-100%) and 99.2% (95% CI, 98.1%-99.7%), respectively.

TABLE 3. Venous Thromboembolic Events (VTEs) During 3-Month Follow-up (n = 3138)*

Variable	No.	Total VTEs, No. (%) [95% CI]	Fatal Pulmonary Embolism, No. (%) [95% CI]
Pulmonary embolism unlikely and normal D-dimer test result	1028	5 (0.5) [0.2-1.1]	0 (0) [0.0-0.3]
Pulmonary embolism excluded by CT	1436	18 (1.3) [0.7-2.0]	7 (0.5)[0.2-1.0]
CT normal	764	9 (1.2)[0.5-2.2]	3 (0.4) [0.1-1.1]
CT alternative diagnosis	672	9 (1.3)[0.6-2.5]	4 (0.6) [0.1-1.5]
Pulmonary embolism diagnosed by CT	674	20 (3) [1.8-4.6]	11 (1.6) [0.8-2.9]

Abbreviations: CI, confidence interval; CT, computed tomography. *A total of 168 patients were excluded due to treatment with anticoagulation outside of protocol, inconclusive CT, or CT not performed.

Patients With CT Excluding Pulmonary Embolism

Of the 1505 patients in whom CT excluded pulmonary embolism, 69 (4.6%) received anticoagulants during follow-up for various reasons other than VTE. Of the 1436 patients who did not receive anticoagulant treatment, 18 experienced VTE events during the 3-month follow-up (1.3% [95% CI, 0.7%-2.0%]). Eleven of these patients had nonfatal symptomatic thromboembolic events (3 pulmonary embolism and 8 DVT). Fatal pulmonary embolism was presumed to have occurred in the other 7 patients (0.5% [95% CI, 0.2%-1.0%]); it was proven by autopsy in 2 and attributed as the cause of death in 5 (Table 4). Follow-up was incomplete in one of the 1436 patients (0.1%). In a "worst case" scenario in which this patient would have developed VTE, the incidence of VTE would have been 19 of 1436 (1.3% [95% CI, 0.8%-2.1%]).

TABLE 4. Deaths Attributed to Pulmonary Embolism

Patient Sex	Age, y	Results of Computed Tomography	Anticoagulant Therapy	Past Medical History	Time of Death After Enrollment, d	Circumstances of Death
Male	60	Normal	No	COPD, alcohol abuse	3	Sudden death at home
Female	65	Alternative diagnosis: pulmonary metastases	No	Colon cancer; multiple metastases in liver, spleen, adrenal glands	18	Dehydration due to chemotherapy-induced diarrhea; morphine for pain complaints; sudden death
Male	46	Normal	No	Multiple myeloma	40	Bedridden due to complaints of pain associated with myeloma; sudden death at home; autopsy result: pulmonary embolism
Female	69	Alternative diagnosis: interstitial pneumonia	No	Progressive dyspnea in past half year due to interstitial pneumonia	41	Computed tomography at day 34 showed pulmonary embolism; progressive respiratory insufficiency; ventilator dependency; palliative care; autopsy result: pulmonary embolism and bilateral pneumonia
Female	60	Alternative diagnosis: pericarditis carcinomatosa	No	COPD, breast cancer	75	Immobilization in electric wheelchair in nursing home; gradual worsening, cardiac failure due to pericarditis
Female	77	Alternative diagnosis: pneumonia; at review, a subsegmental pulmonary embolism had been missed at inclusion	No	Hypertension	86	Collapse on street with swollen face
Female	31	Normal	No	Pulmonary embolism in 2002, diabetes, renal insufficiency, estrogen use	94	Antibiotics for CAPD peritonitis; sudden death

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; COPD, chronic obstructive pulmonary disease.

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

Twenty patients returned with symptoms of pulmonary embolism during follow-up. Computed tomography was again used as the diagnostic method in 13 of these 20 patients and was nor-mal in all. No VTE was demonstrated at later follow-up.

The overall mortality rate in patients in whom CT excluded pulmonary embolism was 8.6% (129 patients).

Patients With CT That Was Inconclusive or Not Performed

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

Patients With Pulmonary Embolism Confirmed by CT

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

DISCUSSION

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

Other management studies have documented the safety of a low clinical probability in combination with a normal D-dimer concentration for the exclusion of pulmonary embolism [3-5,17]. In these studies, the rate of VTE during follow-up ranged from 0% to 1.5%. However, because the sample size was limited, upper confidence limits were as high as 6.0% [3-5, 15].

In contrast to our simple algorithm, a recent study [13] used a more complex flowchart with sequential testing that included clinical probability assessment, D-dimer assay, CUS, CT, as well as pulmonary angiography to exclude pulmonary embolism in patients with high likelihood and negative workup. As the authors pointed out, their study was not a true outcome study, since CUS was performed in all patients with abnormal D-dimer levels, and patients with abnormal CUS and a normal CT scan were treated with anticoagulation. That study had a smaller sample size (674 patients) and a higher rate of exclusion (25% vs 5.6% in our study).

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

Despite concerns that the sensitivity of CT for pulmonary embolism is lower than that of pulmonary angiography,[18,19] the observed risk of subsequent symptomatic VTE in those patients in whom pulmonary embolism was excluded by CT was comparable to the risk reported after a normal pulmonary angiogram (3-month incidence, 1.3% [95% CI, 0.7%-2.0%] vs 1.7%

[95% CI, 1.0%-2.7%],16 respectively). In addition, in our study fatal pulmonary embolism occurred in 0.5% (95% CI, 0.2%- 1.0%) of patients in whom CT had excluded pulmonary embolism, compared with 0.3% (95% CI, 0.02%- 0.7%) after normal pulmonary angiography 16. Computed tomography has the potential advantage of providing additional diagnostic information for the presenting symptoms in patients without pulmonary embolism.

Several potential limitations in our study require comment. First, the absence of pulmonary embolism was not verified by pulmonary angiography. However, the clinical outcome after a 3-month follow-up is widely accepted as an appropriate alternative to establish the safety of a diagnostic strategy, given a near-complete follow-up[20]. Second, while our cohort study has the strength of minimal loss to follow-up (3 patients, 0.1%) and independent blinded adjudication of all outcomes, a randomized controlled study design would have allowed a direct comparison to other validated strategies. Third, CT was again used to exclude pulmonary embolism in 13 of 20 patients who returned during follow-up with symptoms after CT had excluded pulmonary embolism at baseline. Although these could represent false-negative results, these patients were not treated and further follow-up was uneventful, making this unlikely. Fourth, the use of multidetectorrow CT has the potential for overdiagnosis by imaging very small peripheral subsegmental emboli. Because patients did not undergo confirmatory pulmonary angiography, our study design did not permit assessing the false-positive rate of CT scans. Only 10% of our patients underwent single-detector row CT, so we could not make a meaningful comparison of the impact of each test. However, the overall prevalence of pulmonary embolism in our study (20%) is comparable to the prevalence in a previous multicenter study performed with single-detector row CT (24%) [9]. This does not support a concern that multidetector-row CT technology will lead to a high number of false-positive results. Finally, a definitive cause of death could not be established for all patients with normal test results who died during follow-up. However, pulmonary embolism was assigned as the cause of death if it could not be confidently excluded, a conservative assumption that strengthens our conclusions about low risk for this strategy.

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

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

AUTHORS

Christopher Study Writing Group:

Arne van Belle, Department of Pulmonary Medicine, Academic Hospital, Maastricht; Harry R. Büller, Department of Vascular Medicine, Academic Medical Center, Amsterdam; Menno V. Huisman, Department of General Internal Medicine/Endocrinology, Leiden University Medical Center, Leiden; Peter M. Huisman, Department of Radiology, Hilversum Hospital, Hilversum; Karin Kaasjager, Department of Internal Medicine, Rijnstate Hospital, Arnhem; Pieter W. Kamphuisen, Department of General Internal Medicine, Radboud University Medical Center, Nijmegen; Mark H. H. Kramer, Department of Internal Medicine, Meander Medical Center, Amersfoort; Marieke J. H. A. Kruip, Department of Hematology, Erasmus University Medical Center, Rotterdam; Johanna M. Kwakkel-van Erp, Department of Pulmonary Medicine, Rijnstate Hospital, Arnhem; Frank W. G. Leebeek, Department of Hematology, Erasmus University Medical Center, Rotterdam; Mathilde Nijkeuter, Department of General Internal Medicine/Endocrinology, Leiden University Medical Center, Leiden; Martin H. Prins, Department of Clinical Epidemiology, Academic Hospital, Maastricht; Maaike Söhne, Department of Vascular Medicine, Academic Medical Center, Amsterdam; and Lidwine W. Tick, Department of Hematology, Leiden University Medical Center, Leiden; all in the Netherlands

REFERENCES

1. Lee AY, Hirsh J. Diagnosis and treatment of venous thromboembolism. Annu RevMed. 2002;53: 15-33.
2. The PIOPED Investigators. Value of the ventilation/ perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED).JAMA.1990;263:2753-2759.
3. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416-420.
4. Kruip MJ, Slob MJ, Schijen JH, van der Heul C, Büller 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;162:1631- 1635.
5. Ten Wolde M, Hagen PJ, MacGillavry MR, et al. Non-invasivediagnosticwork-up of patientswith clinically suspected pulmonary embolism: results of a management study. J Thromb Haemost. 2004;2:1110- 1117.
6. Schoepf UJ, Goldhaber SZ, Costello P. Spiral computed tomography for acute pulmonary embolism. Circulation. 2004;109:2160-2167.
7. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: asystematic review. Ann Intern Med. 2000;132:227-232.
8. Mullins MD, Becker DM, Hagspiel KD, et al. The role of spiral volumetric computed tomography in the diagnosis of pulmonary embolism. Arch Intern Med. 2000;160:293-298.
9. van Strijen MJ, de Monye W, Schiereck J, et al. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. Ann Intern Med. 2003;138: 307-314.
10. Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multi-center outcome study. Lancet. 2002;360:1914-1920.
11. Moores LK, Jackson WL Jr, Shorr AF, et al. Meta-analysis: outcomes in patients with suspected pulmonary embolism managed with computed tomographic pulmonary angiography. Ann Intern Med. 2004;141:866-874.
12. Perrier A, Roy PM, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter managementstudy. Am J Med. 2004;116:291- 299.
13. Perrier A, Roy P-M, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med. 2005;352:1760- 1768.
14. Wicki J, PernegerTV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: asimple score. Arch Intern Med. 2001;161:92-97.
15. Büller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N EnglJ Med. 2003;349:1695-1702.
16. van Beek EJ, Brouwerst EM, Song B, et al. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism—a critical review. Clin Radiol. 2001;56:838-842.
17. Wolf SJ, McCubbin TR, Feldhaus KM, et al. Prospective validation of Wells criteria in the evaluation of patients with suspected pulmonary embolism. Ann Emerg Med. 2004;44:503-510.
18. Van Strijen MJ, De Monye W, Kieft GJ, Pattynama PM, Prins MH, Huisman MV. Accuracy of single-detector spiral CT in the diagnosis of pulmonary embolism: a prospective multicenter cohort study of consecutive patients with abnormal perfusion scintigraphy. J Thromb Haemost. 2005;3: 17-25.
19. Perrier A, Bounameaux H. Validation of helical computed tomography for suspected pulmonary embolism: a near miss? J Thromb Haemost. 2005;3: 14-16.
20. Kruip MJ, Leclercq MG, van der Heul C, Prins MH, Büller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies: a systematic review. Ann Intern Med. 2003;138:941-951.

Chapter 5

A SIMPLE DIAGNOSTIC STRATEGY IN HOSPITALIZED PATIENTS WITH CLINICALLY SUSPECTED PULMONARY EMBOLISM

Marieke J.H.A. Kruip, Maaike Söhne, Mathilde Nijkeuter, Hanneke M. Kwakkel-van Erp, Lidwine W. Tick, Stijn J.M. Halkes, Martin H. Prins, Mark H.H. Kramer, Menno V. Huisman, Harry R.Büller, Frank W.G. Leebeek, on behalf of the Christopher Study Investigators

Journal of Internal Medicine 2006, in press

ABSTRACT

Objectives Diagnostic strategies in patients with suspected pulmonary embolism have been extensively studied in outpatients; their value in hospitalized patients has not been well established. Our aim was to determine the safety and clinical utility of a simple diagnostic strategy in hospitalized patients with suspected pulmonary embolism.

Design Prospective management study

Setting 12 teaching hospitals (5 academic, 7 general hospitals)

Subject 605 hospitalized patients with clinically suspected pulmonary embolism. All patients completed the study.

Interventions First the clinical decision rule (CDR)-score was calculated. An unlikely CDR-score in combination with a normal D-dimer excluded pulmonary embolism. All other patients underwent helical CT. CT either diagnosed or excluded pulmonary embolism, in which case anticoagulants were started or withheld. All patients were instructed to report symptoms of venous thrombosis. Objective tests were performed to confirm venous thromboembolism. The primary outcome was the incidence of symptomatic venous thrombosis during three months follow-up.

Results The combination of an unlikely CDR-score and a normal D-dimer excluded pulmonary embolism in 60 patients (10% of all patients); no venous thromboembolic event occurred during follow-up (0%; 95% CI 0%-6.7%). CT excluded pulmonary embolism in 380 patients; during follow-up venous thromboembolism occurred in 5 patients (1.4%; 95% CI 0.4%-3.1%).

Conclusions An unlikely CDR-score in combination with a normal D-dimer appears to exclude pulmonary embolism safely in hospitalized patients. Before clinical implementation it is important this safety is confirmed by others. CT testing was obviated in only 10% of patients. CT can safely exclude pulmonary embolism in hospitalized patients.

INTRODUCTION

Hospitalized patients are at high risk for the development of venous thrombosis (deep vein thrombosis or pulmonary embolism) and if they do develop thrombosis the morbidity and mortality increases compared to hospitalized patients without venous thrombosis [1]. Autopsy series of hospitalized patients have shown that pulmonary embolism accounts for 5-10% of hospital deaths [2,3] . Therefore, it is important to be able to safely exclude or confirm thrombosis in patients with a clinical suspicion of this disease. Even more so because unnecessary anticoagulant treatment can lead to morbidity and mortality, i.e. minor (6.2 per 100 patient-years), major (1.1 per 100 patient-years), or fatal (0.25 per 100 patient-years) bleedings [4].

Several diagnostic strategies for patients with clinically suspected pulmonary embolism evaluated in recent years start with the exclusion of the disease by using a low clinical probability assessment in combination with a normal D-dimer test [5-8]. The results of these studies are mainly based on outpatients, sometimes on the combination of in- and outpatients, rarely on hospitalized patients alone. There is a debate about the clinical utility of D-dimer testing in hospitalized patients because of the low proportion with a normal D-dimer concentration [9-11].

Furthermore, the safety of withholding anticoagulant treatment after a normal helical computed tomography (CT) as the only imaging technique is still uncertain, because of the limited studies, again mainly in outpatients [7,12-14].

We recently completed a large outcome study in which the safety of a diagnostic strategy using the combination of a clinical decision rule (CDR) and D-dimer concentration followed by helical CT was evaluated in patients with clinically suspected pulmonary embolism [15]. The aim of the present analysis is to evaluate the safety and clinical utility of this strategy in hospitalized patients.

MATERIALS AND METHODS

This study was part of a large management study in 12 teaching hospitals (5 academic and 7 general hospitals) in the Netherlands which evaluated a diagnostic strategy including a CDR, D-dimer testing and helical CT [15]. Patients were included between November 2002 and September 2004. The Institutional Review Board of all participating hospitals approved the study protocol.

Study participants

Hospitalized patients with clinically suspected pulmonary embolism were eligible for inclusion in this analysis. The hospitalization was for other reasons than suspected pulmonary embolism. Patients were excluded if they had received therapeutic unfractionated or low-molecular-weight-heparin for more than 24 hours before inclusion, were younger than 18 years of age, were pregnant, had a known allergy to intravenous contrast agents, had a life expectancy of less than three months or if there was geographic inability for follow-up.

Diagnostic strategy

The figure shows the diagnostic strategy of the study. A validated clinical decision rule (CDR) was used. This rule consists of seven questions including the presence of symptoms of deep venous thrombosis (3 points), pulse frequency (> 100 beats per minute is 1.5 points), immobilization or surgery within the last four weeks (1.5 points), previous venous thromboembolism (1.5 points), hemoptysis (1 point), malignancy (1 point) and the possibility of an alternative diagnosis (3 points if pulmonary embolism is more likely than an alternative diagnosis) [6]. Patients were classified into those with a likely CDR-score (> 4) or unlikely CDR-score (4 or below).

In case of an unlikely CDR-score, the D-dimer concentration was measured using either the Vidas D-Dimer assay (Biomerieux, Marcy Létiole, France) or the Tinaquant assay (Roche Diagnostica, Mannheim, Germany). A D-dimer concentration of ≤ 500 ng/ml fibrinogen equivalents was defined as normal for both assays. In case of an unlikely CDR-score and a normal D-dimer concentration, pulmonary embolism was considered excluded and anticoagulant treatment was withheld. Patients with an unlikely CDR-score in combination with an abnormal D-dimer concentration or patients with a likely CDR-score, underwent a helical CT. If the CT did not demonstrate pulmonary embolism, anticoagulant treatment was withheld. If the CT demonstrated pulmonary emboli, anticoagulant treatment was initiated, using unfractionated or low-molecular-weight-heparin and vitamin K antagonists, according to the local practice.

Helical CT was performed using single- or multi-slice detector systems according to the protocol as described [15]. The management of the patients in whom helical CT could not be performed was left to the discretion of the attending physician.

Follow-up and outcome

After completing the diagnostic strategy, the patients were instructed to return to the hospital if signs and symptoms of deep venous thrombosis or pulmonary embolism occurred during the 3 months follow-up period. A regular follow-up was scheduled after 3 months and consisted of a telephone interview or a hospital visit. Information on signs and symptoms suggestive of deep venous thrombosis or pulmonary embolism, the use of anticoagulants and comorbidity was obtained. If a patient was clinically suspected of deep venous thrombosis or pulmonary embolism, objective tests were performed to confirm or exclude the diagnosis, i.e. compression ultrasonography for suspected deep venous thrombosis, ventilation-perfusion lung scanning, helical CT, or pulmonary angiography for suspected pulmonary embolism. The results of these tests were adjudicated by an independent committee that was not aware of the original test results. In case of death, information was obtained by reviewing the hospital charts, the results from autopsy or by contacting the general practitioner. All deaths were adjudicated by the independent committee and classified as due to pulmonary embolism in case of confirmation by autopsy, in case of an objective positive test for pulmonary embolism prior to death or if pulmonary embolism could not be confidently excluded as the cause of death.

The primary outcome of the study was the incidence of symptomatic venous thrombosis during three months follow-up, defined as non-fatal or fatal pulmonary embolism or deep venous thrombosis.

Statistical analysis

The incidences of symptomatic venous thromboembolism confirmed by objective testing in the group of patients in whom anticoagulant treatment was withheld were calculated for the groups of patients with 1) an unlikely CDR-score in combination with a normal D-dimer concentration or 2) a helical CT scan that excluded pulmonary embolism. Exact 95% confidence intervals (CI) were calculated around the observed incidences using StatXact software, version 5 (Cytel Software Corp, Cambridge, Mass, USA). Descriptive parameters were calculated using SPSS software, version 11.5 (SPSS, Inc., Chicago, Illinois).

RESULTS

Study patients

The study population consisted of 605 hospitalized patients. These patients were a part of a large management study with 3505 eligible in- and outpatients of whom 197 were excluded because of predefined criteria or no informed consent [15]. The baseline characteristics of the hospitalized patients are presented in Table 1.

Compared to the 2701 outpatients that were included in the original study, the hospitalized patients were older, had higher prevalences of the risk factors such as immobility and recent surgery and more patients were known with comorbid conditions such as cancer, heart-failure and chronic obstructive pulmonary diseases. Two patients were excluded, because the CDR-score was not calculated.

TABLE 1. Baseline characteristics of the hospitalized patients

Characteristics	**hospitalized patients (n = 605)**
Age, years (standard deviation)	61 (18)
Women, n (%)	344 (57)
Immobility, n (%)	156 (26)
Recent surgery, n (%)	113 (19)
Previous venous thromboembolic events, n (%)	53 (9)
Duration of complaints, days, median (IQR*)	6.0 (6)
Cancer, n (%)	156 (26)
Heart-failure with treatment, n (%)	77 (13)
COPD** with treatment, n (%)	103 (17)
Estrogen use, n (%)	27 (5)

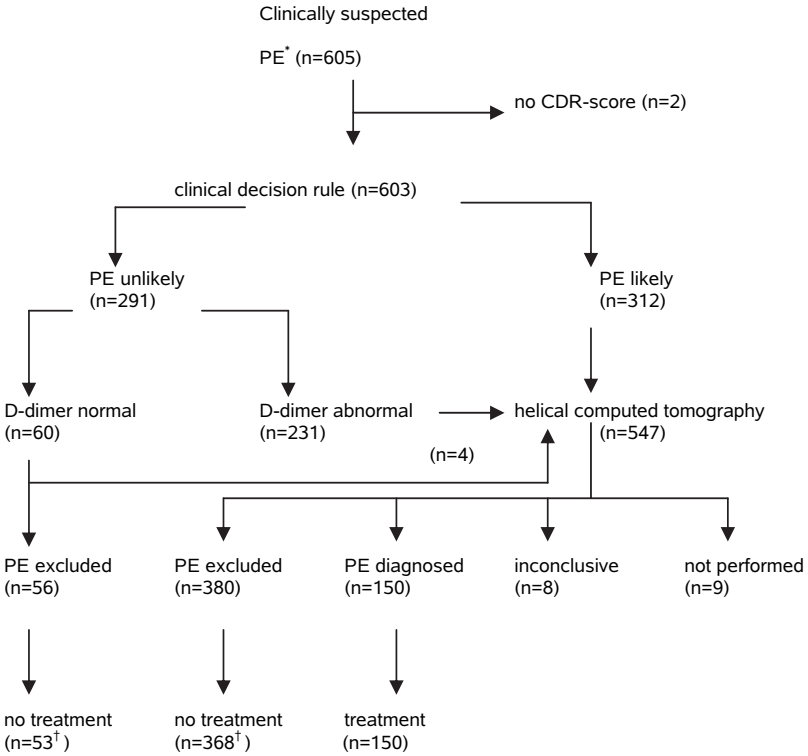
* interquartile range
** chronic obstructive pulmonary disease

Results of the Clinical Decision Rule and D-dimer concentration.

The results of the CDR are presented in Table 2. In this study the dichotomized CDR-score was used. Of the 603 patients 291 (48%) had an unlikely CDR-score (≤ 4). The D-dimer test was normal in 60 of these patients (21% of the patients with an unlikely CDR-score and 10% of all patients). In four patients the protocol was violated and helical CT was performed, which did not demonstrate pulmonary emboli, while another three patients received vitamin K antagonists for various reasons other than venous thromboembolism, such as atrial fibrillation

and valvular heart disease. Therefore, in 53 patients pulmonary embolism was considered excluded and anticoagulant treatment was withheld. During follow-up, completed in all patients, no venous thromboembolic events and no death attributed to pulmonary embolism occurred in these 53 hospitalized patients (failure rate 0%; 95% CI 0%-6.7%) (Table 3, figure). This was comparable with the outcome in outpatients (failure rate 0.5%; 95% CI 0.2%-1.2%). Two hospitalized patients died of other reasons than venous thromboembolism. The CDR of the hospitalized patients revealed more PE-likely CDR-scores (52%), i.e. a CDR-score > 4, as compared to the outpatients (29%) (p<0.001).

FIGURE. Flowchart with outcomes at presentation and at 3 months for hospitalized patients with suspected pulmonary embolism.
* pulmonary embolism
† without patients receiving anticoagulants for other reasons than pulmonary embolism
‡ venous thromboembolic event



follow-up at 3 months , n=603

VTE‡	0	5	6	0	0
Deaths	2	54	25	0	2
Deaths attributable to VTE	0	2	4	0	0

Results of the helical CT.

Both patients with an unlikely CDR-score and elevated D-dimer test (n = 231) as well as patients with a likely CDR-score (n = 312) were scheduled for helical CT (figure).

In 9 patients (2%) the protocol was violated and helical CT was not performed, while in 8 patients (1%) the results were inconclusive.

Of the patients with an unlikely CDR-score and elevated D-dimer test, pulmonary embolism was excluded by helical CT in 179 patients (77% of this group of patients). In total, helical CT excluded pulmonary embolism in 380 patients. During follow-up none of these patients were lost to follow up. Twelve patients received vitamin K antagonists for various other reasons than venous thromboembolism such as atrial fibrillation and valvular heart disease. Five of the remaining 368 patients without anticoagulant treatment had a venous thromboembolic event during the three months follow-up (failure rate 1.4%; 95% CI 0.4%-3.1%); two patients had a deep venous thrombosis, one a non-fatal pulmonary embolism and two patients died in whom pulmonary embolism could not be ruled out. Fifty-four patients died during follow-up due to other causes than venous thromboembolism.

Helical CT demonstrated pulmonary embolism in 150 patients (25% of the total study population). An unlikely CDR-score was present in 43 of these patients with pulmonary embolism. Six patients had recurrent venous thrombosis despite anticoagulant treatment (4%; 95% CI 1.5%-8.5%). This included one deep venous thrombosis, one with non-fatal and four with fatal pulmonary embolism.

TABLE 2. Clinical decision rule (CDR)-score in hospitalized patients with suspected pulmonary embolism (PE) and the frequency of pulmonary embolism calculated per CDR-score range, for the original CDR and for the dichotomized CDR, which was used in the present study.

			original CDR			dichotomized CDR		
CDR-score	**n**	**PE, n (%*)**	**CDR**	**n**	**PE, n (%*)**	**CDR**	**n**	**PE, n(%*)**
0.0 – 1.0	50	3 (6%)	<2	138	15 (11%)			
1.5 – 2.0	88	12 (14%)				≤4	291	44(15%)
2.5 – 3.0	121	17 (14%)						
3.5 – 4.0	32	12 (38%)	2-6	415	112 (27%)			
4.5 – 5.0	134	35 (26%)						
5.5 – 6.0	128	48 (38%)						
6.5 – 7.0	29	14 (48%)				> 4	312	106(34%)
7.5 – 8.0	10	3 (30%)	>6	50	23 (46%)			
≥8.5	11	6 (55%)						
total	603	150 (25%)						

* the percentage of patients with pulmonary embolism in the respective CDR-score range

TABLE 3. Incidence of venous thromboembolic events (VTE) during three months follow-up (FU) for hospitalized patients without anticoagulant treatment.

		VTE during FU
	n	**n (%:95% CI*)**
unlikely CDR**-score and normal d-dimer	53	0 (0:0-6.7)
pulmonary embolism excluded by CT***:	368	5 (1.4: 0.4-3.1)
- CT normal	152	2 (1.3:0.2-4.7)
- CT with an alternative diagnosis	216	3 (1.4:0.3-4.0)

* confidence interval
** clinical decision rule
***computed tomography

Additional observations.

Helical CT was normal in only 160 of the 547 hospitalized patients who underwent CT-scanning (29%) and demonstrated an alternative diagnosis in 220 of 547 patients (40%). These alternative diagnosis were infiltrate (n = 50), pleural effusion (n = 76), tumor (n = 12), or other diagnosis (n = 82). The diagnostic strategy could be completed according to the protocol in 596 patients (99%) and allowed a management decision in 588 patients (97%).

DISCUSSION

This large study in consecutive hospitalized patients with clinically suspected pulmonary embolism shows that the combination of an unlikely CDR-score and normal D-dimer concentration is only present in approximately 10% of patients. Since no venous thromboembolism occurred during follow up, this combination appears to be safe, although the 95% confidence interval is wide (0%-6.7%). If helical CT was indicated according to the diagnostic strategy and did not show pulmonary emboli, pulmonary embolism could be safely excluded without the need for additional imaging, such as compression ultrasonography of the legs, as has been previously used [7,12]. Our fast and simple diagnostic strategy was well accepted by the clinicians involved in the diagnostic work-up of hospitalized patients as shown by the low percentage of protocol violations (2%) and the high proportion of management decisions that could be made with this strategy (97%).

Little is known about the value of clinical probability assessment in hospitalized patients with clinically suspected pulmonary embolism. Most of the previous studies have been performed in outpatients or both in- and outpatients and reported the results for the total patient group [6,16-20]. Miron et al. performed a study in 145 consecutive hospitalized patients with clinically suspected pulmonary embolism and assessed the clinical probability empirically. Hospitalized patients with a low (33% of the population), intermediate (58%) or high (9%) clinical probability according to the physician showed an observed prevalence of pulmonary embolism of 13%, 44%, and 70%, respectively [9]. Ollenberger and Worsley studied the effect of patient location on the performance of two clinical models to predict pulmonary embolism. They found that the area under a fitted receiver operating characteristic curve for both models tested decreased significantly when applied to inpatients in comparison to outpatient [21]. The CDR we used originally divided patients into 3 groups (CDR-score < 2, 2-6 and > 6) with an observed incidence of pulmonary embolism of 3.6%, 30% and 66.7%, respectively [6]. In the present study the CDR was dichotomized. Fourty-eight percent of the hospitalized patients had an unlikely CDR-score with an observed incidence of pulmonary embolism of 15%. This incidence in patients with a likely CDR-score was 35%. In addition, in patients diagnosed with pulmonary embolism 29% had an unlikely CDR-score and 71% a likely CDR-score. This suggests that the dichotomized CDR used in the present study is of diagnostic value, although the CDR with 3 categories is more capable to identify patients with low or high risk of pulmonary embolism, as is shown in table 2. Interestingly, in outpatients the incidence of pulmonary embolism was 12% in patients with an unlikely CDR-score and 40% in patients with a likely CDR-score, which suggests that the ability of the CDR to distinguish between patients with an unlikely or likely risk of pulmonary embolism does not differ between hospitalized patients and outpatients. Future studies may be necessary to improve the diagnostic accuracy of clinical assessment in hospitalized patients.

Several studies have shown that the contribution of a normal D-dimer concentration in excluding venous thromboembolism in hospitalized patients is limited due to the low prevalence of a normal test result (6-19%) and low specificity [20-46%] [9-11, 22]. In our diagnostic algorithm D-dimer was normal in one-fifth of patients with an unlikely CDR-score. Most of the hospitalized patients with an unlikely CDR-score had elevated D-dimer concentrations, which could be attributed in part to the large number of hospitalized patients who had either undergone recent surgery or were known to have malignant disease. In spite of this low yield of normal D-dimer tests, we believe that in hospitalized patients presenting with suspected pulmonary embolism it remains relevant to start the diagnostic work-up by performing two easy and inexpensive tests. The advantage is that CT scanning (and radiation) can be avoided. The counterpart is that D-dimer testing costs time and the diagnosis can be delayed. However, when there is a clinical suspicion of pulmonary embolism anticoagulant treatment can be started while awaiting the results of the diagnostic strategy. By calculating the CDR-score

(with the variables obtained by the history of the patient and physical examination) in all 605 hospitalized patients and measuring the D-dimer concentration in 291 hospitalized patients with an unlikely CDR-score, a total of 60 patients could be withheld from helical CT testing and pulmonary embolism was safely excluded (approximately 10% of all hospitalized patients).

Many studies have assessed the clinical validity of a negative CT in patients with suspected pulmonary embolism, but the incidence rate of venous thromboembolic events in untreated patients with negative CT's varies [7, 12, 23-25]. More recent studies show that CT in combination with compression ultrasonography can be used safely to rule out pulmonary embolism (VTE incidence 0.7%-1.8%; upper 95% CI 3.3%-3.9%) [7,12,24,25]. Our study shows that it is safe to withhold anticoagulant treatment in hospitalized patients with a normal CT as the sole imaging technique. Another advantage of helical CT is the possibility of finding an explanation for the complaints, other than pulmonary embolism, i.e. an alternative diagnosis. In the present study, an alternative diagnosis was suggested in 40% of the hospitalized patients who underwent CT-scanning, which was more frequent than in outpatients. Recently it has been suggested that, especially in patients with a low clinical probability of pulmonary embolism, the positive predictive value of CT might be rather low (58%; 95% CI 40%-73%) [26]. This may overestimate the incidence of pulmonary embolism in our patients. However, the frequency of pulmonary embolism in our cohort was 25%, which is comparable to previous studies using pulmonary angiography [5].

Although this is the largest cohort of hospitalized patients with suspected pulmonary embolism studied so far, the limited number of hospitalized patients with an unlikely CDR-score and normal D-dimer is the major limitation of this study. As a result, in spite of no observed venous thromboembolic events during follow-up, the upper limit of the 95% confidence limit of this observation is 6.7%, which may be consider too high.

In conclusion, the results of the studied simple and fast diagnostic strategy in hospitalized patients show that pulmonary embolism appears to be safely excluded by an unlikely CDR-score in combination with a normal D-dimer concentration, although not frequently observed. By using this diagnostic strategy approximately 10% of the hospitalized patients will not need helical CT to exclude pulmonary embolism. Before clinical implementation of this strategy it is important to confirm the safety of this combination by further studies. The clinical decision rule for pulmonary embolism in hospitalized patients should be improved. If a helical CT is performed and does not show pulmonary embolism, it is safe to withhold anticoagulant treatment.

REFERENCES

1. Zakai NA, Wright J, Cushman M. Risk factors for venous thrombosis in medical inpatients: validation of a thrombosis risk score. J Thromb Haemost 2004, 2(12):2156-2161.
2. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? J R Soc Med 1989, 82(4):203-205.
3. Baglin TP, White K, Charles A. Fatal pulmonary embolism in hospitalised medical patients. J Clin Pathol 1997, 50(7):609-610.
4. Palareti G, Leali N, Coccheri S et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet 1996, 348(9025):423-428.
5. 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.
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. 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.
8. Ten Wolde M, Hagen PJ, Macgillavry MR, et al. Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism; results of a management study. J Thromb Haemost 2004, 2(7):1110-1117.
9. Miron MJ, Perrier A, Bounameaux H, de Moerloose P, Slosman DO, Didier D, Junod A. Contribution of noninvasive evaluation to the diagnosis of pulmonary embolism in hospitalized patients. Eur Respir J 1999, 13(6):1365-1370.
10. Rathbun SW, Whitsett TL, Vesely SK, Raskob GE. Clinical utility of D-dimer in patients with suspected pulmonary embolism and nondiagnostic lung scans or negative CT findings. Chest 2004, 125(3):851-855.
11. Brotman DJ, Segal JB, Jani JT, Petty BG, Kickler TS. Limitations of D-dimer testing in unselected inpatients with suspected venous thromboembolism. Am J Med 2003, 114(4):276-282.
12. van Strijen MJ, de Monye W, Schiereck J, Kieft GJ, Prins MH, Huisman MV, Pattynama PM. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. Ann Intern Med 2003, 138(4):307-314.
13. 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.
14. Roy PM, Colombet I, Durieux P, Chatellier G, Sors H, Meyer G. Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism. Bmj 2005, 331(7511):259.
15. van Belle A, 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.
16. Chagnon I, Bounameaux H, Aujesky D, et al. Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism. Am J Med 2002, 113(4):269-275.
17. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998, 129(12):997-1005.
18. Sanson BJ, Lijmer JG, Mac Gillavry MR, Turkstra F, Prins MH, Buller HR. Comparison of a clinical probability estimate and two clinical models in patients with suspected pulmonary embolism. ANTELOPE-Study Group. Thromb Haemost 2000, 83(2):199-203.
19. Miniati M, Bottai M, Monti S. Comparison of 3 clinical models for predicting the probability of pulmonary embolism. Medicine (Baltimore) 2005, 84(2):107-114.
20. 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.

21. Ollenberger GP, Worsley DF. Effect of patient location on the performance of clinical models to predict pulmonary embolism. Thromb Res 2005.

22. Schrecengost JE, LeGallo RD, Boyd JC, Moons KG, Gonias SL, Rose CE, Jr., Bruns DE. Comparison of diagnostic accuracies in outpatients and hospitalized patients of D-dimer testing for the evaluation of suspected pulmonary embolism. Clin Chem 2003, 49(9):1483-1490.

23. Quiroz R, Kucher N, Zou KH, Kipfmueller F, Costello P, Goldhaber SZ, Schoepf UJ. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review. Jama 2005, 293(16):2012-2017.

24. Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet 2002, 360(9349):1914-1920.

25. Perrier A, Roy PM, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med 2004, 116(5):291-299.

26. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 2006, 354(22):2317-2327.

Chapter 6

ACCURACY OF CLINICAL DECISION RULE, D-DIMER AND SPIRAL COMPUTED TOMOGRAPHY IN PATIENTS WITH MALIGNANCY, PREVIOUS VENOUS THROMBOEMBOLISM, COPD OR HEART FAILURE AND IN OLDER PATIENTS WITH SUSPECTED PULMONARY EMBOLISM

Maaike Söhne, Marieke J.H.A. Kruip, Mathilde Nijkeuter,
Lidwine W. Tick, Hanneke Kwakkel, Stijn J.M. Halkes, Menno V. Huisman
and Harry R. Büller, on behalf of the Christopher Study Investigators

Journal of Thrombosis and Haemostasis 2006; 4: 1042–6.

ABSTRACT

Background The diagnostic work-up of patients with suspected pulmonary embolism (PE) has been optimized and simplified by the use of clinical decision rules (CDR), D-dimer testing and spiral computed tomography (s-CT). Whether this strategy is equally safe and efficient in specific subgroups of patients is evaluated in this study.

Methods A diagnostic strategy including a CDR, D-dimer test and s-CT was evaluated in patients with malignancy, previous venous thromboembolism (VTE), chronic obstructive pulmonary disease or heart failure and in older patients. PE was ruled out by either an unlikely CDR and a normal D-dimer or a s-CT negative for PE. The safety of these tests was assessed by the 3-month incidence rate of symptomatic VTE in those without PE at baseline. The efficiency was evaluated by calculating the numbers needed to test for the different subgroups.

Results The venous thromboembolic incidence rate after the combination of an unlikely CDR and a normal D-dimer varied from 0% (95% CI: 0–7.9%) in the 482 patients older than 75 years of age to 2% (95% CI: 0.05–10.9%) in the 474 patients with a malignancy. For s-CT these incidences varied from 0.3% to 1.8%. The number needed to test in order to rule out one patient from PE with the studied strategy was highest in cancer patients and in the elderly patients (approximately 10).

Conclusion It appears to be safe to rule out PE by either the combination of an unlikely CDR and a normal D-dimer or by a negative s-CT in various subgroups of patients with suspected PE. However, the clinical usefulness of the CDR in combination with the D-dimer as the initial step in the diagnostic process varied among these patient groups.

INTRODUCTION

The main problem in the diagnostic work-up of patients with pulmonary embolism (PE) is the low incidence of PE among those who present with a clinical suspicion of this disease [1,2]. As a consequence of this low incidence, the diagnostic yield of imaging tests is low. Because most imaging techniques for PE have a high radiation dose, use contrast materials, require expertise to interpret and are costly, it is not desirable that all patients with suspected PE immediately undergo imaging. For this purpose a clinical decision rule (CDR) combined with D-dimer testing is frequently used as the first-line method to rule out PE. With these tests approximately 30% of the suspected population can be safely withheld from further diagnostic work-up [3–5]. Although the CDR and D-dimer test have been investigated in various algorithms to exclude PE [6], there is a continuing debate about the safety and diagnostic efficiency of these tests for specific subgroups, such as those with malignancy, previous venous thromboembolism (VTE), chronic obstructive pulmonary disease (COPD) or heart failure and older patients [7–10]. For example, higher incidence of PE in cancer patients and in the elderly can decrease the negative predictive value and thus the safety, while comorbidity may reduce the efficiency because of more frequently abnormal D-dimer results than in patients without those conditions [11]. Spiral computed tomography (s-CT) is increasingly used as the imaging technique of choice in patients with suspected PE. Several large management studies have shown that s-CT followed by ultrasonography of the legs is safe to rule out PE [12–14]. Recently it has been suggested that a s-CT negative for PE without the use of lower-limb ultrasonography might be safe as well [15]. Again, the accuracy and diagnostic yield in the various subgroups is not well studied.

We recently completed a large outcome study that evaluated the safety of a diagnostic strategy using the combination of a CDR and D-dimer test followed by s-CT in 3306 patients referred with clinically suspected PE [16]. The aim of this analysis was to evaluate the safety and clinical usefulness of this strategy in the different subgroups with malignancy, previous VTE, COPD or heart failure, and older age.

METHODS

This study was part of a large management study in 12 teaching hospitals in the Netherlands, evaluating a diagnostic algorithm consisting of a CDR, D-dimer assay and s-CT within 24 hours [16].

Patients were included between November 2002 and August 2004. The Institutional Review Boards of all participating hospitals approved the study protocol.

Study participants

Consecutive patients with clinically suspected PE and a malignancy, previous VTE, COPD, heart failure or an age over 75 years were included in this analysis. Exclusion criteria were: treatment with therapeutic doses of unfractionated or low-molecular-weight heparin (LMWH) for more than 24 h, life expectancy of less than 3 months, pregnancy, geographic inaccessibility precluding follow-up, age below 18 years, allergy to intravenous contrast agents, previous participation in the study or hemodynamic instability.

Diagnostic algorithm

Patients with clinically suspected PE were evaluated by an attending physician using a validated CDR (Table 1) [3]. PE was considered unlikely if the CDR score was ≤ 4 points, and considered likely if the CDR score > 4 points. In patients with a CDR indicating PE unlikely, a D-dimer concentration was measured, using either the Vidas D-dimer assay (Biomerieux, Marcy L'Etoile, France) or the Tina-quant assay (Roche Diagnostica, Mannheim, Germany). A D-dimer concentration of ≤ 500 ng mL was defined as normal. In patients with an unlikely CDR and a normal D-dimer concentration, the diagnosis of PE was considered excluded and anticoagulant treatment was withheld. All other patients underwent s-CT.

Spiral-CT was performed using either single-slice or multislice detector systems according to the protocol as described in the original study 16. Patients with confirmed PE on s-CT received LMWH or unfractionated heparin, followed by vitamin K antagonists, according to local practice. In patients without PE, the presence or absence of an alternative diagnosis was recorded and anticoagulant treatment was withheld. The management of patients in whom the s-CT could not be performed or who had a non-conclusive s-CT scan was left to the discretion of the attending physician.

TABLE 1 Clinical decision rule (CDR) according to Wells et al.[3]. Score ≤ 4: unlikely probability of pulmonary embolism (PE); score > 4: likely probability of PE

Variable	points
Clinical signs and symptoms of deep vein thrombosis (minimum of leg swelling and pain with palpation of the deep veins)	3
Alternative diagnosis less likely than pulmonary embolism	3
Heart rate > 100/min	1.5
Immobilization (> 3 days) or surgery in previous 4 weeks	1.5
Previous pulmonary embolism or deep vein thrombosis	1.5
Hemoptysis	1.0
Malignancy (receiving treatment, treated in the last 6 months or palliative)	1.0

Follow-up

Follow-up consisted of a hospital visit or telephone interview at 3 months. In addition, patients were instructed to contact the study center or their general practitioner immediately in case of complaints suggestive of deep venous thrombosis (DVT) or PE. At each visit information was obtained on complaints suggestive for VTE and use of anticoagulants. In case of clinically suspected DVT or PE, appropriate objective tests (compression ultrasound for suspected DVT, ventilationperfusion scintigraphy or s-CT for suspected PE) were required to confirm or refute the diagnosis. In case of death, information was obtained from the general practitioner, from the hospital records or from autopsy.

Outcome

The primary outcome of the study was the incidence of symptomatic venous thromboembolic events during 3 months follow-up, defined as fatal PE, non-fatal PE or DVT. An independent adjudication committee, members of which were unaware of the results of the diagnostic algorithm, evaluated all suspected venous thromboembolic events and deaths. A diagnosis of PE or DVT was made, based on a priori defined and generally accepted criteria 17. Deaths were classified as being because of PE in case of confirmation by autopsy, in case of an objective positive test for PE prior to death, and if PE could not be confidently excluded as the cause of death.

Statistical analysis

Separate analyses were performed for the patient subgroups with malignancy, with previous VTE, COPD, heart failure and patients older than 75 years of age. The incidences of symptomatic VTE confirmed by objective testing were calculated for the group of patients

in whom anticoagulant treatment was withheld based on (i) a classification of PE unlikely by CDR and a normal D-dimer or (ii) a s-CT scan that excluded PE. Exact 95% confidence intervals (CI) were calculated around the observed incidences using StatXact software, version 5. Descriptive parameters were calculated using SPSS software, version 11.5 (SPSS, Inc., Chicago, IL, USA).

To be able to compare the clinical usefulness of the CDR and D-dimer for the different subgroups, the proportion of useful test results and the number needed to test (NNT) to rule out one PE were calculated. The proportion of useful test results is the number of true negative tests divided by all other test results. In order to calculate the NNT for every subgroup the inverse of this proportion was used.

RESULTS

Study population

The overall study population consisted of 3306 patients with a mean age of 53 years, 82% of whom were outpatients 16. The three subgroups of patients with malignancy, with previous VTE, and older than 75 years of age all consisted of approximately 480 patients, while 341 patients had COPD and 243 patients had heart failure at presentation (Table 2).

The proportion of outpatients was approximately 70% in all subgroups, except for those patients with previous VTE where this figure was 89% (Table 2). The incidence of confirmed PE varied from 16.5% in those with heart failure to 27.4% in those with cancer.

TABLE 2 Baseline characteristics of the overall study population and the different clinical subgroups with suspected PE

	Overall study population	Malignancy	Previous VTE	COPD	Heart failure	Age > 75 years
n (%)	3306	474 (14)	480 (15)*	341 (10)	243 (7)	482 (15)
Female (*n*) (%)	1896 (57)	250 (53)	157 (61)	171 (50)	134 (55)	274 (57)
Mean age (years) (SD)	53 (18.4)	63 (14.4)	55 (18.4)	65 (14.5)	72 (14.5)	82 (5.4)
Outpatient (*n*) (%)	2701 (82)	318 (67)	427 (89)	239 (70)	165 (68)	329 (68)
Overall PE incidence	674 (20)	130 (27)	129 (27)	62 (18)	40 (17)	131 (27)
Lost to follow-up (*n*)	4	0	1	0	0	0
Number of patients receiving anticoagulants for reasons other than VTE	98	10	36	16	22	26

*Two hundred and fifty-nine of the 480 patients (54%) with previous venous thromboembolism (VTE) had previous pulmonary embolism (PE).
COPD, chronic obstructive pulmonary disease.

Results of the combination of CDR and DD test

The proportion of patients with the combination of an unlikely CDR score and a normal D-dimer concentration varied in the different subgroups (Table 3). In patients with a malignancy and patients older than 75 years of age this figure was approximately 10%. Hence, the number of patients that needed to be tested to rule out one PE was around 10, whereas for the other three subgroups this figure was about half and the proportion with an unlikely CDR and normal DD was consequently higher. The incidence of venous thromboembolic events during the 3 months of follow-up in the various studied subgroups was similar and comparable to the overall study population. There was no difference between the two different D-dimer tests used.

TABLE 3 Diagnostic performance of an unlikely clinical decision rules (CDR) in combination with a normal D-dimer (DD) in the overall study population and the different clinical subgroups with suspected PE

	Total study population	Malignancy	Previous VTE	COPD	Heart failure	Age > 75 years
n (% of total)	3306	474 (14)	480 (14)	341 (10)	243 (7)	482 (15)
CDR unlikely (*n*) (%)	2206 (67)	241 (51)	185 (39)	213 (63)	159 (65)	278 (58)
D-dimer (DD) normal (*n*) (%)	1142 (35)	55 (12)	128 (27)	90 (26)	45 (19)	52 (11)
CDR unlikely and normal DD (*n*) (%)	1057 (32)	49 (10)	95 (20)	77 (23)	43 (18)	47 (10)
VTE incidence during FU (*n*) (%; 95% CI)	5 (0.5; 0.2–1.1)	1 (2.0; 0.05–10.9)	1 (1.1; 0.03–5.7)	1 (1.3; 0.03–7.0)	0 (0; 0–8.2)	0 (0; 0–7.9)
NNT for one negative (95% CI)	3.1 (3.0–3.3)	10 (7.5–12.6)	5.1 (4.2–6.1)	4.4 (3.7–5.4)	5.7 (4.3–7.5)	10.6 (7.9–13.5)

COPD, chronic obstructive pulmonary disease; FU, follow up; NNT, number needed to test; VTE, venous thromboembolism; DD, D-dimer.

Results of s-CT in the different subgroups

Of the 417 s-CT scans performed in patients with malignancy, 286 (69%) ruled out PE (Table 4). In the remaining 31% of the performed s-CT scans PE was confirmed, therefore 3.3 scans have to be carried out to detect one PE. Five patients with a s-CT result negative for PE returned with symptomatic venous thromboembolic events (one DVT, one non-fatal PE and three fatal PE) during the 3 months of follow-up. Two of the patients with fatal PE died suddenly during immobilization because of severe pain and weakness on days 18 and 30, respectively, while the third patient died 75 days after inclusion. This latter patient was diagnosed with a pericarditis carcinomatosa. Hence, the VTE incidence after a s-CT without PE in this subgroup was 1.8% (95% CI: 0.6–4.0%). This incidence is comparable to the total study population (1.3%; 95% CI: 0.8–2.1%). For the other studied subgroups both the incidences of VTE during follow-up and the number of tests needed to find one PE were comparable (Table 4). Moreover, there was no difference between the patients who underwent single-slice or multi-slice s-CT.

The percentages of alternative diagnoses varied in the different patient groups. The lowest proportion of alternative diagnoses was shown in the group with patients who had experienced previous VTE (24% of all performed s-CT scans) and the highest percentages were observed in patients with malignancy or COPD: 42% and 50%, respectively. The most frequent pulmonary abnormalities were consolidation and pleural fluid (data not shown).

TABLE 4 Diagnostic performance of spiral computed tomography (s-CT) in the overall study population and in the different clinical subgroups with suspected PE

	Total study population	Malignancy	Previous VTE	COPD	Heart failure	Age >75 years
Performed s-CT scans (*n*)	2199	417	378	258	193	422
PE ruled out by s-CT (*n*) (%)	1505 (67)	286 (69)	249 (66)	196 (76)	153 (79)	289 (68)
Normal *n* (%)	803 (37)	109 (26)	157 (42)	80 (31)	78 (40)	135 (32)
Alternative diagnosis (*n*) (%)	702 (32)	177 (42)	89 (24)	116 (50)	75 (39)	154 (36)
PE confirmed by s-CT (*n*) (%)	674 (31)	129 (31)	129 (34)	62 (24)	40 (21)	131 (31)
Inconclusive s-CT (*n*)	20	2	3	0	0	2
VTE incidence during FU after s-CT ruled out PE (*n*) (%; 95% CI)	19 (1.3; 0.8–2.1)	5 (1.8; 0.6–4.0)	2 (0.8; 0.1–2.9)	2 (1.0; 0.1–3.6)	2 (1.3; 0.2–4.6)	1 (0.3; 0.01–1.9)
NNT to find one positive s-CT (95% CI)	3.2 (3.1–3.5)	3.3 (2.8–3.8)	2.9 (3.3–2.6)	4.2 (3.4–5.2)	4.8 (3.7–6.4)	3.2 (2.8–3.7)

COPD, chronic obstructive pulmonary disease; FU, follow up; NNT, number needed to test; VTE, venous thromboembolism; PE, pulmonary embolism.

DISCUSSION

This study demonstrates that the combination of an unlikely CDR and a normal D-dimer appears to have a similar safety in excluding PE irrespective of the presence of malignancy, previous VTE, COPD, heart failure or older age. However, the proportion of patients with normal results varied and was lowest in those with malignancy and in older patients (approximately 10%). In the other studied subgroups these proportions were approximately twice as high. Consequently, the number of tests needed to rule out one PE was highest in the cancer subgroup and the elderly.

With respect to the negative predictive value of a s-CT without PE for subsequent VTE in the 3 months of follow-up, this appeared to be comparable to the overall study population. The number of s-CT required to have one CT indicating the presence of PE varied from three to five, with the lowest diagnostic yield in those with heart failure.

Although both the combination of an unlikely CDR and normal D-dimer and a s-CT negative for PE appear to be safe in the various subgroups, as described above, it should be noted that the 95% CI of the VTE incidences are sometimes wide owing to the relatively small number of patients in each subgroup. Therefore, safety data have to be considered with caution.

What are the clinical interpretations of these findings? Firstly, the subsequent risk of VTE in those ruled out from PE with an unlikely CDR and a normal D-dimer concentration appears to be similar for the various subgroups. Therefore, the diagnostic yield dominates in the decision of whether or not to use these tests. For the subgroups of patients with previous VTE, COPD or heart failure the NNT is close to that in the overall study population (4.4–5.7 vs. 3.1, respectively), indicating that these tests are clinically useful in managing these patients. However, for the malignancy subgroup and the elderly population the numbers needed to test to rule out PE are higher. Considering the low diagnostic yield of tests in these groups, two approaches are possible. If the existing diagnostic strategy includes an upfront CDR and D-dimer assay this seems useful to do, even in patients with a malignancy, as a CT scan can be prevented at least in one out of every ten patients tested and a D-dimer test is convenient, easy and inexpensive. On the other hand, if the clinical setting is more imaging-oriented and D-dimer results are not readily available, it might be more efficient to directly proceed to s-CT. Moreover, the consequence of the high NNT to rule out one PE with CDR and D-dimer is also reflected in the small improvement in the diagnostic yield of the CT. The incidence of PE in the malignancy subgroup was 27% (Table 2). If s-CT had been performed directly in all these patients, 3.7 scans would have had to be performed to find one positive. With the use of CDR and D-dimer the incidence of PE in the patients who underwent s-CT increased to 31%, leading to 3.3 s-CT scans to be performed for one PE (Table 4). Thus, the increase in diagnostic yield if CDR and D-dimer are included in the diagnostic work-up in the malignancy subgroup is small. However, it is based on the assumption that the diagnostic yield of s-CT includes only the confirmation of PE, while the presence or absence of an alternative diagnosis might be at least as informative.

In conclusion, ruling out PE by either the combination of an unlikely CDR and a normal D-dimer or by a s-CT negative for PE appears safe for subgroups of suspected PE patients with malignancy, previous VTE, COPD or heart failure and in elderly patients. Judgement on the threshold for clinical usefulness of the CDR in combination with the D-dimer as the initial step in the diagnostic process not only depends on the NNT to rule out one PE, but also on the clinical setting.

REFERENCES

1 Lee AY, Hirsh J. Diagnosis and treatment of venous thromboembolism. Annu Rev Med 2002; 53: 15–33.

2 The PIOPED investigators. 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: 2753–9.

3 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: 416–20.

4 Kruip MJ, Slob MJ, Schijen JH, van der Heul C, Büller 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: 1631–5.

5 Ten Wolde M, Hagen PJ, Macgillavry MR, et al. Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism; results of a management study. J Thromb Haemost 2004; 2: 1110–7.

6 Kruip MJ, Leclercq MG, van der Heul C, Prins MH, Büller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med 2003; 138: 941–51.

7 Lee AY, Julian JA, Levine MN, et al. Clinical utility of a rapid whole-blood D-dimer assay in patients with cancer who present with suspected acute deep venous thrombosis. Ann Intern Med 1999; 131: 417–23.

8 ten Wolde M, Kraaijenhagen RA, Prins MH, Büller HR. The clinical usefulness of D-dimer testing in cancer patients with suspected deep venous thrombosis. Arch Intern Med 2002; 162: 1880–4.

9 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: 357–61.

10 Brotman DJ, Segal JB, Jani JT, Petty BG, Kickler TS. Limitations of D-dimer testing in unselected inpatients with suspected venous thromboembolism. Am J Med 2003; 114: 276–82.

11 Kelly J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. Arch Intern Med 2002; 162: 747– 56.

12 van Strijen MJ, de Monye W, Schiereck J, et al. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. Ann Intern Med 2003; 138: 307–14.

13 Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet 2002; 360: 1914–20.

14 Perrier A, Roy PM, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med 2004; 116:291–9.

15 Perrier A, Roy PM, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med 2005; 352: 1760–8.

16 The Christopher Study Group. Safety of a diagnostic algorithm combining clinical probability, D-dimer testing and spiral CT in patients with clinically suspected pulmonary embolism. JAMA 2006; 295: 172–9.

17 Büller HR, Davidson BL, Decousus H, et al; Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003; 349: 1695–702.

Chapter 7

OBSERVER VARIABILITY IN THE ASSESSMENT OF CLINICAL PROBABILITY IN PATIENTS WITH SUSPECTED PULMONARY EMBOLISM

Monique G.L. Leclercq, Marieke J.H.A. Kruip, Melvin R. Mac Gillavry, M. Van Marwijk Kooy, Harry R. Büller

Journal of Thrombosis and Haemostasis 2004; 2: 1204–6.

Assessment of the clinical pretest probability in patients with clinically suspected pulmonary embolism (PE), based on clinical judgement alone (further referred to as 'clinical probability estimate') or a structured prediction model, in order to guide further diagnostic testing has aroused new interest. Wells and colleagues derived a clinical model based on information from the medical history, physical examination, blood gas analyses, chest X-ray, electrocardiography and the likelihood of an alternative diagnosis[1]. This model was subsequently simplified[1,2]. These models have now successfully been applied in several management studies in patients with suspected PE[3–5].

However, the diagnostic accuracy of the clinical probability assessment in previous studies varied significantly [1–4,6]. The reason for this observed heterogeneity in test accuracy is not fully explained. An important determinant of test accuracy is its reproducibility, which so far has not been studied. We therefore evaluated the interobserver variability of the original clinical probability assessment using a previously described structured clinical model. In addition, we compared the results of the clinical model with those of the clinical probability estimate in the same patient as assessed by the same physician.

The investigation was performed within the framework of a management study in a large teaching hospital, in which the outcome of the clinical probability was used in combination with a D-dimer test to guide further diagnostic and therapeutic management[4]. In consecutive in- and outpatients with clinically suspected PE, clinical probability was assessed by two independent physicians using an estimate and a structured clinical model as described by Wells and colleagues (further referred to as `extended clinical model') with the classification of low, moderate or high probability of PE[1]. After completion of the study, the obtained information was used to calculate the result (low, moderate or high and unlikely or likely probability) of the simplified clinical model, as described by Wells and colleagues[2]. The primary analysis was performed in the patient group with a duplicate assessment of the clinical probability of PE using the extended and simplified clinical model. The agreement between distinct observers was expressed by a weighted kappa (κ). A weighted κ value of 1 corresponds to perfect agreement, 0 to agreement as expected by chance. We also calculated a weighted κ for the agreement between the results of the extended clinical model and the clinical probability estimate.

In a total of 45 consecutive patients independent, duplicate assessments of the clinical pretest probability of PE using the clinical model were available for analyses. Of the 45 patients, 13 had the diagnosis of PE established according to the studyprotocol, i.e. a prevalence of 29%. The mean age of the study population was 56 years (range 19–89 years), 66% was female and 89% were outpatients.

In 38 of the 45 study patients various items in the extended structured clinical model were completed differently. This resulted in a different category of clinical probability in 14 patients.

The κ value of the duplicate scores of clinical probability was 0.54 [95% confidence interval (CI) 0.28 - 0.80]. The weighted κ value for low and moderate grouped together was 0.48 (95% CI 0.03 - 0.93). The discrepancies included a different score for the presence or absence of dyspnea or worsening of chronic dyspnea (14 patients), nonpleural chest pain (14 patients), likelihood of an alternative diagnosis (12 patients), risk factors for venous thromboembolism (9 patients), pleural chest pain (8 patients), interpretation of chest X-ray (8 patients), temperature between 37.8 and 38.6 °C (8 patients), heart rate > 90 min^{-1} (6 patients), pleural rub (5 patients) and leg symptoms suspicious for deep vein thrombosis (4 patients).

Using the simplified model, duplicate assessment in the categories low, moderate and high, resulted in a different category in 11 patients with a κ value of 0.6 (95% CI 0.34 - 0.85). These differences were mainly due to a different score for the likelihood of an alternative diagnosis (8 patients). The weighted κ value for low and moderate grouped together was 0.54 (95% CI 0.01 - 1.07). Of the 45 patients the duplicate assessment in the categories unlikely/likely resulted in a different category in six patients, κ value 0.66 (95% CI 0.41 - 0.91). These differences were mainly due to a different score with respect to an alternative diagnosis (5 patients).

In 31 unselected patients the attending physicians completed the clinical probability of PE as assessed both by the clinical model and by estimating the overall likelihood of PE using the same information from medical history and physical examination. The clinical probability was scored differently in 18 patients in the extended clinical model compared with the estimate, resulting in a κ value of 0.23 (95% CI 0.05 - 0.42).

The present investigation shows that the reproducibility of the clinical probability assessment using a structured prediction model is at best moderate in patients with suspected PE. Despite the use of a standardized diagnostic algorithm, it is insufficiently objective to allow for a reproducible outcome by different physicians. This may in part explain the heterogeneity in the reported estimates of test accuracy of the clinical probability in patients with suspected PE.

It is well known that the signs and symptoms associated with PE are seen in many other medical conditions and are therefore non-specific for PE. The presumed advantage of the clinical models over the clinical probability estimate is that they may have less interobserver variability due to the fact that they are based on defined, relatively objective clinical findings. However, we found a significant interobserver variability in the clinical model evaluated. Clinical disagreement was present on all aspects of the model, i.e. regarding the patients' history, physical examination and interpretation of diagnostic tests. Despite the use of standardized case record forms, they were usually completed differently by the two independent physicians. Most of the differences were due to interpretation of features in the patients' history. Some of the questions have to be read properly, i.e. the likelihood of an alternative diagnosis, which is not objective, is very often conclusive for the outcome of the clinical probability in the model.

Components of the patients' history and physical findings which caused most of the differences in the extended model are not present in the simplified model. This resulted in a better κ value for the simplified model (i.e. 0.60), especially for the simplified model with likely and unlikely categories. If the likelihood of an alternative diagnosis had not been incorporated in the simplified model, the reproducibility would even have been better. The κ value of the simplified model with likely and unlikely categories would then be higher than the κ value of 0.66 we observed.

Clinical disagreement over patients' histories is also observed in other studies where clinicians agreed about the history in only 75% of cases[7,8]. It is not less of a problem in the physical examination. The usual κ values for most components of clinical findings are about 0.4–0.6 [9,10]. Some experts have termed these x values `moderate' [11]. The problem of clinical disagreement also extends to the interpretation of diagnostic tests, as is the case for X-rays and ECGs. When two cardiologists examined the same ECG from 38 patients, a κ value of 0.3 was found [12].

The reproducibility of the clinical probability is moderate, but comparable to other clinical examinations used in daily medical practice. The question is, given the observed clinical disagreement about patients' history, physical findings and interpretation of diagnostic tests, whether it is possible to develop a more objective clinical model. Until this has been accomplished, the moderate reproducibility of clinical probability assessment is a limitation of its clinical utility and therefore clinicians should be aware of this when they use it for the assessment of patients.

REFERENCES

1 Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998; 129: 997–1005.

2 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: 416–20.

3 Kruip MJ, Slob MJ, Schijen JHEM, van der Heul C, Büller 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: 1631–5.

4 Leclercq MG, Lutisan JG, van Marwijk Kooy M, et al. Ruling out clinically suspected pulmonary embolism by assessment of clinical probability and D-dimer levels: a management study. Thromb Haemost 2003; 89: 97–103.

5 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: 98–107.

6 Sanson BJ, Lijmer JG, MacGillavry MR, Turkstra F, Prins MH, Büller HR. Comparison of a clinical probability estimate and two clinical models in patients with suspected pulmonary embolism. ANTELOPE Study Group. Thromb Haemost 2000; 83: 199–203.

7 Hall R, Horrocks JC, Clamp SE, De Dombal FT. Observer variation in assessment of results of surgery for peptic ulceration. Br Med J 1976; 1:814–6.

8 Rose GA. Ischaemic heart disease. Chest pain questionnaire. Milbank Mem Fund Q 1965; 43: 32.

9 Aoki N, Horibe H, Ohno Y, Hayakawa N, Kondo R. Epidemiological evaluation of funduscopic findings in cerebrovascular diseases. III. Observer variability and reproducibility for funduscopic findings. Jpn Circ J 1977; 41: 11–7.

10 Cook DJ. Clinical assessment of central venous pressure in the critically ill. Am J Med Sci 1990; 299: 175–8.

11 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 159–74.

12 Blackburn H. The exercise electrocardiogram. Differences in interpretation. Report of a technical group on exercise electrocardiography. Am J Cardiol 1968; 21: 871.

Chapter 8

FURTHER VALIDATION AND SIMPLIFICATION OF THE WELLS CLINICAL DECISION RULE IN PULMONARY EMBOLISM

Nadine S. Gibson, Maaike Söhne, Marieke J.H.A. Kruip,
Lidwine W. Tick, Victor E. Gerdes, Patrick M. Bossuyt,
Philip S. Wells, Harry R. Büller

on behalf of the Christopher Study Investigators

Journal of Thrombosis and Haemostasis 2006, under revision

ABSTRACT

Background The Wells rule is a widely applied clinical decision rule, in the diagnostic work-up of patients with suspected pulmonary embolism (PE). The objective of this study was to validate and simplify this rule.

Methods The clinical probability of PE, the odds ratios for the separate variables and the areas under the ROC curve for the original and two newly derived simplified Wells rules were calculated in 3306 consecutive patients with clinically suspected PE. Furthermore, the safety in ruling out PE in combination with a normal D-dimer test was assessed by comparing the incidence of venous thromboembolism (VTE) during follow-up and the clinical utility by comparing the proportion of patients safely excluded by these combined methods.

Results The discriminative potential of the prediction rule was comparable to that of the original study, although the odds ratios decreased.

The performance of the original and simplified rules was similar with areas under the curve ranging from 0.72 to 0.74.

The VTE incidence at 3 months with the Wells rule (score ≤ 4) and a normal D-dimer was 0.8%. For the modified rule (1 or 2 points per variable, cut-off ≤ 2) and the simplified rule (1 point per variable, cut-off ≤ 1) these incidences were 0.6% and 0.5%, respectively. Proportion of patients safely excluded for PE was 32%, 31% and 30%, respectively.

Conclusions This study further validates the diagnostic utility of the Wells rule and indicates that the scoring system can be simplified to one point for each variable.

INTRODUCTION

The diagnostic work-up of patients with clinically suspected pulmonary embolism is challenging because of the relatively low prevalence of the disease in this population. In the past, several attempts have been made to include clinical information in the diagnostic process in order to rule out pulmonary embolism and withhold expensive and time-consuming imaging techniques without compromising patient's safety. However, the majority of these attempts have not been clinically successful [1-5]. The main concern with these assessments of clinical probability involved the use of many variables including subjective elements as well as the often complicated scoring methods.

The quantitative clinical decision rule (CDR) published by Wells and colleagues in 2000 incorporated 7 items from the medical history and physical examination easily obtained in the initial diagnostic work-up [6]. Because of its relative comprehensiveness and therefore ease of use in a clinical setting this rule is now widely accepted in the exclusion of pulmonary embolism and has been incorporated in several guidelines [7-12]. It was obtained by selecting the most predictive variables for the presence or absence of pulmonary embolism from an extended 40-item list. These variables were initially tested in a univariate regression analysis and those variables that were significant after the stepwise regression analysis were selected for the final rule. According to the value of the odds ratios scoring points of 1, 1.5 or 3 were assigned (Table 1).

However, there is evidence that over time prediction rules may loose their discriminatory power [13-15]. In addition, the different weights given in the Wells rule may make the rule difficult to memorize and could lead to summing mistakes in the acute care setting. We speculated whether a simplified rule would yield similar results.

In order to further validate and possibly simplify the clinical decision rule of Wells and colleagues we used the data of a large management study in consecutive patients with suspected pulmonary embolism [16]. In all patients the clinical decision rule was assessed while the D-dimer test and spiral CT were obtained when indicated. First, we assessed the discriminative power of the rule for the presence of pulmonary embolism and compared this with the original study cohort of Wells et al. Subsequently, the relative contribution of the different elements of the rule was analysed, and we investigated whether the existing scoring system could be simplified.

METHODS

Data were derived from a large prospective diagnostic management study that included patients with clinically suspected pulmonary embolism enrolled between November 2002 and August 2004 in 12 hospitals in the Netherlands [16].

Patients and management

Consecutive in- and outpatients with clinically suspected acute pulmonary embolism were eligible. Patients were excluded if they had received (low molecular weight) heparin for more than 24 hours, were younger than 18 years of age, were pregnant, had a known hypersensitivity for iodinated contrast fluid, had a life expectancy of less than three months or if there was geographic inability for follow-up.

At presentation the CDR of Wells and colleagues was performed in all patients [6]. With a CDR score ≤ 4, pulmonary embolism was considered unlikely and a D-dimer test was performed (Tinaquant, Roche Diagnostica, Mannheim, Germany or Vidas D-dimer, Biomerieux, Marcy L'Etoile, France) [16]. The D-dimer test was defined as normal if the concentration was ≤ 0.5 mg/l. The combination of pulmonary embolism unlikely and a normal D-dimer result was considered to rule out pulmonary embolism and anticoagulant treatment was withheld. These patients were followed up for three months, all other patients underwent spiral CT. The CT scan was considered positive for pulmonary embolism if intraluminal filling defects were present or if a vessel was totally occluded.

In case of clinically suspected venous thromboembolism (VTE) in the three months follow-up period, compression ultrasound for suspected DVT and ventilation-perfusion scintigraphy or CT for suspected pulmonary embolism were required to confirm or refute the diagnosis.

Validation of the Wells clinical decision rule

The original study distinguished three probability categories (low, moderate and high). For purpose of comparison the prevalence of pulmonary embolism in these three probability categories was calculated in the present study cohort and compared with the derivation and validation population of the original study of Wells et al. [6].

Development of the simplified clinical decision rules

Subsequently we recalculated the coefficients of the variables of the Wells rule by fitting a multivariable logistic regression model in our study group. The estimated coefficients and the 95% confidence intervals (CI) were transformed to odds ratios. These odds ratios were compared to the original odds ratios reported by Wells et al. [6].

Rather than using three different sets of points, as in the original Wells rule, we developed a **modified** rule with two sets of points, by assigning two points to the variable with the highest odds ratios and one point to the remaining variables in the model. In addition, a **simplified** rule was developed by assigning only unit weights to all variables in the model.

For all patients in our study, we calculated their score with the modified and the simplified rule. With the simplified rule, for example, a patient receives one additional point for each of the seven variables that is present.

To determine the performance of the two novel rules the area under the Receiver Operating Characteristic (ROC) curve was calculated and compared to the area under the curve of the original Wells rule. ROC curves show the performance of a diagnostic test; the area under the curve of an ideal rule would be 1.00 and that of a useless rule 0.50. The significance for the ROC curves was tested by the method described by Hanley and McNeil [17]. The discriminative power of the novel rules for distinguishing into two pulmonary embolism probability groups was also analysed, using the method described previously [6].

Safety and clinical utility of the different scoring options of the clinical decision rules combined with D-dimer testing

Since the CDR is never used as the only test to rule out pulmonary embolism, the diagnostic safety and utility of the combination of the CDR and the D-dimer test were evaluated. The **safety** of this combination was defined as the observed incidence of symptomatic venous thromboembolic events during the three months of follow-up in patients in whom pulmonary embolism was considered unlikely based on the CDR with a normal D-dimer test result. The clinical **utility** was assessed by calculating the proportion of patients in whom further diagnostic testing could be safely withheld. The safety as well as the clinical utility of these two new simplified scores was compared to the classical CDR score with a dichotomized cut-off score of ≤ 4 for pulmonary embolism unlikely 16.

The 95 % CI for the three month VTE incidence rate for each possible score of the CDR in combination with a normal D-dimer result were calculated. The upper limit of the 95% CI was chosen to be acceptable with a VTE incidence rate below 3.0%.

One cut-off score was chosen leading to a dichotomized rule instead of the classically used three categories in order to increase simplicity.

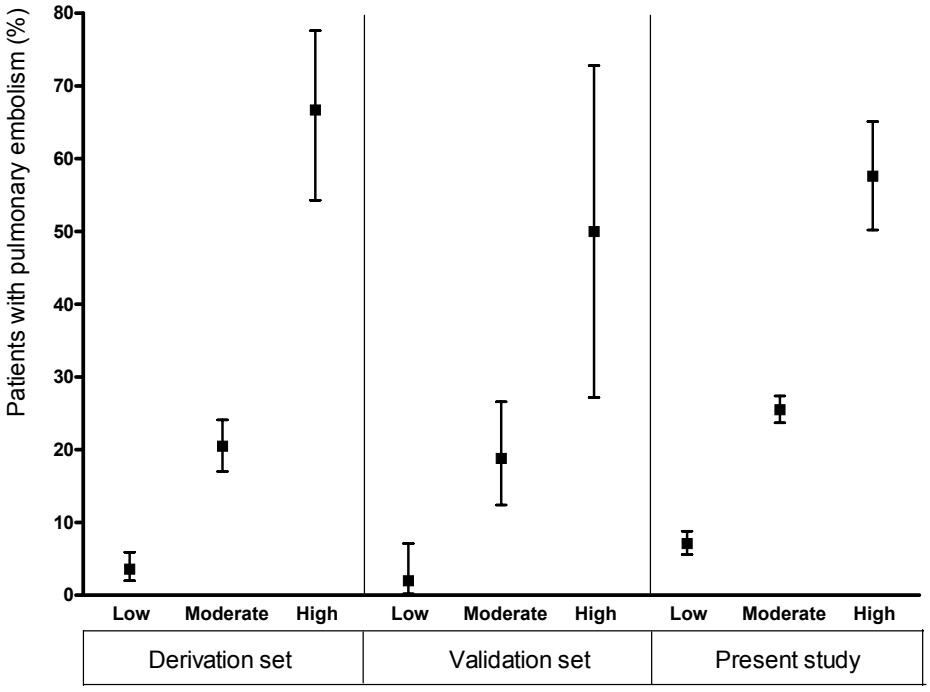
RESULTS

Baseline characteristics

A total of 3306 consecutive patients with clinically suspected acute pulmonary embolism were included in the study of whom 2701 (82%) were outpatients. The mean age of the study cohort was 53 years (range 18 to 110 years). The CDR was available in 3298 patients (99.8%). The variable most frequently observed in the study patients was 'pulmonary embolism is more likely than an alternative diagnosis' (n=2032, 62%). The two variables with the lowest frequency were 'clinical signs and symptoms of DVT' (n=190, 6%) and 'hemoptysis' (n=176, 5%), whereas the other variables varied from 11% (malignancy) to 26% (tachycardia). The prevalence of proven pulmonary embolism in the entire study cohort was 20%.

Of the 2199 patients with an unlikely CDR score according to Wells et al. the D-dimer test result was available in 98%. The D-dimer was positive in 1105 patients.

Figure 1: Prevalence of pulmonary embolism in the low, moderate and high probability groups in the original study [6] (derivation and validation set), as well as in the present study.



Validation of the Wells clinical decision rule

A comparison of the prevalence of pulmonary embolism among the three probability categories between our study population and the derivation and validation population of Wells et al. is shown in Figure 1. The discriminative power of the rule is comparable in the three study populations, although a tendency of the expected regression to the mean is shown.

Development of the simplified clinical decision rules

The second column of Table 1 shows the odds ratios of the CDR variables, generated by multivariable regression analysis, in our dataset as well as the original odds ratios of the study of Wells et al. in the first column. The odds ratios of all included variables are slightly lower in our population compared to the population of Wells et al.

Table 2 details the two new scoring options. In the modified rule two points are assigned to 'clinical signs and symptoms of DVT' and to 'pulmonary embolism is more likely than an alternative diagnosis', whereas in the simplified rule all variables are given one point if present.

TABLE 1: Odds ratios for the variables of the Wells clinical decision rule and those observed in the present study.

		Odds Ratio with 95%CI	
	Variable	**Wells et al. [6]**	**Present study**
1.	Clinical signs & symptoms DVT	5.8	4.3 (3.1-5.9)
2.	Tachycardia (>100/min)	3.0	1.8 (1.5-2.2)
3.	Immobilization or surgery in the previous four weeks	2.5	2.1 (1.7-2.6)
4.	Previous DVT/PE	2.4	1.8 (1.4-2.3)
5.	Hemoptysis	2.4	1.9 (1.3-2.6)
6.	Malignancy	2.3	1.4 (1.1-1.8)
7.	An alternative diagnosis is less likely than PE	4.6	3.6 (2.9-4.5)

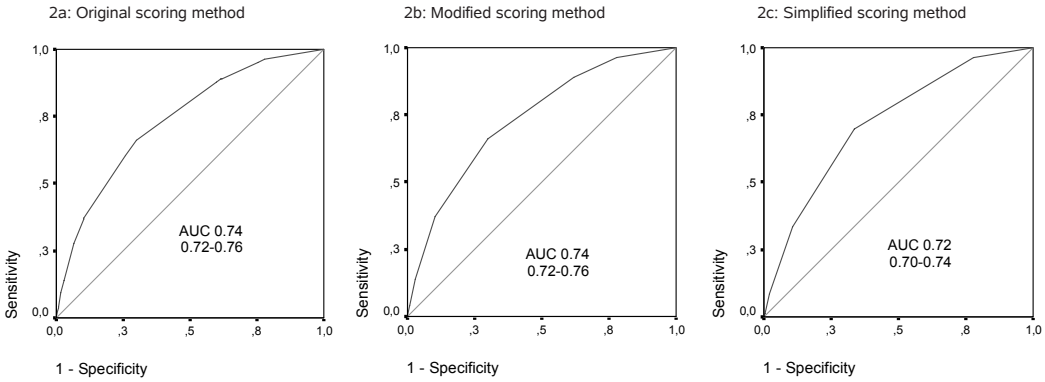
DVT, deep venous thrombosis; PE, pulmonary embolism

TABLE 2: Scoring of the various variables in the original, the modified and simplified Wells rule.

		Original	Modified	Simplified
1.	Clinical signs & symptoms DVT	3	2	1
2.	Tachycardia (>100/min)	1.5	1	1
3.	Immobilization or surgery in the previous four weeks	1.5	1	1
4.	Previous DVT/PE	1.5	1	1
5.	Hemoptysis	1	1	1
6.	Malignancy	1	1	1
7.	An alternative diagnosis is less likely than PE	3	2	1
	Cut-off for PE unlikely	≤ 4	≤ 2	≤ 1

DVT, deep venous thrombosis; PE, pulmonary embolism

FIGURE 2: ROC curves of the original, the modified and simplified Wells scoring method



In Figure 2 the ROC curves of the original scoring method of Wells et al. and the two novel scoring options are depicted. The areas under the curve of the three different scoring methods varied from 0.72 to 0.74 with overlapping 95% confidence intervals. The discriminative power for the three scores is shown in figure 3 and is very similar.

Safety and clinical utility of the different scoring options of the clinical decision rules combined with D-dimer testing

The 3 month incidence of VTE for the dichotomized cut-offs with the two new CDRs in combination with a normal D-dimer test result, were calculated (Table 3). For comparison the results with the original dichotomized Wells score combined with D-dimer, as used in our study, are also shown.

Both the modified rule with a cut off score of ≤ 2 and the simplified rule with a cut-off score of ≤ 1 in combination with a normal D-dimer had similar incidence rates of VTE during follow-up. The efficiency to reliably exclude patients for pulmonary embolism was around 30% for all three scoring options, in combination with a normal D-dimer test.

If the cut-off score of the modified rule was increased to ≤ 3, the 3 month incidence of VTE would have increased to 1.0% (95% CI 0.5% to 1.8%). However, the additional patient group with a score of 3 points consisted of 109 patients of whom 5 patients had VTE (4.6%; 95% CI 2.0% to 10.3%).

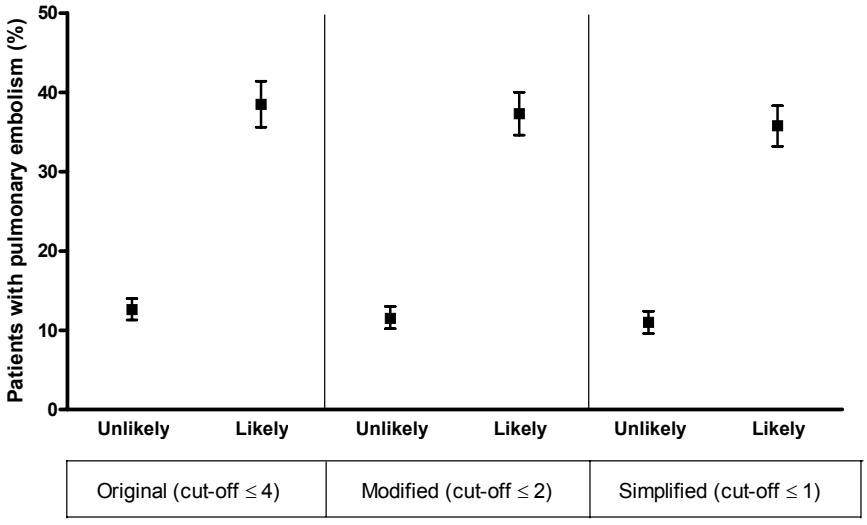
Similarly increasing the cut-off to ≤ 2 in the simplified rule, 6 of 135 patients with a score of 2 points would have had VTE (4.4%; 95% CI: 1.7% to 9.4%).

TABLE 3: Safety and clinical utility of the different scoring options of the clinical decision rules combined with D-dimer testing

	Incidence of VTE during 3 months follow-up	**Proportion of patients in whom spiral CT can be withheld**
Wells ≤ 4 and normal D-dimer	0.8% (95% CI 0.3-1.5%)	32% (95% CI 30-33%)
Modified ≤ 2 and normal D-dimer	0.6% (95% CI 0.3-1.3%)	31% (95% CI 29-32%)
Simplified ≤1 and normal D-dimer	0.5% (95% CI 0.2-1.2%)	30% (95% CI 28-31%)

VTE, venous thrombo-embolic event; CT, computed tomography

Figure 3: Prevalence of pulmonary embolism depicted for the original, the modified and the simplified Wells rule, using pulmonary embolism likely and unlikely categories.



DISCUSSION

Although the literature indicates that shrinkage and regression to the mean is often seen in the life span of prediction rules [18,19], the present analysis shows that the discriminative power of the Wells CDR compares favourably with the original derivation and validation set. The prevalence of thrombosis of 7.1% in the low probability group appears to be slightly higher as compared to the 3.6% and 2.0% in the derivation and validation set respectively, whereas the observed prevalence of 58% in the high probability group is similar to that in the two other sets. Our findings indicate that in general the odds ratios for the seven variables were moderately lower than observed by Wells et al[6]. However, this occurred without affecting the validity of the rule. Moreover, the two most informative variables remained the same i.e. 'alternative diagnosis less likely than pulmonary embolism' and 'clinical signs & symptoms of DVT'.

In the original rule three different weights were assigned to the various variables based on their odds ratios in order to produce a user friendly CDR (Tables 1 and 2). When we simplified this by giving two different weights to the variables, i.e. two points for the two variables with the highest odds ratios and one point to the other variables, little diagnostic information was lost. Most interestingly, when using unit weights, i.e. one point for each variable, in what we call the **simplified rule** the diagnostic accuracy remained unchanged (Fig. 2a, b and c). The simplified Wells rule indicates diagnostic testing is required if any of the variables is present or if the D-dimer test is positive. If no variables are present and the D-dimer test is negative very low rates of VTE during follow-up (0.5%: 95%CI 0.2 to 1.2%) can be expected. With this combination of tests approximately 30% of patients with suspected pulmonary embolism can be safely withheld from further diagnostic imaging techniques, a similar proportion to that observed with the original Wells rule. It should be noted that the cut-off value is the critical factor. If the cut-off in the modified and in the simplified rule was increased by one point, the incidence of VTE during follow-up would be 5% in the added patient group, which is unacceptably high.

As is noted above the present findings indicate that giving different weights to the variables does not improve the diagnostic efficiency of the clinical decision rule. This could be caused by the slight regression to the mean of the odds ratios. Theoretically, the explanations for regression to the mean are diverse. It could be caused by the influence of interobserver variability, differences in interrater reliability and variation in referral pattern [10]. A variable with an overestimated regression coefficient is more likely to be selected for the specific decision rule than an underestimated one. Consequently the selected variables are likely to have too large coefficients [19]. Furthermore, a prediction rule is often validated in the same clinical setting, or even in the same patient group in which the derivation was done. If this group is not representative for the patient population

at large, it may reflect changes in morbidity over time. It is temptative to speculate, why the Wells rule has been widely accepted while previous attempts with sometimes similar variables have failed [1-5, 20]. This could partly be due to the fact that the variables in these rules were too numerous and were complicated by the need for additional tests such as blood gas analysis, electrocardiography or chest X-ray. The strategy of neural networks which are computerized clinical decision rules, popular in the early nineties, was also quickly forgotten, most likely because the networks were perceived to be too complicated [21, 22]. More recently the application of multivariable logistic regression techniques gave more insight into the predictive strength and independency of the signs and symptoms for pulmonary embolism, and therefore reliable diagnostic models could be created which became more appealing to clinicians [3]. The wide acceptance of the Wells rule is possibly due to the inclusion of only seven relevant variables which are simple to obtain at the bedside [23]. The addition of the clinical opinion of the clinician in the subjective variables 'clinical signs and symptoms of DVT' and 'alternative diagnosis less likely than pulmonary embolism' probably further contributed to its popularity.

Several aspects of our study require comment. This study has a retrospective design which implicates that the novel simplified rule has to be validated in a prospective study. However, we included a large cohort of consecutive patients and believe that selection bias is very unlikely, and therefore we expect that a validation study will confirm the present observation. The safety of excluding pulmonary embolism was determined by the subsequent incidence of VTE during the three month follow-up. Using follow-up has increasingly been accepted as an appropriate reference standard for clinical outcome, if some basic methodological principles are adhered to, such as withholding anticoagulant treatment, complete follow-up and appropriate diagnostic work-up in case of suspected recurrence of VTE [24]. We used the combination of an unlikely clinical probability and a normal D-dimer test to rule out pulmonary embolism. It should be noted, that the addition of D-dimer testing is mainly responsible for the low subsequent incidence of VTE during follow-up.

In conclusion we validated the Wells rule and although the odds ratios did diminish slightly, the performance of the rule remained adequate. Simplification of the rule by assigning only one point to each of the seven variables had a similar diagnostic accuracy and clinical utility. This simplified rule requires validation.

REFERENCE LIST

1 Celi A, Palla A, Petruzzelli S, et al. Prospective study of a standardized questionnaire to improve clinical estimate of pulmonary embolism. Chest 1989;95(2):332-7.

2 Hoellerich VL, Wigton RS. Diagnosing pulmonary embolism using clinical findings. Arch Intern Med 1986;146(9):1699-704.

3 Michel BC, Kuijer PM, McDonnell J, van Beek EJ, Rutten FF, Büller HR. The role of a decision rule in symptomatic pulmonary embolism patients with a non-high probability ventilation-perfusion scan. Thromb Haemost 1997;78(2):794-8.

4 Petruzzelli S, Palla A, Citi M, Giuntini C. Improvement of screening for pulmonary embolism with a standardized questionnaire. Respiration 1990;57(5):329-37.

5 Miniati M, Prediletto R, Formichi B, et al. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med 1999;159(3):864-71.

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):416-20.

7 Chunilal SD, Eikelboom JW, Attia J, et al. Does this patient have pulmonary embolism? JAMA 2003;290(21):2849-58.

8 Righini M, Aujesky D, Roy PM, et al. Clinical usefulness of D-dimer depending on clinical probability and cutoff value in outpatients with suspected pulmonary embolism. Arch Intern Med 2004;164(22):2483-7.

9 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.

10 Wolf SJ, McCubbin TR, Feldhaus KM, Faragher JP, Adcock DM. Prospective validation of Wells Criteria in the evaluation of patients with suspected pulmonary embolism. Ann Emerg Med 2004;44(5):503-10.

11 Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected pulmonary embolism. Ann Emerg Med 2003;41(2):257-70.

12 British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax 2003;58(6):470-83.

13 Diamond GA. Future imperfect: the limitations of clinical prediction models and the limits of clinical prediction. J Am Coll Cardiol 1989;14(3 Suppl A):12A-22A.

14 Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15(4):361-87.

15 McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS, for the Evidence-Based Medicine Working Group. Users' Guides to the Medical Literature: XXII: How to Use Articles About Clinical Decision Rules. JAMA 2000;284(1):79-84.

16 Writing Group for the Christopher Study Investigators. Effectiveness of Managing Suspected Pulmonary Embolism Using an Algorithm Combining Clinical Probability, D-Dimer Testing, and Computed Tomography. JAMA 2006;295(2):172-9.

17 Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148(3):839-43.

18 Charlson ME, Ales KL, Simon R, MacKenzie CR. Why predictive indexes perform less well in validation studies. Is it magic or methods? Arch Intern Med 1987;147(12):2155-61.

19 Copas JB. Using regression models for prediction: shrinkage and regression to the mean. Stat Methods Med Res 1997;6(2):167-83.

20 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):92-7.

21 Patil S, Henry JW, Rubenfire M, Stein PD. Neural network in the clinical diagnosis of acute pulmonary embolism. Chest 1993;104(6):1685-9.

22 Wyatt J. Nervous about artificial neural networks? Lancet 1995;346(8984):1175-7.

23 Wyatt JC, Altman DG. Commentary: Prognostic models: clinically useful or quickly forgotten? BMJ 1995;311(7019):1539-41.

24 Kruip MJ, Slob MJ, Schijen JH, van der Heul C, Büller 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):1631-5.

Chapter 9

EVALUATION OF THE AUTODIMER D-DIMER ASSAY FOR THE EXCLUSION OF PULMONARY EMBOLISM

Marieke JHA Kruip, Huub HDM van Vliet,
Peter MT Pattynama, Alice Kars, Anton H van den Meiracker,
Kon-Siong G Jie, Frank WG Leebeek

**Haemostasis and Thrombosis 2006,
accepted in shortened version as letter**

ABSTRACT

Introduction If patients with suspected pulmonary embolism have a normal D-dimer concentration, this diagnosis becomes unlikely. Many D-dimer assays are available with differences in specificity and sensitivity. The aim of the present study is to compare the diagnostic accuracy of a fast and easy to perform D-dimer assay (AutoDimer) with an established D-dimer assay (Vidas).

Materials and Methods In 401 patients with clinically suspected pulmonary embolism D-dimer was measured using both assays.

Results Pulmonary embolism was diagnosed in 92 patients (23%). At a cut-off value of 110 ng/ml, AutoDimer was as accurate as Vidas D-dimer with a sensitivity of 97% (95% CI; 90-99%), negative predictive value of 97% (95% CI; 91-99%), specificity of 32% (95% CI; 27-38%) and positive predictive value of 35% (95% CI; 30-42%). In combination with an unlikely clinical decision rule-score, no venous thrombosis occurred during follow up (failure rate 0%: 95% CI; 0%-5.7%). However, the combination of an unlikely clinical decision rule-score and AutoDimer D-dimer ≤ 110 ng/ml was only present in 20% of the patients.

Conclusion At a cut-off value of 110 ng/ml the AutoDimer is as safe as Vidas D-dimer in excluding pulmonary embolism in symptomatic patients with an unlikely clinical decision rule-score, although less efficient. These results should be validated in a prospective management study.

INTRODUCTION

For diagnosing or excluding pulmonary embolism a diversity of diagnostic tools are available, including validated clinical decision rules (CDR), spiral computed tomography (CT) and D-dimer testing [1-4]. D-dimers, degradation products of cross-linked fibrin, are an indicator of fibrin turnover. If a patient with clinically suspected pulmonary embolism has a normal D-dimer concentration, the diagnosis of pulmonary embolism becomes very unlikely [5,6]. Nowadays most diagnostic strategies use the combination of an unlikely clinical probability assessment and a normal D-dimer concentration to exclude pulmonary embolism in a simple and fast way with a high accuracy [4,7-9]. For this central role the D-dimer assay has to be accurate with a high sensitivity and negative predictive value (NPV). Especially in outpatients the test results should be available to the clinician within a short time frame.

There are many D-dimer assays available, all with their own characteristics and methodology. As a consequence, the test results and cut-off values of the various assays are not interchangeable [5,6,10]. A new D-dimer test, the Biopool AutoDimer is a rapid immunoturbidimetric assay. It has recently been evaluated in patients with suspected deep vein thrombosis (DVT) and found to be accurate in the exclusion of DVT [11]. The accuracy of the AutoDimer in excluding pulmonary embolism has not been established yet.

In this study the diagnostic performances of the AutoDimer was analyzed in comparison to an established D-dimer ELISA method in patients with suspected pulmonary embolism.

MATERIALS AND METHODS

Data were collected as part of a large diagnostic management study that was carried out in 12 teaching hospitals in the Netherlands, evaluating a diagnostic strategy including CDR, D-dimer and spiral CT [4]. Patients were included between November 2002 and August 2004 in our hospital, a large tertiary university referral center. The study protocol was approved by the local medical ethical committee.

Patients

Consecutive patients with clinically suspected pulmonary embolism presenting in the Erasmus University Medical Center, Rotterdam, were eligible for inclusion in this analysis. Patients were excluded if they had received therapeutic unfractionated or low-molecular-weight-heparin for more than 24 hours before inclusion, they were younger than 18 years of age, they were pregnant, they had a known allergy to intravenous contrast agents, they had a life expectancy of less than three months, if a CT scan could not be performed because of overweight, or there was geographic inability for follow-up.

Diagnostic work-up

Using a validated CDR, patients with clinically suspected pulmonary embolism were categorized as pulmonary embolism unlikely (≤ 4 points) or likely (>4 points) [4,12]. In case of an unlikely CDR-score, the D-dimer concentration was measured, using the Vidas D-dimer assay. In case of an unlikely CDR-score and a normal D-dimer concentration, pulmonary embolism was considered excluded and anticoagulant treatment was withheld. Patients with an unlikely CDR-score in combination with elevated D-dimers or patients with a likely CDR-score underwent spiral CT. If spiral CT did not demonstrate pulmonary embolism, anticoagulant treatment was withheld. If the spiral CT demonstrated pulmonary emboli, anticoagulant treatment was initiated. Spiral CT was performed using multi-slice detector systems, as described previously [4].

After completing the diagnostic strategy, patients were instructed to return to the hospital if signs and symptoms of DVT or pulmonary embolism occurred. All patients were followed for 3 months, during which adverse events were recorded and adjucated. If there was a clinical suspicion of DVT or pulmonary embolism, objective tests were performed to confirm or exclude the diagnosis.

D-dimer assays

Before anticoagulant therapy was initiated, blood was collected in 0.105 M sodium citrate. The samples were centrifuged at 2000 g for 10 minutes at 4°C. D-dimer was immediately measured with a quantitative automated ELISA D-dimer assay (Vidas D-Dimer, Biomerieux, Marcy L'étiole, France) with a variation coefficient of 5.8% in the linear range of 45-10.000 ng/ml fibrinogen equivalent units. The cut-off value for a positive test result is 500 ng/ml [4]. The measurements were carried out by technicians, who were unaware of the outcome of the CDR or the spiral CT. Plasma aliquots were stored at -80°C. Samples were thawed at 37°C for measurements of the D-dimer levels with the Biopool Autodimer (Trinity Biotech, Kordia), an immunoturbidimetric assay on a Sysmex coagulation CA-1500 analyzer (Dade-Behring)

with a variation coefficient of 5.4% in the linear range 40-2400 ng/ml D-dimer units. A possible influence of storage on the results was studied by measurement of the D-dimer concentrations in the same randomly selected samples before and after storage.

The AutoDimer was evaluated using two cut-off values; 1) the cut-off value of 189 ng/ml calculated by Gardiner and coworkers in outpatients with suspected DVT [11] and 2) the calculated cut-off value which achieved a NPV similar to Vidas D-dimer in the present study using a receiver-operator characteristic (ROC) curve analysis.

Statistical Analysis

The accuracy parameters (sensitivity, NPV, specificity and positive predictive value (PPV)) of the Vidas D-dimer and of two cut-off values of the AutoDimer were calculated on the basis of the results of the diagnostic strategy. The area under a ROC curve was optimized to obtain the best discrimination between patients who did and did not have a thromboembolic event. ROC curves depict the trade-off in true-positive versus false positive rates as the cut point for defining 'positive' and 'negative' is shifted along the full spectrum of D-dimer values, where an area under the curve of 1.0 would indicate a perfect test. A value of 0.5 would represent a non-informative test. The analysis was performed using SPSS version, 11.5 (SPSS Inc. Illinois, USA).

The exclusion efficacy, i.e. the percentage of patients in whom pulmonary embolism was excluded, was calculated for two situations. First, the exclusion efficacy if pulmonary embolism was excluded by a normal D-dimer concentration as the only test and secondly, the exclusion efficacy if pulmonary embolism was excluded by the combination of an unlikely CDR-score and normal D-dimer concentration.

RESULTS

Eight of the 409 consecutively screened patients with suspected pulmonary embolism were excluded due to lack of stored blood samples. The clinical characteristics are shown in table 1. In 91 patients pulmonary embolism was diagnosed by spiral CT. Pulmonary embolism was excluded in the other 310 patients by either the combination of an unlikely CDR-score and a normal Vidas D-dimer concentration (n = 102, 25%), or by helical CT (n = 205, 34%). In three patients CT was inconclusive and pulmonary embolism was excluded by perfusion scintigraphy. During the 3 month follow-up period one patient developed a DVT after a normal

CT (Vidas D-dimer at presentation 7800 ng/ml). In the present analysis this patient was considered as having pulmonary embolism at the time of the study, hence 92 patients (23%) had pulmonary embolism.

ROC analysis showed comparable results for both tests with estimated AUC of 0.820 for the AutoDimer and 0.821 for the Vidas D-dimer assay (figure 1).

The accuracy parameters of both assays for excluding pulmonary embolism are shown in table 2. The Vidas D-dimer assay had a high NPV and sensitivity. However, two of the 150 patients with pulmonary embolism on spiral CT had a normal D-dimer concentration (≤ 500 ng/ml). The AutoDimer had a NPV of 96% using the cut-off value of 189 ng/ml. Seven of the 150 patients with pulmonary embolism on spiral CT had a D-dimer concentration ≤ 189 ng/ml. Using ROC analysis the calculated cut-off value at which a accuracy similar to Vidas D-dimer was reached with AutoDimer was 110 ng/ml.Three of the 150 patients with pulmonary embolism on spiral CT had a AutoDimer D-dimer concentration ≤ 110 ng/ml.

TABLE 1. Clinical characteristics of the 401 patients with clinically suspected pulmonary embolism.

Characteristic	**value**
Mean age, years (SD)	52 (18)
Women, n (%)	210 (52)
Outpatients, n (%)	250 (62)
Recent surgery, n (%)	28 (7)
Previous VTE, n (%)	61 (15)
Malignancy, n (%)	74 (18)

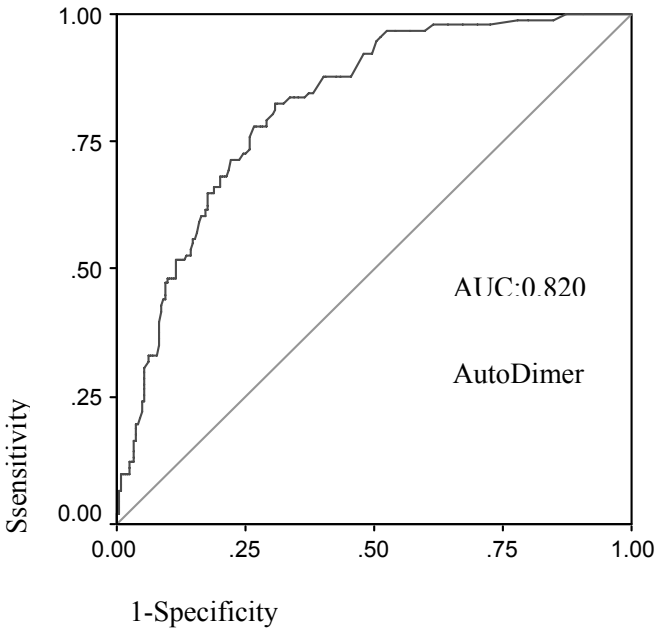
SD, standard deviation; VTE, venous thromboembolic events

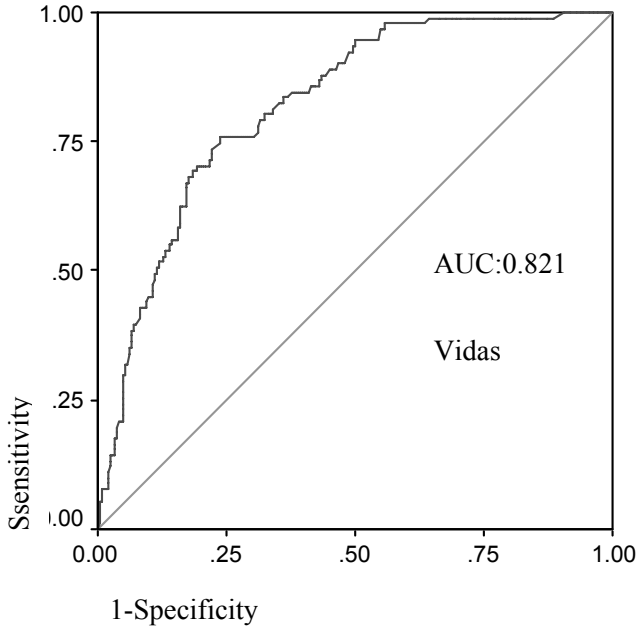
TABLE 2. Accuracy parameters of two D-dimer assays and the exclusion efficacy in 401 patients

	Vidas	**AutoDimer**	
Parameter	≤ 500 ng/ml	≤ 189 ng/ml	≤ 110 ng/ml
sensitivity % (95% CI)	98 (92-99)	92 (84-97)	97 (90-99)
specificity % (95% CI)	41 (36-47)	52 (46-58)	32 (27-38)
NPV % (95% CI)	98 (94-99)	96 (91-98)	97 (91-99)
PPV % (95% CI)	33 (28-39)	36 (30-43)	35 (30-42)
Exclusion efficacy:			
normal D-dimer (%)	32	42	26
unlikely CDR-score + normal D-dimer (%)	25	33	20

NPV, negative predictive value; PPV, positive predictive value; exclusion efficacy is the percentage of patients with the test result mentioned in the table; CDR, clinical decision rule.

FIGURE 1 Receiver operating characteristics curves for the AutoDimer and Vidas.
AUC , Area under the curve





The performance of the AutoDimer with the two cut-off values (189 ng/ml and 110 ng/ml) in combination with the CDR was evaluated (table 2). If we had used the AutoDimer with a cut-off level of 189 ng/ml in the diagnostic strategy of the original study, 132 patients would have had the combination of an unlikely CDR-score and normal D-dimer concentration, hence an exclusion efficacy 33%. Three patients with pulmonary embolism would have been missed, resulting in a failure rate of 2.3% (95% CI; 0.6-7.0%). Eighty patients had the combination of an unlikely CDR-score and a D-dimer concentration of ≤ 110 ng/ml, hence an exclusion efficacy of only 20%. Pulmonary embolism, however would not have been missed, resulting in a failure rate of 0% (95% CI; 0-5.7%).

Comparison of the Vidas and AutoDimer results showed a good correlation (r^2 = 0.85). A possible influence of storage on the results was studied by measurement of D-dimer levels in the same samples before and after storage. There was no difference between the results before and after storage (Vidas (n = 40): slope 0.97 (± 0.02), Y-intercept 0.06 (± 0.05), Sy|x 0.23; AutoDimer (n = 20): slope 1.02 (± 0.01), Y-intercept -0.11 (± 0.05), Sy|x 0.17).

DISCUSSION

In patients with clinically suspected pulmonary embolism, D-dimer measurement has gained a definitive role in the diagnostic strategy. For this central role in excluding pulmonary embolism accuracy and a fast test result are two essential characteristics. The Vidas D-dimer assay has been shown to be a test with a high sensitivity and NPV for excluding pulmonary embolism [6,13]. The performance of the AutoDimer in excluding pulmonary embolism has not been established yet. Recently, the use of AutoDimer was evaluated in patients with suspected DVT. A cut-off value of 189 ng/ml for excluding DVT in outpatients was assessed as optimal [11]. Our study shows that the optimal cut-off value of the AutoDimer with a high sensitivity and NPV for excluding pulmonary embolism is 110 ng/ml. This difference may in part be explained by a possible difference in duration of symptoms before the D-dimer concentration was measured, since higher D-dimer levels have been reported in acute DVT compared to patients presenting after longer time [14].

The present study shows that the performance of the AutoDimer strongly depends on the cut-off value used. Using ROC analysis the performance of the AutoDimer is similar to results of the Vidas D-dimer assay when the cut-off value was 110 ng/ml. In combination with an unlikely CDR-score, both assays excluded pulmonary embolism safely as no venous thromboembolism occurred during the 3 month follow up period.

As anticipated, by lowering the cut-off value of the AutoDimer from 189 to 110 ng/ml, the exclusion efficacy of the D-dimer assay as the only test to exclude pulmonary embolism decreased from 42% to 26%. This value is still as efficient as the Vidas D-dimer or other established D-dimer tests [6,13]. The exclusion efficacy of the combination of an unlikely CDR-score and AutoDimer D-dimer concentration of ≤ 110 ng/ml was 20%. This combination is less efficient than the Vidas D-dimer assay in combination with an unlikely CDR-score (exclusion efficacy 25%) [12 4,9].

With respect to speed, the Vidas D-dimer assay is known to take at least 40 minutes. The results of the AutoDimer can be available within 10 minutes. This gain of time can be important especially in the outpatient setting, where most patients with clinically suspected pulmonary embolism present. Another advantage apart from its speed, is that the AutoDimer can be performed on a coagulation analyzer present in many laboratories.

A major limitation of this analysis is that it is performed in retrospect. Although the population is comparable to other management studies in patients with suspected pulmonary embolism, the results should be validated in a prospective management study. Another limitation might be that the D-dimer levels were measured with the AutoDimer assay in defrosted samples. However, we did not find a difference of D-dimer levels in samples before and after storage using both assays. This indicates that the storage procedure did not influence our results, as has been previously reported [15].

In conclusion, the combination of an unlikely CDR-score and a normal D-dimer concentration is a safe strategy to exclude pulmonary embolism. Our results confirm that for every D-dimer assay the optimal cut-off value has to be established. Although it has to be validated in a prospective management study, an unlikely CDR-score in combination with a D-dimer concentration of ≤ 110 ng/ml measured with the AutoDimer D-dimer assay seems to be accurate in excluding pulmonary embolism.

Acknowledgment

The test kits for the Biopool Autodimer were kindly supplied by Trinity Biotech (Ireland) and Kordia Life sciences (the Netherlands).

We thank Dr. M.P.H. de Maat for her advice and assistance with the results and statistical analysis of this manuscript.

REFERENCES

1. Kruip MJ, Leclercq MG, van der Heul C, Prins MH, Buller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med. 2003;138:941-951.
2. Schoepf UJ, Goldhaber SZ, Costello P. Spiral computed tomography for acute pulmonary embolism. Circulation. 2004;109:2160-2167.
3. Perrier A, Roy PM, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med. 2005;352:1760-1768.
4. van Belle A, 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;295:172-179.
5. Anderson DR, Wells PS. D-dimer for the diagnosis of venous thromboembolism. Curr Opin Hematol. 2000;7:296-301.
6. 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;140:589-602.
7. 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;135:98-107.
8. 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;162:1631-1635.
9. Ten Wolde M, Hagen PJ, Macgillavry MR, et al. Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism; results of a management study. J Thromb Haemost. 2004;2:1110-1117.
10. Spannagl M, Haverkate F, Reinauer H, Meijer P. The performance of quantitative D-dimer assays in laboratory routine. Blood Coagul Fibrinolysis. 2005;16:439-443.
11. Gardiner C, Pennaneac'h C, Walford C, Machin SJ, Mackie IJ. An evaluation of rapid D-dimer assays for the exclusion of deep vein thrombosis. Br J Haematol. 2005;128:842-848.
12. 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;83:416-420.
13. Ghanima W, Abdelnoor M, Mowinckel MC, Sandset PM. The performance of STA-Liatest D-dimer assay in out-patients with suspected pulmonary embolism. Br J Haematol. 2006;132:210-215.
14. Knecht MF, Heinrich F. Clinical evaluation of an immunoturbidimetric D-dimer assay in the diagnostic procedure of deep vein thrombosis and pulmonary embolism. Thromb Res. 1997;88:413-417.
15. Schutgens RE, Haas FJ, Ruven HJ, Spannagl M, Horn K, Biesma DH. No influence of heparin plasma and other (pre)analytic variables on D-dimer determinations. Clin Chem. 2002;48:1611-1613.

Chapter 10

CLINICAL UTILITY OF C-REACTIVE PROTEIN IN RULING OUT PULMONARY EMBOLISM

Maaike Söhne, Marieke J.H.A. Kruip, Carlo J.J. van Dongen,
Stijn J.M. Halkes, Patrick M.M.Bossuyt, Frank W.G. Leebeek, Harry R. Büller

submitted

ABSTRACT

Background A clinical decision rule (CDR) combined with a D-dimer test is commonly used to rule out suspected pulmonary embolism. However, still 70% of the patients need to undergo further imaging tests. C-reactive protein (CRP) has been shown to be related to the presence or absence of pulmonary embolism.

Objective To evaluate the safety and usefulness of a highly sensitive CRP assay in the diagnostic work-up of patients with suspected pulmonary embolism, either alone or combined with the CDR and D-dimer.

Methods A diagnostic strategy using CDR, D-dimer and spiral computed tomography was used to confirm or rule out pulmonary embolism. Test characteristics of CRP at a cut-off concentration of 3 mg/l were calculated based on the outcome of this strategy and three months of follow-up. CRP was combined and compared to the CDR and D-dimer test.

Results For the 790 included patients the sensitivity and the negative predictive value of CRP at a cut-off concentration of 3 mg/l were both 99% (95%CI: 96-100%). The specificity was 27%. The exclusion efficiency of the combination of an unlikely CDR and a low CRP was lower than an unlikely CDR combined with a normal D-dimer, 19% versus 32% respectively. A diagnostic algorithm using all three tests increased the percentage of patients ruled out from pulmonary embolism from 32% to 40%, with a 3-month incidence of venous thromboembolism of 1.3% (95% CI: 0.3% to 3.2%)

Conclusions The safety of CRP is comparable to D-dimer to rule out pulmonary embolism, but the usefulness of CRP in addition to CDR and D-dimer is marginal.

INTRODUCTION

Rapid confirmation of the presence of pulmonary embolism is important due to the high mortality rate associated with missed disease [1]. However, only 20% of patients presenting with suspected pulmonary embolism actually have emboli confirmed by objective testing [2-4]. Therefore, inexpensive and quick but highly sensitive tests to rule out the diagnosis are desirable in the early phase of the diagnostic work-up of these patients. Several diagnostic methods have become available in recent years, which appear promising for this goal.

A clinical decision rule (CDR) and a highly sensitive D-dimer assay are now commonly used tools to safely exclude pulmonary embolism. Because of the low specificity of these tests, pulmonary embolism can only be ruled out in approximately 30% of patients presenting with suspected pulmonary embolism [5]. This implies that 70% still needs to undergo further imaging tests, such as ventilation/perfusion scintigraphy (V/Q scan) or spiral computed tomography (CT).

Low levels of C-reactive protein (CRP), which is measured by an easy to perform, inexpensive and readily available blood test, have also been shown to be related to the absence of venous thromboembolism [6-11]. Sensitivities of CRP for detecting venous thromboembolism varied from 60% to 100% with CRP cut-off values between 5 mg/l and 10 mg/l, although most studies had a small sample size and lacked an appropriate reference method for the presence or absence of pulmonary embolism. One study determined whether the CRP test in combination with clinical probability assessment in patients with suspected pulmonary embolism could be an alternative to D-dimer testing[11]. Diagnostic performance of the CRP test in the low clinical probability group at a 5 mg/l cut-off value was not equivalent to a rapid D-dimer assay, mainly due to a lower sensitivity of the CRP test[11]. Recently more sensitive CRP assays have become available.

The aim of the present study was to evaluate a CRP assay with a detection limit of 3 mg/l in the diagnostic work up of suspected pulmonary embolism, either alone or in combination with the clinical decision rule and the D-dimer test. In addition, we evaluated whether the accuracy could result in a decrease of the number of patients that have to undergo further imaging.

METHODS

Data were collected in a large diagnostic management study in 12 teaching hospitals in the Netherlands, which evaluated a diagnostic strategy including CDR, D-dimer and spiral CT [12]. Patients were included between November 2002 and August 2004. The study protocol was approved by the Institutional Review Boards.

Patients

Consecutive in- and outpatients with clinically suspected acute pulmonary embolism were eligible for inclusion. Patients were excluded if they had received (low molecular weight) heparin for more than 24 hours, were younger than 18 years of age, were pregnant, had a known hypersensitivity for iodinated contrast, had a life expectancy of less than three months or if there was geographic inability for follow-up. For the analysis reported here, data from two hospitals were used (Academic Medical Center, Amsterdam and Erasmus Medical Center, Rotterdam).

Diagnostic strategy

Upon referral, the simplified clinical decision rule (CDR) of Wells et al.[13] was completed by the attending physician. This rule consists of seven questions including the presence of symptoms of deep venous thrombosis, pulse frequency, immobilization or surgery within the last four weeks, previous venous thromboembolism, hemoptysis, malignancy and the possibility of an alternative diagnosis. Patients were classified into those with a likely CDR-score (above 4) or unlikely CDR-score (4 or below).

Blood was obtained from all patients for the measurement of D-dimer concentration (Tinaquant D-dimer, Roche Diagnostica, Mannheim, Germany) and of CRP (Tinaquant CRP test, Roche Diagnostica). The lowest detection limit of CRP for the test was set at 3 mg/l. The CRP concentration did not influence the management decisions.

In patients with an unlikely CDR score and a D-dimer concentration equal or below 0.5 mg/l no further imaging was performed and no anticoagulant treatment was initiated. Patients with a likely CDR score or a D-dimer concentration above 0.5 mg/l underwent spiral CT to confirm or rule out pulmonary embolism. Spiral CT was performed with a thin collimation, multi-detector row spiral CT scanner and 1.25 mm coupes were made. Spiral CT was performed using 100 ml of iodinated contrast (Visipaque 320® Nycomed, Oslo, Norway) administered at a rate of 4 ml/sec using a bolus tracking protocol. Central intraluminal filling defects or totally

occluded vessels were considered as positive for pulmonary embolism. A negative spiral CT ruled out pulmonary embolism.

Patients were instructed to contact the hospital if signs or symptoms of pulmonary embolism or deep venous thrombosis occurred during these three months of follow-up. All included patients were contacted by phone or seen at the outpatient department after three months. To confirm the suspicion of venous thromboembolic events objective testing was needed and the results were adjudicated by a blinded committee. In addition all deaths were adjudicated.

Analysis

A multiple reference standard was used to evaluate the diagnostic accuracy of CRP. Patients were classified as having pulmonary embolism in case of a positive helical CT or in case of positive testing for venous thromboembolism during follow-up. All other patients were classified as not having pulmonary embolism.

A receiver operating curve (ROC) for the CRP test was composed to evaluate the discriminative power to distinguish patients with and without pulmonary embolism. The concentration of 3 mg/l was used to calculate the test characteristics of the CRP test. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for the total study population. Test characteristics were also calculated for the combination of CRP with the CDR, and they were compared to the combination of D-dimer assay and the CDR. The McNemar test statistic was used to test the difference. We also evaluated the exclusion efficiency of both combinations; i.e. the percentage of patients in whom further testing could be safely withheld. Finally, the combination of all three tests, CDR, D-dimer and CRP, was explored to see whether adding CRP to the currently established diagnostic algorithm with CDR and D-dimer increased the exclusion efficiency.

RESULTS

Patients characteristics

In 790 non selected patients data on CRP, D-dimer, and the CDR score at presentation were available (Figure 1). Baseline characteristics of the study population are detailed in Table 1. The mean age was 53 years, 422 (54%) were female and 556 (70%) were outpatients.

In total 254 (32%) patients had both an unlikely CDR score and a normal D-dimer. These patients were considered not to have pulmonary embolism and anticoagulant therapy was withheld. During a three-month follow-up two of these patients experienced objectively confirmed venous thromboembolism.

The remaining 536 patients with a likely CDR and/or a high D-dimer concentration underwent spiral CT of which 162 (30%) had confirmed PE, 196 (37%) had a completely normal CT and 172 (32%) had no pulmonary embolism but an alternative diagnosis. During follow-up of the 368 patients with a CT negative for pulmonary embolism and consequently no anticoagulant therapy, four patients experienced objectively confirmed venous thromboembolism.

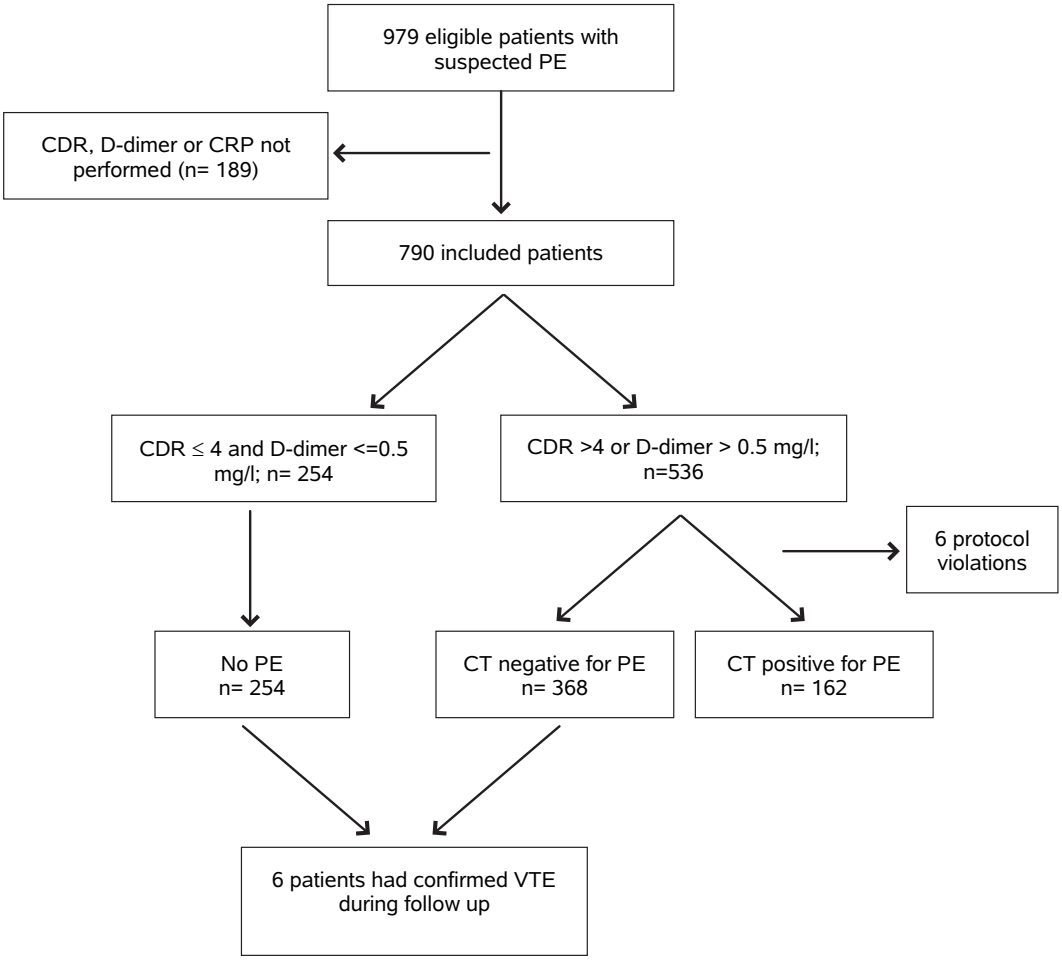
In total 162 patients had pulmonary embolism (prevalence 21%).

TABLE 1: Baseline characteristics of 790 study patients

Characteristic	Number (%)
Mean age (range)	53 (19-97)
Female sex	422 (54)
Outpatients	556 (70)
Median duration of symptoms in days (range)	2 (1 to 90)
Paralysis, paresis or plaster leg < 4 weeks	24 (3)
Immobilization	124 (16)
Surgery	64 (8)
Previous deep venous thrombosis	42 (5)
Previous pulmonary embolism	57 (7)
Heart failure	90 (11)
Chronic obstructive pulmonary disease	96 (12)
Malignancy	122 (15)
Hormone therapy	80 (10)

FIGURE 1 Flow chart of diagnostic management strategy

PE, pulmonary embolism; CDR, clinical decision rule; CT, computed tomography; VTE, venous thromboembolic event



CRP analysis

The median CRP value for the patients with pulmonary embolism was 52.0 mg/l (IQR: 17.5 to 127.0 mg/l) compared to 15.0 mg/l (IQR: 3.0 to 63.3 mg/l) for the patients without pulmonary embolism ($p<0.001$).

At the set level of CRP measurement of 3 mg/l, the sensitivity was 99% (95% CI: 96 to 100%). The negative predictive value at this cut-off was 99% (95%CI: 96 to 100%), while the specificity was 27% (95% CI: 24 to 31%). Figure 1 shows the discriminative power of CRP when used as the sole test in the diagnostic work-up of suspected pulmonary embolism. The

area under the curve for CRP was 0.70 (95% CI: 0.66 to 0.74). Increasing the CRP cut-off concentration from 3 to 4 or 5 mg/l would result in a minor increase of the specificity, but in an associated decrease in sensitivity (Figure 2). At a cut-off concentration of 5 mg/l, the sensitivity would have been 95%, with a negative predictive value of 96% and a specificity of 32%.

The diagnostic performance of CRP at the cut-off concentration of 3 mg/l when combined with the CDR is shown in Table 2. The negative predictive value of CRP in the unlikely clinical risk category was 99% (95% CI: 96 to 100%). In the likely CDR category the negative predictive value was 96%, but due to the smaller group size (280 patients) the 95% confidence interval was wider (80 to 100%). The specificities in the two CDR categories were 33% (95%CI: 29 to 37%) and 14% (95%CI: 9 to 19%), respectively. Therefore, the combination of an unlikely CDR score with a CRP concentration of 3 mg/l or lower was present in 149(19%) from the initial cohort of patients with suspected pulmonary embolism.

CRP in combination with the CDR was compared to the combination of the D-dimer test and the CDR. The negative predictive value of the D-dimer in the unlikely clinical risk category was 99% (95%CI: 97 to 100%) and the specificity was 56% (95%CI: 52 to 67%); compared to a specificity of 33% for CRP; (p-value <0.001).

The combination of a normal D-dimer and an unlikely CDR score would have ruled out pulmonary embolism without further imaging in 254 patients (32%). This is a higher exclusion efficiency than CRP combined with an unlikely CDR score (32% versus 19%, respectively (p-value <0.001).

Finally, adding CRP to the currently used algorithm of CDR and D-dimer to rule out pulmonary embolism resulted in the following two options. First, the use of CRP only in the unlikely CDR category of patients with an abnormal D-dimer. An unlikely CDR score in combination with a normal D-dimer result was present in 254 patients (32% of the study population), whereas 259 patients within the unlikely CDR patient category had an abnormal D-dimer result. Of these 259 patients 31(12%) had a low CRP concentration. This addition of CRP to the strategy of an unlikely CDR and normal D-dimer was, during three months of follow-up, associated with a VTE incidence of 1.1% (3 patients; 95% CI: 0.2% to 3.0%).

Secondly, a low CRP concentration could also be used to rule out pulmonary embolism in the likely CDR category as well. As above, 254 patients (32%) had an unlikely CDR score and a normal D-dimer result. Of the remaining 536 patients 59 had a low CRP concentration, which is 10%. Therefore, the use of this diagnostic algorithm would have ruled out pulmonary embolism in 313 patients (i.e. 40% of the initial cohort with suspected pulmonary embolism). Four patients with pulmonary embolism would have been missed (3-month VTE incidence 1.3%; 95%CI: 0.3% to 3.2%).

FIGURE 2 ROC curve for CRP with the sensitivity and specificity of three different CRP cut-off concentrations (mg/l) detailed. (AUC, area under the curve)

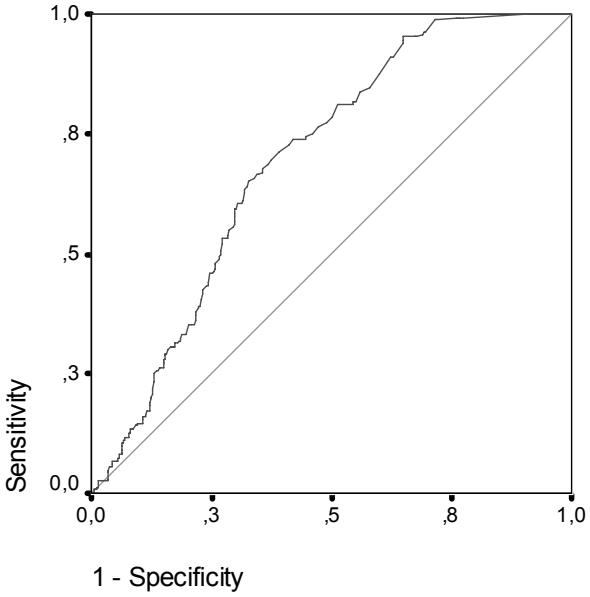


TABLE 2 Test characteristics (including 95% confidence interval) of CRP at a cut-off concentration of 3 mg/l

	All patients n= 790	**CDR unlikely* n= 510**	**CDR likely* n= 280**
PE prevalence n(%)	164 (21%)	61 (12%)	103 (37%)
CRP			
Sensitivity	99% (96%-100%)	98% (91%-100%)	99% (95%-100%)
Specificity	28% (24%-31%)	33% (29%-37%)	14% (9%-19%)
Negative predictive value	99% (96%-100%)	99% (96%-100%)	96% (80%-100%)
Positive predictive value	26% (23%-30%)	17% (13%-21%)	67% (59%-74%)

PE, pulmonary embolism; CDR, clinical decision rule
*CDR unlikely = 4 or less points; CDR likely = more than 4 points

DISCUSSION

This study shows that CRP at a cut-off concentration of 3 mg/l is as sensitive and has a comparable negative predictive value as D-dimer, implying that it can be safely used in the diagnostic work-up of patients with suspected pulmonary embolism. Because of the lower specificity, the efficacy to exclude pulmonary embolism is lower for CRP than for D-dimer.

Several other studies with CRP have been performed in patients with suspected pulmonary embolism providing varying sensitivities and specificities [6-8] [9;10] [11]. Only one study had an appropriate reference standard for pulmonary embolism and was carried out in a sufficient number of patients [11]. In that study, the sensitivity and negative predictive value of CRP were considerably lower compared to our study. This could be due to the use of a different CRP test and a cut-off concentration of 5 mg/l. Using a cut-off of 5 mg/l in our study would have produced a sensitivity and negative predictive value that exceed those reported by Aujesky et al. Another reason may be the lower prevalence of pulmonary embolism in our study (21% versus 30%).

What could be the potential contribution of CRP in the diagnostic work-up of patients with suspected pulmonary embolism? Our analysis showed that low CRP values were observed in 12% of the patients with an abnormal D-dimer result in the unlikely CDR category, implying that in this specific subgroup 8 CRP tests would have to be performed to rule out one patient from having pulmonary embolism. In clinical practice, the D-dimer and CRP will usually be measured at the same time, thus in all patients with an unlikely CDR score. The number of CRP tests to rule out one patient from pulmonary embolism would then increase to 17, which appears to be a marginal diagnostic yield.

An interesting observation in this study was the high sensitivity and negative predictive value of CRP in the likely CDR category. It could therefore be argued to use CRP as the first and only test to rule out pulmonary embolism, followed by the currently used combination of an unlikely CDR score with a normal D-dimer result. With this diagnostic algorithm, 40% of the patients would be excluded from having pulmonary embolism, an increase of 8% as compared to the strategy without CRP. This might be clinical relevant, in particular since CRP is an easy to perform and widely available test that is already regularly measured in patients with chest-symptoms. Two aspects of this assumption require comment. First, although the negative predictive value in the likely CDR score group is high (96%), the 95% confidence interval in that group is wide, precluding a definitive conclusion on the safety of CRP in this patient category. This should therefore be confirmed in future studies. Moreover, as with the D-dimer assay, clinicians feel uncomfortable in relying on a single laboratory test to rule out a potentially fatal

disease in patients with a high clinical probability. Therefore, this strategy might not be widely accepted even if proven safe in a prospective study.

Some aspects of this study require comment. Data on the combination of CRP test, D-dimer test and CDR score at presentation were available for 81%, which could have resulted in selection bias. However, the baseline characteristics as well as the prevalence of pulmonary embolism were not different for the patients from the entire cohort. The analyses of CRP in this study were performed retrospectively and although the CRP test characteristics were good and our population is comparable to other diagnostic management studies in patients with suspected pulmonary embolism, these have to be confirmed prospectively.

In conclusion, the sensitivity and negative predictive value of the CRP test at a cut-off value of 3 mg/l were high and comparable to a rapid ELISA D-dimer test. The negative predictive value was also high in the subgroup of patients with a likely clinical probability. However, the specificity of CRP was too low to substitute D-dimer testing. Addition of CRP to the currently used diagnostic algorithm would have increased the exclusion efficiency only marginally. Therefore, additional studies are required to evaluate whether varying the cut-off values of CRP, D-dimer and CDR might improve the exclusion efficiency.

REFERENCES

1. Dalen JE. Pulmonary embolism: what have we learned since Virchow? Natural history, pathophysiology, and diagnosis. Chest 2002; 122:1440-1456.
2. Ten Wolde M, Hagen PJ, Macgillavry MR et al. Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism; results of a management study. J Thromb Haemost 2004; 2:1110-1117.
3. Perrier A, Roy PM, Aujesky D et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. Am J Med 2004; 116:291-299.
4. van Strijen MJ, de Monye W, Schiereck J et al. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. Ann Intern Med 2003; 138:307-314.
5. Kruip MJ, Leclercq MG, van der Heul C, Prins MH, Buller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med 2003; 138:941-951.
6. Cooper TJ, Prothero DL, Gillett MG et al. Laboratory investigation in the diagnosis of pulmonary thromboembolism. Q J Med 1992; 83:369-379.
7. Bucek RA, Reiter M, Quehenberger P, Minar E. C-reactive protein in the diagnosis of deep vein thrombosis. Br J Haematol 2002; 119:385-389.
8. Franco JA, Gonzalez-Mangers E, Butler TT. Negative predictive value of C-reactive protein testing. J Nucl Med 1994; 35:189-190.
9. Wong NA, Laitt RD, Goddard PR, Virjee J. Serum C reactive protein does not reliably exclude lower limb deep venous thrombosis. Thromb Haemost 1996; 76:816-817.
10. Maskell NA, Butland RJ. A normal serum CRP measurement does not exclude deep vein thrombosis. Thromb Haemost 2001; 86:1582-1583.
11. Aujesky D, Hayoz D, Yersin B et al. Exclusion of pulmonary embolism using C-reactive protein and D-dimer. A prospective comparison. Thromb Haemost 2003; 90:1198-1203.
12. The Christopher Study Group. Safety of a diagnostic algorithm combining clinical probability, D-dimer testing and spiral CT in patients with clinically suspected pulmonary embolism. Accepted for publication JAMA
13. 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; 83:416-420.

GENERAL DISCUSSION AND SUMMARY

The main objective of this thesis was to improve the diagnostic strategies for patients presenting with clinically suspected pulmonary embolism. Therefore several studies were initiated focusing on different aspects of the currently available as well as newly developed diagnostic tools for this patient population.

A large proportion of patients with clinically suspected pulmonary embolism do not have the disease. The first aim of a diagnostic strategy is to safely exclude pulmonary embolism. A systematic overview of the effectiveness of the available diagnostic tests and combined strategies to exclude pulmonary embolism is presented in **Chapter 2**. Several invasive and non-invasive tests for excluding pulmonary embolism are safe. The combination of a clinical probability assessment together with D-dimer testing is an elegant, efficient and patient friendly approach to exclude pulmonary embolism.

A clinical management study evaluated a diagnostic strategy consisting of an extended clinical decision rule, D-dimer testing, compression ultrasonography and pulmonary angiography (**Chapter 3**). The clinical decision rule divided patients into three categories with a low, moderate or high clinical probability of pulmonary embolism. In patients with a low clinical probability and a normal D-dimer concentration, pulmonary embolism was considered to be excluded and anticoagulant treatment was withheld. All other patients underwent compression ultrasonography and, if normal, subsequently also pulmonary angiography. Among all 234 consecutive patients with clinically suspected pulmonary embolism, 60 had the combination of a low clinical probability and normal D-dimer concentration. In these patients pulmonary embolism was considered excluded (i.e. 26% of the study population). During 3 months of follow up no venous thromboembolic events occurred (failure rate 0%; 95% CI 0-6%). In the other 174 patients (74%) a compression ultrasonography was performed, which revealed deep venous thrombosis in 27 patients and anticoagulant treatment was started. Pulmonary angiography was performed in the remaining 147 patients, and confirmed the presence of pulmonary embolism in 25 patients. Thus, the incidence of pulmonary embolism was 22% of the total study population. Although the study showed that it was safe to exclude pulmonary embolism and withhold anticoagulant treatment in patients with a low clinical probability and normal D-dimer concentration (failure rate 0%), it should be noted that the upper limit of the confidence interval of this point estimate is still high (6%). This study also confirms that pulmonary angiography is a safe technique to assess the presence or absence of pulmonary embolism, with a rate of angiography associated complications of 0.4% (95% CI: 0.09-1.25%). However, in many hospitals pulmonary angiography is not readily available. This would argue for using other noninvasive imaging techniques, such as spiral CT, that is more widely applied and is gaining popularity.

In **Chapter 4** a diagnostic strategy using spiral computerized tomography as the sole imaging technique was evaluated in a large management study. The study enrolled 3306

patients with clinically suspected pulmonary embolism. This so called Christopher study was performed in 12 general and academic hospitals in The Netherlands. The diagnostic strategy consisted of a dichotomized clinical decision rule, i.e. a clinical decision rule-score indicating pulmonary embolism unlikely or likely, D-dimer testing and spiral computerized tomography (single or multi slice). Pulmonary embolism was excluded in 1057 patients with an unlikely CDR-score in combination with a normal D-dimer concentration (32% of the entire study population). During 3 months of follow up 5 patients returned with documented venous thromboembolism (failure rate 0.5%; 95% CI: 0.2-1.1%). This validates our strategy described in Chapter 3. In all other patients (n=2249) a subsequent spiral computerized tomography scan was performed which was negative for pulmonary embolism in 1505 patients. Venous thromboembolic events became apparent in 11 patients during follow up (failure rate 1.3%; 95% CI: 0.7-2.0%). Pulmonary embolism was documented by spiral computerized tomography in 674 patients (20% of the study population). These results allowed us to conclude that this relatively simple and fast strategy can safely exclude or confirm pulmonary embolism. The compliance as regards the application of the strategy was high. The diagnostic strategy was completed according to the protocol in 98.5% of the patients and allowed a management decision in 97.9% of them, which makes it suitable for daily practice in both academic and general hospital settings.

It has been debated whether this diagnostic strategy can be generally applied to all patients, including those of older age, those with cancer and hospitalized patients. In these patients clinical probability assessment is in most instances high and D-dimer concentrations may be nonspecifically elevated due to the presence of concomitant disease. To address this question we analyzed the effectiveness of the diagnostic strategy in hospitalized patients (**Chapter 5**). In 605 hospitalized patients with clinically suspected pulmonary embolism, the disease was excluded by the combination of an unlikely clinical decision rule-score and normal D-dimer in 60 patients (10% of the study population). Venous thrombosis did not appear during follow up (failure rate 0%; 95% CI: 0-6.7%). Pulmonary embolism was excluded by spiral computerized tomography in 380 of these patients with a 3 month failure rate of 1.4% (95% CI: 0.4-3.1%). An alternative diagnosis for the symptoms was documented in 216 patients.

In **Chapter 6**, this diagnostic strategy was studied in other subgroups including elderly patients, patients with chronic obstructive pulmonary disease, heart failure or cancer in whom pulmonary embolism was clinically suspected. As expected, the proportion of patients that actually had the combination of an unlikely clinical decision rule-score and a normal D-dimer concentration was low in this selected population in comparison to the original study cohort, especially in elderly patients and patients with cancer. The results from these studies indicate that the diagnostic algorithm using a clinical decision rule, D-dimer and spiral computerized tomography overall furnishes a reliable and simple strategy in these particular and selected subgroups of patients.

Presently, the diagnostic strategy in patients with clinically suspected pulmonary embolism starts with a clinical probability assessment using a clinical decision rule. This assessment is in part based on subjective criteria and the reproducibility is moderate. In **Chapter 7** we show that the reproducibility can be improved by dichotomizing the short clinical decision rule compared to the originally used extended clinical decision rule. The most optimal result, albeit with still a moderate reproducibility, was obtained by this dichotomized short clinical decision rule (kappa value 0.66; 95% CI: 0.41-0.91). An explanation for the limited reproducibility was that a standardized clinical decision rule comprises in part subjective items, as for instance the absence of an alternative diagnosis.

As is shown in Table, the dichotomized clinical decision rule contains 7 variables with 1, 1.5 or 3 points assigned per variable. Can this clinical decision rule can be further simplified using for instance only 1 or 2 points or 1 point for all variables? This question was addressed in **Chapter 8**. There were no differences in safety or clinical utility using the simplified clinical decision rules as compared to the original clinical decision rule presented by Wells and colleagues. This simplified clinical decision rule should be validated and its reproducibility assessed in a prospective management study.

The safety of the diagnostic strategy is also strongly dependent upon the test characteristics of the D-dimer assay used. Several assays, including ELISA, latex-based and semi-quantitative assays have been developed. In the Christopher study two of these assays, that had previously been shown to be reliable, were used to determine the D-dimer concentration. In the Erasmus Medical Center in Rotterdam, the Vidas D-dimer assay was used. Most patients with clinically suspected pulmonary embolism were initially seen at the emergency department. It is important that after assessing an clinical decision rule-score indicating pulmonary embolism unlikely, the D-dimer results become available immediately. One of the disadvantages of the Vidas D-dimer assay is that it takes at least 40 to 60 minutes to obtain a test result. In addition, the Vidas D-dimer test can only be performed on a special analyzer. We assessed the accuracy and exclusion efficacy of a fast D-dimer latex immuno assay (AutoDimer) on a routine analyzer in a study described in **Chapter 9**. At a cut-off value of 110 ng/ml, the test had a negative predictive value of 97% (95% CI: 91-99%), which is as accurate as the Vidas D-dimer assay. However, the exclusion efficacy of this assay in combination with an unlikely clinical decision rule-score was only 20% compared to 25% with the Vidas D-dimer assay. Whether the AutoDimer in combination with an unlikely clinical decision rule-score can be used to safely exclude pulmonary embolism with an acceptable exclusion efficacy remains to be evaluated.

Although the combination of an unlikely clinical decision rule-score and normal D-dimer concentration can safely exclude pulmonary embolism in 25 to 35% of the patients, a large proportion of patients needs further diagnostic imaging. C-reactive protein concentration correlates with the presence or absence of pulmonary embolism. In **Chapter 10** the safety and

clinical utility of a high sensitivity C-reactive protein assay in the diagnostic strategy of patients with suspected pulmonary embolism was assessed. The exclusion efficacy increased from 32% using clinical decision rule-score and D-dimer concentration to 40% when C-reactive protein was also included in the diagnostic strategy, with a 3 months failure rate of 1.3% (95% CI: 0.3-3.2%). Therefore, the use of C-reactive protein in addition to D-dimer and clinical decision rule allows for some improvement of the exclusion efficacy.

Future perspectives

Excluding or diagnosing pulmonary embolism remains a challenge for the physician who is confronted with a patient with signs and symptoms suggestive of pulmonary embolism. During the past years the diagnostic strategy has evolved from a complex and time-consuming strategy based on invasive techniques to a simple and fast algorithm, based on mostly non-invasive techniques, including a dichotomized clinical decision rule, D-dimer testing and if necessary spiral computerized tomography. One of the main advantages of this strategy is that it can be applied in most academic and non-academic hospitals. Furthermore this strategy gives an early answer allowing a management decision in nearly all patients within a few hours or even less.

Obviously, this simple strategy should be optimized further. Future challenges are amongst others to develop a simple and fast strategy for patients with recurrent pulmonary embolism and pregnant patients. In addition, future studies should be focused on further simplification of clinical decision rules and reducing their dependence on subjective variables. Furthermore, faster or bed-side accurate D-dimer assays are needed. New biomarkers including markers of cardiac dysfunction (e.g. brain natriuretic peptide or heart–type fatty acid binding protein) may improve the diagnostic strategy. Finally, improvement of diagnostic imaging techniques with advanced spiral computerized tomography or magnetic resonance pulmonary angiography will be of major importance to optimize the diagnosis of pulmonary embolism.

TABLE. Clinical decision rule according to Wells

Variable	points
Clinical signs and symptoms of deep vein thrombosis (minimum of leg swelling and pain with palpation of the deep veins)	3
Alternative diagnosis less likely than pulmonary embolism	3
Heart rate > 100/min	1.5
Immobilization (> 3 days) or surgery in previous 4 weeks	1.5
Previous pulmonary embolism or deep vein thrombosis	1.5
Hemoptysis	1.0
Malignancy (receiving treatment, treated in the last 6 months or palliative)	1.0

ALGEMENE DISCUSSIE EN SAMENVATTING

Bij patiënten met een klinische verdenking op een longembolie zijn diverse diagnostische strategieën mogelijk. Het doel van dit proefschrift was het verbeteren van deze strategieën.

Een groot deel van de patiënten met verdenking longembolie blijkt de ziekte niet te hebben. Het eerste doel van een diagnostische strategie is dan ook het veilig uitsluiten van longembolie. Een overzicht van de diagnostische waarde van de verschillende testen en strategieën wordt gegeven in **hoofdstuk 2**. Meerdere invasieve en niet-invasieve testen voor het uitsluiten van longembolie zijn veilig en betrouwbaar. De combinatie van een klinische kansschatting op het hebben van longembolie en een D-dimeer test is een efficiënte en patiëntvriendelijke manier om longembolie uit te sluiten, echter de betrouwbaarheid dient met verder onderzoek te worden aangetoond.

In een klinische management studie werd een diagnostische strategie geëvalueerd, bestaande uit een uitgebreide klinische beslisregel, een D-dimeer test, compressie-echografie van de benen en longangiografie (**hoofdstuk 3**). De klinische beslisregel verdeelde de patiënten in drie categorieën met respectievelijk een lage, matige of hoge waarschijnlijkheid op het hebben van longembolie. Bij patiënten met een lage waarschijnlijkheid en een normale D-dimeer concentratie werd de diagnose longembolie verworpen. Alle overige patiënten ondergingen een compressie-echografie van de beenvenen en, indien de echo geen trombose toonde, een longangiografie. Van de 234 achtereenvolgende patiënten met een verdenking longembolie hadden 60 (26%) de combinatie lage waarschijnlijkheid en normale D-dimeer concentratie. De diagnose longembolie werd verworpen. Tijdens de 3 maanden daarop volgend zijn er geen veneuze trombo-embolische complicaties waargenomen (0%; 95% betrouwbaarheidsinterval (BI): 0-6%). Alle overige patiënten (n=174) ondergingen een compressie-echografie van de beenvenen. Zevenentwintig patiënten hadden een diepe veneuze trombose en antistolling werd gestart. Longangiografie werd uitgevoerd bij 147 patiënten en bij 25 werden longembolieën aangetoond. De incidentie van longembolie was 22% voor de totale populatie. Alhoewel de studie toonde dat het veilig is longembolie uit te sluiten in patiënten met een lage waarschijnlijkheid en een normale D-dimeer concentratie dient opgemerkt te worden dat de bovengrens van het betrouwbaarheidsinterval hoog is (6%). Deze studie laat ook zien dat longangiografie een veilige techniek is om longembolie aan te tonen of uit te sluiten met een complicatie percentage van slechts 0.4% (95% BI 0.09-1.25%). Echter, in veel ziekenhuizen kan een longangiografie niet meer worden uitgevoerd. Spiraal computer tomografie daarentegen, is in vrijwel alle ziekenhuizen aanwezig.

In **hoofdstuk 4** wordt een grote management studie geëvalueerd waarin spiraal computer tomografie de enige beeldvormende techniek is. In deze studie werden 3306 patiënten met verdenking longembolie geïncludeerd. Deze (Christopher) studie werd uitgevoerd in 12 algemene en academische ziekenhuizen in Nederland. De diagnostische strategie startte met een klinische beslisregel, waarbij de kans op het hebben van longembolie werd onderverdeeld

in waarschijnlijk en onwaarschijnlijk, en een D-dimeer test. Longembolie werd in 1057 patiënten (32 %) met een onwaarschijnlijke kans op het hebben van longembolie en een normale D-dimeer concentratie uitgesloten. Tijdens de daaropvolgende drie maanden keerden slechts 5 patiënten terug met veneuze trombo-embolische complicaties (0.5%; 95% BI: 0.2-1.1%). Dit ondersteunt de eerder beschreven bevindingen uit hoofdstuk 3, namelijk dat de strategie veilig is. Alle overige patiënten (n=2249) ondergingen een spiraal computer tomografie. Deze toonde geen longembolie bij 1505 patiënten. Elf patiënten keerden terug met veneuze trombo-embolische complicaties binnen 3 maanden na inclusie (1.3%; 95% BI: 0.7-2.0%). Bij 674 patiënten werd de diagnose longembolie gesteld (20% van de populatie). Deze eenvoudige en snelle strategie maakte het mogelijk met voldoende zekerheid longembolie aan te tonen of uit te sluiten. De strategie werd gevolgd bij 98.5% van de patiënten en maakte een beslissing over wel of niet behandelen mogelijk bij 97.9% van de patiënten. Deze strategie is daarom bruikbaar in zowel algemene als academische ziekenhuizen.

Of deze diagnostische strategie bruikbaar is voor alle patiënten, waaronder ouderen, patiënten die zijn opgenomen in een ziekenhuis of patiënten met kanker, is onderwerp van discussie. In deze groepen zal de klinische kansschatting meestal een waarschijnlijke kans opleveren en de D-dimeer concentratie zal vaak verhoogd zijn door de aanwezigheid van andere ziekten. In **hoofdstuk 5** is een subanalyse van de Christopher-studie uitgevoerd om de betrouwbaarheid van de diagnostische strategie te onderzoeken bij 605 patiënten opgenomen in het ziekenhuis. De diagnose werd bij 60 patiënten (10% van de populatie) verworpen, omdat de kans op het hebben van longembolie onwaarschijnlijk was en de D-dimeer concentratie normaal. In de drie opvolgende maanden zijn er geen veneuze trombo-embolische complicaties opgetreden (0%; 95% BI: 0-6.7%). Longembolie werd uitgesloten met spiraal computer tomografie bij 380 patiënten, waarvan bij 1.4% tijdens de drie opvolgende maanden veneuze trombo-embolische complicaties werden vastgesteld (95% BI: 0.4-3.1%). Bij 216 patiënten werd op basis van het computer tomografisch onderzoek een alternatieve diagnose gesteld.

In **hoofdstuk 6** wordt de diagnostische strategie onderzocht in andere groepen patiënten, waaronder ouderen, patiënten met chronische obstructief longlijden, hartfalen en kanker. Zoals verwacht had slecht een klein deel van deze patiënten de combinatie van een onwaarschijnlijke kans op het hebben van longembolie en een normale D-dimeer concentratie. Toch toonde deze analyse aan dat een strategie bestaande uit een klinische beslisregel, D-dimeer test en spiraal computer tomografie ook een betrouwbare en eenvoudige strategie is voor deze specifieke groepen patiënten.

De diagnostische strategie voor patiënten met verdenking longembolie begint vaak met een klinische kansschattig met behulp van een klinische beslisregel. Deze beslisregel is deels gebaseerd op subjectieve criteria en de reproduceerbaarheid is matig. In **hoofdstuk 7** wordt

getoond dat de reproduceerbaarheid verbeterd kan worden door de beslisregel te verkorten en de patiënten onder te verdelen in niet 3 maar 2 categorieën. Dit leverde het meest optimale resultaat met nog steeds een matige reproduceerbaarheid (kappa waarde 0.66; 95% BI: 0.41-0.91). Een verklaring voor de beperkte reproduceerbaarheid is dat de beslisregel voor een deel bestaat uit subjectieve variabelen. De belangrijkste subjectieve variabele is de inschatting van een arts of longembolie waarschijnlijker is dan een alternatieve diagnose.

De verkorte klinische beslisregel bestaat uit 7 variabelen waaraan 1, 1.5 of 3 punten worden toegekend (tabel). Kan deze beslisregel verder worden vereenvoudigd door bijvoorbeeld alleen 1 of 2 punten toe te kennen of aan alle factoren 1 punt? Deze vraag wordt behandeld in **hoofdstuk 8**. Er waren geen verschillen in veiligheid en bruikbaarheid tussen de oorspronkelijke en de twee bestudeerde puntenverdelingen. Deze vereenvoudigde puntenverdeling moet nog gevalideerd worden in een prospectieve management studie.

De veiligheid van de diagnostische strategie is onder andere afhankelijk van de karakteristieken van de D-dimeer test. Er zijn verschillende testen ontwikkeld, waaronder ELISA, latex en semi-kwantitatieve testen. In de Christopher studie zijn 2 soorten testen gebruikt om de D-dimeer concentratie te meten. In het Erasmus Universitair Medisch Centrum in Rotterdam werd gebruik gemaakt van de Vidas D-dimeer test. Het merendeel van de patiënten met klachten passend bij longembolie presenteert zich op de spoedeisende hulp. Vandaar dat het belangrijk is dat na het bepalen van de waarschijnlijkheid op het hebben van longembolie de D-dimeer concentratie snel bekend is. Een nadeel van de Vidas D-dimeer test is dat het 40 tot 60 minuten duurt voordat het resultaat bekend is. Daarnaast kan de Vidas D-dimeer test alleen uitgevoerd worden op een speciaal daarvoor aan te schaffen apparaat. De accuraatheid en exclusie efficiëntie van een snelle D-dimeer latex immuno test (AutoDimer) op een routine apparaat werd bestudeerd in **hoofdstuk 9**. Bij een grenswaarde van 110 ng/ml had deze test een negatief voorspellende waarde van 97% (95% BI: 91-99%), overeenkomstig met die van de Vidas D-dimeer test. Echter, de combinatie van een onwaarschijnlijke kans op het hebben van longembolie met een D-dimeer concentratie onder of gelijk aan 110 ng/ml was slechts aanwezig in 20% van de patiënten, in tegenstelling tot 25% van de patiënten bij de Vidas D-dimeer test. Of de Autodimer in combinatie met een onwaarschijnlijke kans veilig gebruikt kan worden om longembolie uit te sluiten met een acceptabele exclusie efficiëntie zal nog prospectief geëvalueerd moeten worden.

Hoewel de combinatie van een onwaarschijnlijke kans op het hebben van longembolie en een normale D-dimeer concentratie longembolie veilig uitsluit in 25 tot 35% van de patiënten, heeft nog steeds een groot deel van de patiënten aanvullende diagnostische testen nodig. C-reactief proteïne (CRP) concentratie is gecorreleerd met de aan- of afwezigheid van longembolie. In **hoofdstuk 10** wordt de veiligheid en bruikbaarheid onderzocht van een sensitieve CRP test in de diagnostische strategie van patiënten met verdenking longembolie.

De strategie bestond uit een klinische beslisregel, een D-dimeer concentratie en de hoogte van CRP. De exclusie efficiëntie steeg van 32% , indien alleen van een klinische beslisregel en D-dimeer concentratie werd gebruikt, naar 40% wanneer daaraan meting van CRP werd toegevoegd. Tijdens de 3 maanden opvolging waren er 1.3% veneuze trombo-embolische complicaties (95% BI: 0.3-3.2%). Het inzetten van CRP naast een klinische beslisregel en D-dimeer concentratie geeft dus enige verbetering van de exclusie efficiëntie.

Toekomst perspectieven

Het aantonen of uitsluiten van longembolie zal een uitdaging blijven van de arts die geconfronteerd wordt met een patiënt met klachten en symptomen die zouden kunnen passen bij longembolie. In de afgelopen jaren is de diagnostische strategie veranderd van een complexe en langdurige strategie op basis van invasieve technieken naar een eenvoudig en snel algoritme bestaand uit een klinische beslisregel, een D-dimeer test en indien nodig een spiraal computer tomografie. Eén van de voordelen van deze strategie is dat deze kan worden toegepast in zowel de meeste academische als algemene ziekenhuizen. Daarnaast kan meestal al binnen een paar uur de diagnose longembolie worden bevestigd of verworpen. Dit komt een goede behandeling van de patiënt ten goede.

Deze strategie kan uiteraard nog verbeterd worden. Uitdagingen voor in de toekomst zijn onder andere het ontwikkelen van een eenvoudige en snelle strategie voor patiënten met verdenking recidief longembolie en zwangeren met klachten verdacht voor longembolie. Daarnaast zullen toekomstige studies zich richten op een verdere vereenvoudiging van de klinische beslisregel met minder subjectieve variabelen. Ook zullen er snellere D-dimeer testen ontwikkeld worden. Nieuwe biomarkers zoals markers voor hartfalen (bijvoorbeeld brain natriuretic peptide of heart-type fatty acid binding protein) kunnen een vooruitgang betekenen. Tenslotte zullen ook verbeterde beeldvormende technieken een grote bijdrage gaan leveren aan het optimaliseren van het diagnostisch traject.

TABEL. Klinische beslisregel volgens Wells

variabele	**punten**
Klinische tekenen en symptomen van diep veneuze trombose (minimaal zwelling van been en pijn bij palpatie diepe venen)	3
Alternatieve diagnose minder waarschijnlijk dan longembolie	3
Hartfrequentie > 100/min	1.5
Immobilisatie (> 3 dagen) of operatie in afgelopen 4 weken	1.5
Longembolie of diep veneuze trombose in voorgeschiedenis	1.5
Haemoptoë	1.0
Maligniteit (waarvoor behandeling in afgelopen 6 maanden of tijdens palliatie)	1.0

CO-AUTHORS

Academic Hospital Maastricht, Maastricht

Department of Clinical Epidemiology and Technology Assessment

Martin H. Prins

Department of Pulmonary Medicine

Arne van Belle

Academic Medical Center, Amsterdam

Department of Vascular Medicine

Harry R. Büller, Maaike Söhne, Nadine S. Gibson, Victor E. Gerdes,

Department of Clinical epidemiology and Biostatistics

Patrick M. Bossuyt, Carlo J.J. van Dongen

Atrium Medical Center, Heerlen

Department of Internal Medicine

Kon-Siong G. Jie

Erasmus Medical Center, Rotterdam

Department of Hematology

Frank W.G. Leebeek

Department of Pulmonary Medicine

Alice Kars

Department of Radiology

Peter M.T. Pattynama

Department of Vascular Medicine

Anton H. van de Meiracker

Hilversum Hospital, Hilversum

Department of Radiology

Peter M. Huisman

Isala Clinics, location Sophia, Zwolle

Department of Internal Medicine

M. van Marwijk Kooy

Leiden University Medical Center, Leiden

Department of General Medicine and Endocrinology

Menno V. Huisman, Mathilde Nijkeuter

Department of Hematology

Lidwine W. Tick

Meander Medical Center, Amersfoort

Department of Internal Medicine

Mark H.H. Kramer, Stijn J.M. Halkes

Medisch Spectrum Twente, Enschede

Department of internal medicine

Monique G.L. Leclercq

Rijnstate Hospital, Arnhem

Department of Pulmonary Medicine

Hanneke M. Kwakkel- van Erp, Erik F. Ullmann

Department of Internal Medicine

Karin Kaasjager

Sint Elisabeth Hospital, Tilburg

Department of Internal Medicine

Cees van der Heul

Department of Pulmonary Medicine

Joost H.E.M. Schijen

Department of Radiology

Marjan Slob

Slotervaart Hospital, Amsterdam

Department of Internal Medicine

Melvin R. McGillavry

University of Ottawa, Ottawa Hospital & Ottawa Health Research Unit, Ottawa, Ontario, Canada

Department of Medicine

Philip S. Wells

University Medical Center, Nijmegen

Department of General Internal Medicine

Pieter W. Kamphuisen

DANKWOORD

In 1997 ben ik begonnen met de voorbereidingen voor de eerste klinische studie. Nu, bijna 10 jaar later, worden alle inspanningen bekroond met dit proefschrift. Dat ik uiteindelijk een proefschrift heb kunnen maken, heb ik te danken aan de vele mensen die mij de ruimte en mogelijkheden gaven en mij motiveerden om vooral door te gaan. Een aantal van hen ben ik in het bijzonder dankbaar.

Prof. Dr. H.R. Büller, beste Harry, mijn dank dat je vanaf het begin mijn begeleider hebt willen zijn. Het heeft altijd als een voorrecht gevoeld. Ik ben heel wat keren vanuit Tilburg en later vanuit Rotterdam voor overleg en opbeurende woorden bij jou geweest. Het was nooit te vergeefs. Als geen ander verstond jij de kunst mij het idee te geven dat het belangrijk was wat ik deed, waardoor ik met opgeheven hoofd weer naar huis ging. Jij hebt mij veel geleerd, was het niet in levende lijve dan ging het via de telefoon of op papier.

Prof. Dr. B. Löwenberg, beste Bob, dankzij jou kon ik aan mijn Rotterdams avontuur beginnen en heb ik dit proefschrift kunnen afronden. Dank voor deze mogelijkheden en voor de kans om verder te gaan op de ingeslagen weg.

Dr. F.W.G. Leebeek, beste Frank, na mijn overstap van Tilburg naar Rotterdam heb jij mij weer op de goede (Christopher-) weg gekregen. Jij hebt mij gemotiveerd het proefschrift nu echt eens af te maken. Dank voor je correcties, reacties, ideeën en collegialiteit. Ik kijk uit naar onze verdere samenwerking.

Dr. C. van der Heul, beste Cees, in 1997 heb jij mij in contact gebracht met Harry en heb je mij tijd en ruimte gegeven de studie voor te bereiden en uit te voeren. Ik heb er uiteindelijk iets langer over gedaan het proefschrift af te ronden, maar de basis ligt toch echt in Tilburg!! Het St. Elisabeth ziekenhuis zal gevoelsmatig altijd een beetje mijn ziekenhuis blijven. Ik heb er veel meegemaakt, maar vooral veel geleerd. Mijn dank daarvoor.

In het St. Elisabeth ziekenhuis te Tilburg hebben veel collega arts-assistenten meegewerkt aan de studie. Ik weet dat het telkens veel werk was de lange beslisregel van Wells in te vullen en de patiënten te vragen. Iedereen bedankt!! Beste Asiong, als jij er niet was geweest om mij telkens maar weer te motiveren om door te gaan met de studie..... dank. Alle internisten van toen wil ik bedanken voor de goede en plezierige opleiding. Ook alle anderen specialisten wil ik danken voor de soepele samenwerking, met name de radiologen en longartsen.

Marianna, bedankt voor de gezelligheid en alle hulp. Monique, jij was mijn mede-buitenbeentje-vanuit-de-periferie. Succes met je eigen boekje?!

En dan Rotterdam. Hier heb ik het proefschrift kunnen afronden. Alle collega's, verpleegkundigen en medewerkers wil ik bedanken voor de goede sfeer en de mogelijkheid om het vak hematologie te leren en te beoefenen. De Christopher studie is mogelijk gemaakt

door de medewerking van veel afdelingen, waaronder de interne geneeskunde, longziekte en radiologie, waarvoor mijn dank. Asiong en Tamara; dank voor jullie inzet! Ik wil ook de medewerkers van het hemostase laboratorium danken voor de verwerking van alle monsters en het geduld om ze later weer uit de vriezer te halen. Huub en de “stollers” van de 13e, bedankt voor alle uitleg en de mogelijkheid tot overleg en discussie. Ik verheug mij op een voortgaande samenwerking.

Alle mede-Christopher onderzoekers; dank dat jullie mij als laatkomer lieten meewerken. Het was een bijzondere samenwerking met een prachtig resultaat. Beste Maaike, Mathilde, Hanneke, Lidwine en Stijn; het is geweldig om te zien dat er telkens weer een nieuw artikel verschijnt!

Mijn dank gaat uiteraard ook naar alle patiënten die toestemden in deelname aan een studie.

Beste Ka Lung en Dimitri, het was mij een waar genoegen om met jullie een kamer te delen. De sfeer was altijd opperbest en dat maakte het werken en ploeteren minder zwaar (of kwam dat toch door het snoep?). Beiden veel succes in Antwerpen. Ka Lung, dank dat jij mijn paranimf wilde zijn. Binnenkort ben jij aan de beurt!

Lieve vrienden, ook al zien we elkaar weinig, uit het oog is zeker niet uit het hart.

Lieve Selma, waarom jij mijn paranimf bent hoef ik niet uit te leggen. Dank voor je vriendschap, je gezelligheid, je lach, je wandelingen, je mening en je warmte.

Lieve Jac en Lies, ook jullie wil ik bedanken voor de warmte en de vele logeerpartijen met steeds meer kinderen. Het is altijd erg gezellig, hoewel de Janssen-Houben-grapjes voor mij soms nog steeds te snel gaan.

Lieve papa en mama, ik wil jullie graag bedanken voor de ruimte en het vertrouwen dat jullie mij gaven. Ik weet nu hoe moeilijk het soms moet zijn geweest om mij los te laten en je er niet mee te bemoeien. Papa, ik weet dat je trots zou zijn geweest; mama straalt zeker voor twee.

Lieve Evert, Imke, Merijn en Janne, wat hebben we toch een heerlijk gezinnetje. Geloof het of niet, maar door jullie komst heb ik dit proefschrift kunnen maken. Evert, veel dank voor je geduld. Ik weet dat ik een computeranalfabeet ben. Ik hou veel van jou en wat de toekomst ons brengt ...wzw.

Marieke

Taege nemes zègke want ich mein det ich gelökkig bin
Zèk ‘t neet te hel
ich bin zo bang det ‘t dan sjtop
Want ich vinj ‘t moeilijk óm van gelök te sjpraeke
Maar mit get mazzel hölt
mien gelök nog lang neet op

- Gé Reinders

LIST OF PUBLICATIONS

Kruip MJHA, Söhne M, Nijkeuter M, Kwakkel- van Erp HM, Tick LW, Halkes SJM, Prins MH, Kramer MHH, Huisman MV, Büller HR, Leebeek FWG. A simple diagnostic strategy in hospitalized patients with clinically suspected pulmonary embolism. J Int Med 2006, in press.

Söhne M, **Kruip MJ**, Nijkeuter M, Tick L, Kwakkel H, Halkes SJ, Huisman MV, Büller HR. Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD or heart failure and in older patients with suspected pulmonary embolism. J Thromb Haemost. 2006;4:1042-1046.

van Belle A, Büller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, Kramer MH, **Kruip MJ**, Kwakkel-van Erp JM, Leebeek FW, Nijkeuter M, Prins MH, Söhne M, Tick LW. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. Jama. 2006;295:172-179.

Leclercq MG, **Kruip MJ**, Mac Gillavry MR, Van Marwijk Kooy M, Büller HR. Observer variability in the assessment of clinical probability in patients with suspected pulmonary embolism. J Thromb Haemost. 2004;2:1204-1206.

Kruip MJ, Leclercq MG, van der Heul C, Prins MH, Büller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med. 2003;138:941-951.

Kruip MJ, Slob MJ, Schijen JH, van der Heul C, Büller 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;162:1631-1635.

Wallis JW, **Kruip M**, de Jongh-Leuvenink J, Büller HR. A comparative study of two rapid D-dimer tests for the exclusion of pulmonary embolism in symptomatic patients. Thromb Haemost. 2000;84:925.

Kruip MJ, Slob MJ, Büller HR, van der Heul C. A prospective clinical study on the feasibility and safety of a combined noninvasive/pulmonary angiography strategy in patients with suspected pulmonary embolism: an interim analysis. Clin Appl Thromb Hemost. 1999;5:222-225.

Kruip MJ, Tromp SC, Verweij M, Petri H. First-time pregnancy, an apparent motive for referral to a Zimbabwean district hospital. Trop Doct. 1994;24:138-139.

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 11 december 1970 te Roermond. Na het behalen van het Gymnasium-B diploma in 1989 aan het Bisschoppelijk College Broekhin te Roermond, studeerde zij Geneeskunde aan de Rijksuniversiteit Limburg (tegenwoordig: Universiteit Maastricht). Zij behaalde haar artsexamen met genoegen in 1996, waarna zij als arts-assistent ging werken in het St. Elisabeth ziekenhuis te Tilburg. In 1998 startte zij in dit ziekenhuis met de opleiding tot internist (opleider Dr. C. van der Heul), welke in 2002 werd voortgezet op de afdeling hematologie van het Erasmus MC te Rotterdam (opleiders Prof. Dr. H.A.P. Pols (Interne Geneeskunde) en Prof. Dr. B. Löwenberg (Hematologie)). De registratie als internist vond plaats in 2004, de registratie als internist-hematoloog in 2005. Vanaf 2005 is zij werkzaam als internist-hematoloog op de afdeling hematologie, centrumlokatie van het Erasmus MC. Gedurende de gehele opleiding tot internist en vervolgens internist-hematoloog heeft zij aan het proefschrift gewerkt. Zij is gehuwd met Evert Janssen en samen hebben zij 3 dochters, Imke, Merijn en Janne.

LIST OF ABBREVIATIONS

CDR	clinical decision rule
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	computed tomography
CUS	compression ultrasonography
DD	D-dimer
DVT	deep vein thrombosis
IPG	impedance plethysmography
PA	pulmonary angiography
PE	pulmonary embolism
s-CT	spiral computed tomography
VTE	venous thromboembolic event