The diagnosis and prognosis of pulmonary embolism

Söhne, M.

Publication date
2005
Document Version
Final published version

The diagnosis and prognosis of pulmonary embolism

The diagnosis and prognosis of pulmonary embolism
Thesis, University of Amsterdam, the Netherlands
ISBN-10 9090198024

Cover by Rogier Söhne

Manuscript editor: Margot Visser (www.GoGoWise.com)
Printed by Buijten en Schipperheijn, Amsterdam

Publication of this thesis is financially supported by: Stichting Amstol, Stichting tot Steun Promovendi Vasculaire Geneeskunde, Novo Nordisk, Novartis, Roche Diagnostics, Pfizer, AstraZeneca, Sanofi-Aventis, Bristol-Myers Squibb, MSD, University of Amsterdam, Servier, AGEN Biomedical, Inverness Medical Innovations.

The diagnosis and prognosis of pulmonary embolism

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus prof. mr. P.F. van der Heijden ten overstaan van een
door het college voor promoties ingestelde commissie, in het openbaar te verdedigen in de
Aula der Universiteit op

donderdag 6 oktober 2005, te 12.00 uur

door

Maaike Söhne

geboren te Purmerend

Promotiecommissie

Promotor:	Prof. dr. H.R. Büller
Co-promotor:	Dr. V.E.A. Gerdes
Overige leden:	Dr. D.P.M. Brandjes
	Prof. dr. M.M. Levi
	Prof. dr. M.H. Prins
	Prof. dr. R.J.G. Peters
	Prof. dr. G.J. den Heeten

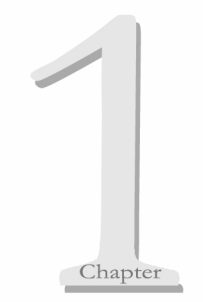
Faculteit der Geneeskunde

The study described in this thesis was supported by a grant of the Netherlands Heart Foundation (NHF-2002B088). Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

Aan Ron en Joke

Contents

Part II Prognosis of pulmonary embolism



General introduction and outline of the thesis

MAAIKE SÖHNE AND HARRY R. BÜLLER

The diagnosis of pulmonary embolism

A turning point in the diagnostic work-up of patients with suspected pulmonary embolism is the year 1963. Williams and Sasahara introduced pulmonary angiography in that year and Wagner the perfusion scan in 1964 [1-3]. This was the first time that one could directly or indirectly visualize the presence of clots in the lungs. Before this time the diagnostic tools available to physicians existed mainly of an arterial blood gas, the chest x-ray and an electrocardiogram. Although these techniques had some value in diagnosing or excluding alternative diagnoses resembling pulmonary embolism, such as myocardial infarction, pneumothorax or pneumonia, the usefulness in confirming or ruling out pulmonary embolism was minimal [4].

The introduction of the ventilation scan in 1968 which increased the specificity of the perfusion scan was the next step forward in the diagnostic process of pulmonary embolism [5]. However, the definition of a proper classification of the ventilation/perfusion scan has long been a matter of debate. It is now well established that a normal perfusion scan safely rules out pulmonary embolism and that anticoagulant treatment can be withheld, while a high probability scan, defined as at least one segmental perfusion defect with locally normal ventilation, confirms the presence of the disease with a specificity of 97% [6]. Ventilation/perfusion scintigraphy has two major disadvantages: the need for the availability of the costly ventilation materials and the fact that 40% to 60% of patients with suspected disease will have a non-diagnostic test result. On the other hand, with pulmonary angiography non-diagnostic test results occur in approximately 4%, but there is a risk for major complications. Although with modern techniques, pulmonary angiography is associated with a 0.1% mortality rate and major non-fatal complications in 0.4%, clinicians remain reluctant to perform angiography [7]. Moreover, expertise is necessary and not available in all hospitals.

To reduce the need for often expensive imaging techniques and to increase the diagnostic yield, easy to perform non-invasive tests were desired to rule out pulmonary embolism. A major breakthrough in this perspective surfaced in the late nineties with the introduction of the D-dimer test in combination with clinical probability scores, either as a probability estimate or as a standardized clinical decision rule [8-10]. D-dimers are degradation products of fibrin and its concentration increases in the presence of coagulation activation and subsequent fibrinolysis. Although the absence of D-dimers in combination with a low clinical probability makes pulmonary embolism highly unlikely, an increase of D-dimers is very non-specific. As revealed by several clinical outcome studies, the combination of these

tests can safely spare 20% to 30% of patients with suspected pulmonary embolism the need to undergo imaging techniques [11;12]. In the remaining large proportion of patients diagnostic imaging remains necessary, with its known accompanying difficulties. Other assessment such as inflammatory markers, including C-reactive protein, may allow for enlarging the 20 to 30% of patients in whom further testing can be withheld.

However, the need for performing ventilation/perfusion scanning and/or pulmonary angiography might come to an end with the recent introduction of spiral computed tomography (CT), initially single slice, but now multi slice. Several large management studies regarding the clinical utility of spiral CT appeared since 2002, in which the position of spiral CT within the diagnostic work-up was initially unclear and therefore surrounded by other diagnostic techniques [13-15]. However, as recent as 2005 it has been suggested that spiral CT might be used as the only imaging test to guide management decisions[16].

Whether this strategy can be adopted in clinical practice remains to be resolved in a large outcome study as well as whether extending the cut-off score of the clinical decision rule in combination with D-dimer could increase the proportion of patients in whom spiral CT can be withheld. Moreover the robustness of this strategy has to be determined for the different patient subgroups with suspected pulmonary embolism.

In **chapter 2** diagnostic accuracy of the currently available diagnostic techniques for pulmonary embolism are reviewed. In **chapter 3** the findings of a large clinical follow-up study in patients with suspected pulmonary embolism is presented. In this study the safety of excluding pulmonary embolism and withholding anticoagulant therapy in patients with either the combination of an unlikely clinical decision rule score and a normal D-dimer concentration or a normal CT is evaluated. Whether this novel diagnostic algorithm can also be applied to patients with a malignancy, heart failure, COPD, previous venous thromboembolism or in older patients is described in **chapter 4**.

A potential advantage of using spiral CT as the principal imaging technique is the possibility of diagnosing other diseases which may explain the signs and symptoms of the patients once pulmonary embolism has been excluded. This is evaluated in **chapter 5**. In **chapter 6** the potential clinical utility of C-reactive protein, alone or in combination with the clinical decision rule and D-dimer is assessed in a subgroup of the patients studied in chapter 3.

Patients with cancer as well as older patients with co morbid conditions often have raised D-dimer levels, decreasing the clinical applicability. The combination of the clinical decision rule and the D-dimer test is assessed in cancer and older patients with suspected pulmonary embolism in **chapter 7** and **chapter 8**, respectively.

The prognosis of pulmonary embolism

Case fatality rates of treated patients with proven pulmonary embolism vary in the different studies depending on the study populations selected, the hemodynamic status at presentation and the duration of follow-up. A review from Douketis and collegues reported a 2-week fatality rate of 2.3% [17]. The patients included in this review were enrolled in randomized clinical trials and very few were hemodynamically unstable. Higher mortality rates up to 15% for 1 to 6 months of follow-up have been described in other studies[18].

There has been a long interest in the ability to predict adverse outcomes, i.e. the development of recurrent pulmonary embolism or death due to pulmonary embolism, in order to be able to decide on the best treatment for the individual patient. There is consensus that patients who present with hemodynamically instable pulmonary embolism should be given a short course of thrombolytic therapy, which is associated with a relative decrease in mortality of approximately 50% (12.7% for heparin versus 6.2% for thrombolytic therapy) [19;20]. However, thrombolytic therapy is associated with a risk of major bleeding and is therefore not indicated in the large group of patients who are hemodynamically stable, but in whom (fatal) recurrent venous thromboembolism occurs at a lower rate, i.e. approximately in 4 to 8% during three months of follow-up [13;14;21;22]. If this subgroup can easily and non-invasively be detected, it would be interesting to determine the potential benefit of thrombolytics in these patients. Right ventricular dysfunction on echocardiography appears to be such a tool, while brain natriuretic peptide (BNP) and cardiac troponins have been suggested as easy measurable biomarkers that might predict adverse outcomes in hemodynamically stable patients with pulmonary embolism.

Chapter 9 reviews the prognostic value of echocardiography to predict adverse outcome and in **chapter 10** an overview of the biomarkers and their relation to pulmonary embolism is presented**. Chapter 11** and **12** describe the results of studies in which BNP was measured to predict adverse outcome in hemodynamically stable pulmonary embolism, while **chapter 13** evaluates this relation for the cardiac troponins.

Reference List

1. Williams JR, Wilcox C, et al. Angiography in pulmonary embolism. JAMA 1963; 184:473-476.
2. Sasahara AA, Stein M, Simon M, Littmann D. Pulmonary angiography in the diagnosis of thromboembolic disease. N Engl J Med 1964; 270:1075-1081.
3. Wagner HN, Sabiston DC, McAfee JG. Diagnosis of massive pulmonary embolism in man by radioisotope scanning. N Engl J Med 1964; 271:377-384.

4. Dalen JE. Pulmonary embolism: what have we learned since Virchow? Natural history, pathophysiology, and diagnosis. Chest 2002; 122:1440-1456.
5. Wagner HN, Jr., Lopez-Majano V, Langan JK, Joshi RC. Radioactive xenon in the differential diagnosis of pulmonary embolism. Radiology 1968; 91:1168-1174.
6. 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; 263:2753-2759.
7. 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.
8. 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.
9. 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.
10. Wells PS, Anderson DR, 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.
11. Kruip MJ, Slob MJ, Schijen JH, van der HC, 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.
12. 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.
13. 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.
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; 116:291-299.
15. 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.
16. Perrier A, Roy PM, Sanchez O et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med 2005; 352:1760-1768.
17. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998; 279:458-462.
18. White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107:I4-I8.
19. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis Compared With Heparin for the Initial Treatment of Pulmonary Embolism. A Meta-Analysis of the Randomized Controlled Trials. Circulation 2004.
20. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:401S-428S.
21. 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.
22. Buller HR, Davidson BL et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003; 349:1695-1702.

Part I

One

Pulmonary embolism

MAAIKE SÖHNE, MARIJE TEN WOLDE, EDWIN J.R.VAN BEEK,
HARRY R.BÜLLER

DAVID A. LIPSON, EDWIN VAN BEEK. FUNCTIONAL LUNG IMAGING.
1ST ED. UNITED KINGDOM; TECHSET: 480-492

Introduction

In western society, pulmonary embolism is a common disease in both in- and outpatients, with an estimated incidence of 1 to 2 per 1000 inhabitants per year. This number increases with age, likely because of the higher prevalence of known risk factors for pulmonary embolism in the elderly. Besides increasing age, many other factors are known to increase the incidence of pulmonary embolism. These include previous venous thromboembolism, malignancy, immobilisation, surgery, pregnancy, the use of oral contraceptives and genetic risk factors.

It is well known that the clinical diagnosis of pulmonary embolism is inaccurate because of the nonspecificity of the signs and symptoms in patients presenting with a suspicion of this disease. On one hand overestimation of pulmonary embolism is prevalent, as the disease is confirmed by objective testing in only 25% of patients. On the other hand, however, the diagnosis is frequently missed in clinical practice as revealed by autopsy studies. Therefore, objective diagnostic strategies are mandatory to safely confirm or exclude pulmonary embolism. Until recently, pulmonary angiography was the gold standard diagnostic method for establishing and ruling out pulmonary embolism. Nowadays, less invasive diagnostic tests are available to confirm or refute the presence of thrombosis. In this chapter we will discuss different strategies to exclude or confirm the presence of pulmonary embolism. First, a general overview of the etiology, natural history and treatment will be presented.

Etiology

Our understanding of the etiology of venous thromboembolism has markedly improved in the last decades due to many studies that have been exploring the role of inherited and acquired risk factors. Currently, venous thromboembolism is considered to be a multifactorial disease; a result of the interaction between different risk factors. In a majority of patients with deep venous thrombosis or pulmonary embolism, one or more underlying causes can be identified. This knowledge may be helpful in optimizing the duration and intensity of therapy to prevent recurrent venous thromboembolism in the individual patient.

Inherited Risk Factors

A number of hereditary abnormalities of the coagulation system are associated with an increased risk for venous thromboembolism. These genetic risk factors can be detected in

approximately 50% of patients with a first episode of venous thromboembolism.

Antithrombin, protein C and protein S deficiencies

The first inherited risk factor for venous thrombosis was described by Egeberg in 1965 in a Norwegian family with a tendency for venous thromboembolism [1]. This family showed a deficiency of antithrombin, an important physiological inhibitor of activated coagulation factors. Since then, almost all components of the coagulation cascade have been investigated and many risk factors have been identified. The initial studies revealed two more deficiencies of natural anticoagulants associated with a higher risk of venous thromboembolism, i.e. protein C and protein S [2-4]. These deficiencies, together with the antithrombin deficiency, are present in 5 to 10% of patients diagnosed with thrombosis [5] whereas the prevalence in the general population is less than 1% [6-8]. Patients with heterozygous deficiencies of one or more of these natural anticoagulants are at increased risk of developing thrombosis at a young age, which often occurs spontaneously. Moreover, thrombotic events in these patients have a tendency to recur. Figures on the absolute incidence of venous thromboembolism in subjects with one of these natural anticoagulant deficiencies vary from 3% per year in retrospective family studies [9] to 0.8% per year in a prospective family study [10].

Factor V Leiden

Factor V Leiden is the most common thrombophilic risk factor, with a prevalence varying from 2-15% in the Caucasian population [11] up to 15-25% in unselected patients with venous thromboembolism [11-13]. A point mutation in the factor V gene causes a hypercoagulable state by slowing the inactivation of factor Va by activated protein C [14]. Two large studies show a 2 to 7 fold increased risk of venous thromboembolism for heterozygous carriers over non-carriers [12;15]. Homozygous carriers have an approximately 80-fold increased risk compared to non-carriers [16]. The prevalence of the factor V Leiden mutation in patients with primary deep vein thrombosis is twice as high as compared to those with primary pulmonary embolism [17]. Therefore, it is likely that factor V Leiden mutation more often predisposes to deep venous thrombosis than to pulmonary embolism. Furthermore, recent data show that the risk of recurrent venous thromboembolism is similar among carriers and noncarriers of the factor V Leiden mutation [18].

Prothrombin G20210A mutation

The prothrombin G20210A mutation is found in 2 to 4% of the Caucasian population [19] and in 6 to 16% of patients with unselected deep venous thrombosis [20]. Patients with this mutation have an approximately 30% increase in plasma prothrombin levels, which therefore likely generates more thrombin. Carriers have a higher risk to develop venous thromboembolism, with an odds ratio of approximately 4 [20].

Furthermore, there are risk factors for which at present it is unknown whether they are congenital. Mild hyperhomocysteinemia, high factor VIII, IX, XI and thrombin activatable fibrinolysis inhibitor (TAFI) levels, activated protein C resistance without factor V Leiden and dysfibrinogenemia or high levels of fibrinogen belong to this category and are all found to be associated with a higher risk for the development of venous thrombo-embolism.

Acquired risk factors

Most of the acquired risk factors are transient. However, increasing age and a history of previous venous thromboembolism are independent and persistent risk factors for life. Estimated incidences of venous thromboembolism in the elderly are 10 times higher than in people under the age of 40 [21]. Malignancy and major surgery are probably the strongest risk factors for venous thromboembolism. The association between cancer and venous thromboembolism was already recognized in the 19th century by Trousseau. Thrombosis most commonly occurs in advanced stage of disease with certain types, such as prostatic, pancreatic, ovarian, gastrointestinal and pulmonary tumours, being most associated [22]. Furthermore, in patients with a first episode of idiopathic thrombosis there is a 10-20% probability of having occult cancer at time of diagnosis or which becomes apparent within the following 2 years [21].

Regarding different types of surgery, orthopedic and neurosurgery are associated with the highest risk of developing thrombosis in the postoperative period. Incidences of 45-70% (asymptomatic) deep venous thrombosis have been described if no prophylaxis is given after total knee or hip replacement.

Pregnancy and the post-partum period carry a 6 to 10-fold increased thromboembolic risk, with yearly incidences of 0.8 to 1.3 per 1000, with the highest risk during the postpartum period. The presence of antiphospholipid antibodies is another acquired risk factor and is associated with a 9- fold increased risk of venous thrombosis [21]. Finally, oral contraceptives are known to increase the risk of venous thromboembolism and use of the second or third generation pills have odds ratios of 4 to 8 towards developing thrombosis as compared to non-users.

Prognosis

Ninety percent of patients with acute pulmonary embolism will reach hospital to allow a diagnosis to be made, and a classification of massive, sub-massive and non-massive pulmonary embolism has been proposed [23]. Massive pulmonary embolism, consisting of patients with hemodynamic instability, is relatively rare, occuring in less than 5% of patients. These patients will require aggressive therapy to prevent death. Fibrinolytic therapy is the first line of treatment for this critically ill patient population [24]. In the group of hemodynamic stable patients with pulmonary embolism, standard treatment consists of (low molecular weight) heparin followed by a course of vitamin K antagonists. In the subgroup of patients with echocardiographic signs of right ventricular dysfunction, there is some evidence that more aggressive therapy may be helpful in preventing clinical deterioration [25;26].

Mortality rates over a 3-month observation period in hemodynamically stable patients ranges from 1 to 7%, with only a small proportion due to recurrent pulmonary embolism. Whether or not a patient with an adequate blood pressure will die as a result of pulmonary embolism is difficult to predict. Therefore, prognostic parameters are needed to select those patients who might benefit from more aggressive therapy to prevent a bad outcome. Echocardiographic right ventricular dysfunction and laboratory parameters like brain natriuretic peptide (BNP) and cardiac troponines are advocated as prognostic parameters in recent studies.

Echocardiography

In patients with acute pulmonary embolism a minimal to severe rise in pulmonary artery pressure can occur, depending on the extent and localization of the embolus as well as the pre-existing cardiopulmonary status of the patient. With the subsequent increase in right ventricular afterload, the right ventricle may dilate, become hypokinetic and ultimately fail. Several studies have been performed showing an association between echocardiographic right venticular dysfunction in patients with pulmonary embolism and a poor prognosis. Prevalence of right ventricular dysfunction in these studies varied from 40% in normotensive patients to 70% in patients with more extensive pulmonary embolism. They suggest an at least two-fold increased risk of pulmonary embolism related mortality in patients with right ventricular dysfunction. However, this predictive potential seems less strong in hemodynamically stable patients with acute pulmonary embolism. The studies in normotensive patients show a low specificity of 60% and a poor positive predictive value of 5% [24;27]. Therefore, it remains unclear whether right ventricular dys-

function is a reliable predictor of adverse outcomes in normotensive patients with acute pulmonary embolism.

BNP and cardiac troponins

BNP is a plasma neurohormone secreted in the cardiac ventricles in response to stretch or pressure increase. Cardiac troponins are released when myocardial injury occurs. Three studies investigating elevated troponine levels in patients with pulmonary embolism have been performed. Elevated levels occur in 20 to 40% of patients with acute pulmonary embolism [28-30]. These studies show that there is a strong association between elevated troponin levels and mortality in patients with pulmonary embolism, with odds ratios up to 29. However, with small numbers of patients the confidence intervals of these odds ratios are very wide with all the studies including hemodynamically unstable patients. BNP levels are known to correlate with left ventricular dysfunction. One clinical study in 110 hemodynamically stable patients with pulmonary embolism showed an odds ratio of 9 for the risk of death if BNP levels are above 21.7 pmol/L [31].

Therefore, cardiac troponins as well as BNP have the potential to be prognostic indicators and may be useful for optimizing management of patients with acute pulmonary embolism in the future. Prospective studies need to confirm these assumptions.

Therapy

After confirming the diagnosis, treatment is mandatory since the natural history of untreated pulmonary embolism is unfavorable. Mortality is as high as 25% as shown by the only randomized, non-treatment controlled trial by Barrit and Jordan in 1960. In patients receiving anticoagulant therapy mortality varies from 1 to 7%. Standard treatment of patients with hemodynamically stable pulmonary embolism consists of a 5 to 10 day course of (low molecular weight) heparin, during which oral vitamin K antagonists are started in a dose to achieve an international normalized ratio (INR) between 2.0 and 3.0. Vitamin K antagonists are then continued for 3 to 12 months, depending on the presence of risk factors and co-morbidity. After this period the treatment is usually stopped, although recurrent venous thromboembolism occurs in 5 to 10 percent of patients in the first year. Extended use of full-dose vitamin K antagonists is associated with reduced rates of recurrent venous thromboembolism [32;33], but this benefit does not outweigh the annual bleeding rate of this therapy in the long term. A recent trial suggested that long-term, low-intensity warfarin therapy given with a target INR of 1.5 to 2.0 results in a large and significant reduction in the risk of recurrent venous thrombosis and is safe regarding to

major bleeding [34]. However, this intensity was less effective when compared to an INR of 2-3, while the bleeding rate was similar [35]. Hence, the optimal duration remains unknown.
Placement of an inferior vena cava filter to prevent lower extremity thrombi from embolizing to the lungs, should be considered when a patient cannot be given anticoagulant treatment, when recurrent embolism occurs despite adequate therapy or if significant bleeding complications are encountered during anticoagulation.
The indication for fibrinolytic therapy in patients with pulmonary embolism is limited to those patients with massive embolism, accompanied by hypotension and/or shock. The use of fibrinolytic therapy in patients with submassive pulmonary embolism and right ventricular dysfunction is still a matter of debate.

Diagnostic strategies

Proper methodological evaluation of diagnostic strategies

Over the last decades many new diagnostic strategies have been introduced in the work-up of patients suspected of pulmonary embolism. In contrast to the development and introduction of new drugs, wherefour subsequent phases must be adequately completed before registration, there are no mandatory guidelines for the evaluation of new diagnostic methods or procedures. To prevent premature introduction and inappropriate use of new diagnostic techniques it would be desirable to evaluate a new diagnostic strategy analogous to the four phase hierarchical model for the evaluation of new drugs.

Summary of phases in implementing new diagnostic strategies

Phase 1

The first phase consists of developing specified technical details of the test. Equipment and use should be defined, as well as physical and/or biochemical parameters specific to the test (e.g minimal detection level, circadian fluctuation, resolution, amount of contrast). Objective diagnostic criteria regarding a normal and an abnormal test result should be established and inter-/intraobserver variability needs to be assessed.

Phase 2

In phase two the diagnostic accuracy of the test is assessed. The results of the test under evaluation are compared with the outcome of the gold standard method. This should be performed in sufficiently large numbers of consecutive patients and the readers blinded to the other test results. The accuracy of the test can then be evaluated in terms of sensitivity, specificity, positive and negative predictive values. If necessary, adjustments of the criteria set in the first phase can be made.

Phase 3

When sufficient accuracy of the test has been proven in the second phase, the third phase can be executed, in which the test will be implemented in the diagnostic process through management studies. Therapeutic decisions will be made, based on the results of the new diagnostic test. Follow-up of all patients will detect false negative test results. In general, a test is considered to be safe if the upper limit of the 95% confidence interval of the number of false negative test results doesn't exceed 3%. The test can now be introduced into routine clinical practice.

Phase 4

In the fourth and last phase cost-effectiveness of the new test will be evaluated in comparison to the existing strategies.

Criteria in reviewing clinical outcome studies

Clinical outcome management studies play an important role in the implementation of strategies to exclude or confirm pulmonary embolism. We reviewed different studies to evaluate various diagnostic strategies to exclude or confirm pulmonary embolism. To ensure that the different strategies were safe, we used the following methodological criteria: inclusion of consecutive patients suspected of pulmonary embolism; a predefined diagnostic strategy is used to refute or confirm the diagnosis; anticoagulant treatment is withheld or given based on the outcome of the diagnostic strategy; a follow-up of minimally three months, with an adequate description of the method of follow-up and less then 10% of patients lost during this time.

Clinical strategies to exclude or confirm pulmonary embolism

Since less than 30% of patients presenting with signs and symptoms suggestive of pulmonary embolism actually have the disease confirmed after objective testing [24;36;37], the diagnostic approach has gradually changed over the years. From strategies only trying to confirm pulmonary embolism, the objective of many studies these days is to also identify strategies in which the disease can safely and quickly be ruled out.

Which strategies have proven to safely exclude pulmonary embolism?

Strategies to refute pulmonary embolism have been evaluated in clinical outcome studies. Primary outcomes are defined as death due or possibly due to pulmonary embolism and the development of symptomatic deep venous thrombosis or pulmonary embolism in the follow-up period. Sensitivity of these strategies should approach 100%, because with every

Table 1: Diagnostic strategies to exclude pulmonary embolism

Reference	Number of patients	Number of VTE complications	Percentage (upper limit 95% CI)
Normal D-dimer[41,42]	201	0	0 (1.8)
Normal D-dimer plus low clinical probability[40,43-50]	894	2	0.2 (0.8)
Normal angiography[36]	480	4	0.8 (2.1)
Normal perfusion lung scintigraphy[51-57]	441	4	0.9 (2.3)
Non-diagnostic V/Q scan and normal serial IPG[51,56,71]	779	13	1.7 (2.8)
Non-diagnostic V/Q scan and normal serial ultrasound[44,72]	875	9	1.0 (2.0)
Normal spiral CT and normal ultrasound[45,65,73]	1264	16	1.3 (2.0)

2% decrease in sensitivity, 1 per 1000 patients evaluated will die as a result of inappropriately withholding anticoagulant therapy [38]. In general, a failure rate with an upper limit of the 95% confidence interval of 3% is considered to be safe. In the next section we will discuss the diagnostic strategies that have proven to safely exclude pulmonary embolism (Table 1).

Clinical decision rule, probability estimates and D-dimer

In excluding pulmonary embolism it is desirable to perform tests that are not invasive. Clinical assessment can be used to identify patients with a low or a high probability for pulmonary embolism. Intuitive clinical probability estimates, as well as structured algorithms are able to achieve a stratification of low, moderate and high probability categories in patients with suspected pulmonary embolism. According to several studies, the prevalence is expected to be ≤ 10% in patients with a low clinical probability, about 25% in the group with an intermediate probability and ≥ 60% in patients with a high probability [39]. However, one may not exclude pulmonary embolism solely on the basis of clinical assessment, because approximately 1 in 10^{40} of the patients with a low clinical probability still have the disease confirmed by objective testing.

D-dimers are formed when cross-linked fibrin is lysed by plasmin. Therefore, patients with thrombosis usually have elevated D-dimer concentrations. Unfortunately, elevations of D-dimer concentrations are nonspecific (e.g levels can be increased by aging, inflammation and cancer). Thus, an abnormal result has a low positive predictive value. The utility of measuring D-dimer concentration in patients suspected of pulmonary embolism is its high negative predictive value. There are many different D-dimer assays available with widely varying sensitivities and negative predictive values. With the

current rapid ELISA test and immunoturbidimetric assay, both sensitivity and negative predictive values are high (90-100% and 94-100% respectively). Nevertheless, most D-dimer assays do not have a sufficiently high sensitivity to be used as the only method to exclude pulmonary embolism. Two studies have been perfomed using a normal D-dimer concentration, measured with a rapid ELISA test, as the only step to exclude the disease in all referred patients [41;42]. A total of 201 patients were included and none of the patients experienced venous thrombotic events during a 3-month follow-up period (failure rate 0%; upper limit 95% CI 1.8%).

The combination of a normal D-dimer concentration together with a low clinical probability to exclude pulmonary embolism in all referred patients was evaluated in four studies [43;44;40;45]. Of the 894 patients included, there were two venous thrombotic events during follow-up (failure rate 0.2%; upper 95% CI 0.8%). Hence, the combination of low clinical probability and a normal high sensitive D-dimer assay is safe to rule out pulmonary embolism.

Pulmonary angiography

The procedure for the performance of a pulmonary angiography is standardised and criteria for a normal and an abnormal test result are well formulated [46;47]. Inter observer variability has been found to be minimal, especially with use of intra-arterial digital subtraction angiography [48;49]. Since pulmonary angiography is generally accepted as the 'gold standard' or reference method in the diagnostic process of pulmonary embolism, sensitivity and specificity of this technique cannot be evaluated formally. Nevertheless, the technique has shown its reliability in several clinical studies where follow-up of patients with normal angiographies revealed a recurrent thromboembolic event rate of 1.9%. In one multi-center study of 931 in-and outpatients, 755 (81%) underwent pulmonary angiography. Results were normal in 480 patients and these patients did not receive anticoagulant treatment. During follow-up 4 patients died of pulmonary embolism (failure rate 0.8%; upper limit 95% CI: 2.1%) [36].

Ventilation-perfusion scintigraphy and serial leg testing

Ventilation-perfusion scintigraphy (V/Q scan) has completed all phases of a proper methodological evaluation of a diagnostic test. The first phase started with the introduction of the perfusion scan in 1964. The technique is safe [50], but the criteria for interpretation of the scans have long been a matter of debate. Presently, a classification of normal, high probability and non-diagnostic scan outcomes is clinically most applicable and widely accepted. A comprehensive assessment of the sensitivity and specificity of V/Q scans was reported in the PIOPED study [36]. In this study 755 patients suspected of

pulmonary embolism underwent V/Q scanning and pulmonary angiography. 251 patients (33%) had angiographic proven pulmonary embolism. 98% of these patients had abnormal V/Q scan findings, with 41% having high probability scans. Sensitivity and negative predictive value of the near normal/normal scan were 98% and 91% respectively. Thus, in using scintigraphy in the management of patients with suspected pulmonary embolism, a normal perfusion scan safely rules out the diagnosis and treatment can be withheld [51-57]. Unfortunately, this only occurs in a minority (about 25 %) of patients. In the 40-60% of patients with a non-diagnostic scan a second diagnostic test is necessary to exclude pulmonary embolism. For this purpose serial leg testing (ultrasound or impedance plethysmography) over a period of approximately 10 days or angiography can be used [44;58].

Helical computed tomography

Helical computed tomography (CT), also known as spiral CT, has been developed as a diagnostic tool in confirming and excluding pulmonary embolism since 1992, when the first clinical study with spiral CT was performed [59]. Criteria for diagnosing pulmonary embolism have been established. Interobserver variability is demonstrated to be good in several studies, although there is a clear learning curve for reliably interpreting spiral CT [60]. Considering pulmonary angiography as the reference standard, the reported sensitivities in different studies with spiral CT ranges from 64% to 93%, with specificity from 89% to 100% [61]. These wide ranges may be related to differences in patient selection and other study design aspects [60;61]. Recently, a new generation helical CT has become available, the multi-detector helical CT, which has a shorter imaging time and thinner collimation. Initial studies with this multi-detector helical CT suggest higher sensitivities, especially for subsegmental embolism [62-64]. However, management studies have not been performed yet.

Thus far, a few management studies have been performed using single-detector spiral CT. These studies show reasonable results. In two studies, single-detector spiral CT was combined with ultrasound to exclude pulmonary embolism in either patients with a low/intermediate clinical probability or in patients with a moderate/high probability. The study of Musset et al. shows venous thromboembolic events during a 3-month follow-up in 1.8% (upper 95% CI 3.3%). Anderson et al. did not observe any thrombotic events during follow-up (upper 95% CI 1.3%) in patients with a moderate/high probability or an abnormal D-dimer and normal spiral CT and ultrasound. The only management study using normal single detector spiral CT and normal serial ultrasound to exclude pulmonary embolism in all referred patients showed a sensitivity above 99% [65]. Ultrasound was positive in only 2 of these 248 (0.8%) patients. It could therefore be suggested that with the

new multidetector spiral CT it might even be safe to exclude pulmonary embolism based on the result of normal spiral CT only. However, this needs to be confirmed in future prospective studies.

Which strategies have proven to adequately confirm pulmonary embolism?

In evaluating whether a diagnostic strategy is accurate enough to confirm pulmonary embolism, the most important parameters are the positive predictive value and the specificity. This should be high, because incorrect diagnosis of the condition (false positive) exposes the patient to anticoagulant therapy and therefore to the risk of major bleeding. Several strategies are available to confirm the presence of pulmonary embolism.

Pulmonary angiography

Pulmonary angiography visualizes emboli through a persistent intraluminal filling defect or an abrupt cut-off in an artery with a diameter of > 2 mm [66]. Specificity figures are unknown since it is the reference method. Interobserver variability is good and non-diagnostic results occur in approximately 4%. 10 to 20% of patients are unable to undergo angiography because of contraindications [46;67]. With modern techniques, pulmonary angiography is associated with a 0.1% mortality rate and major nonfatal complications in 0.4% of patients [68;69]. Because of this known risk of fatal complications, although minimal, clinicians often hesitate to perform angiography.

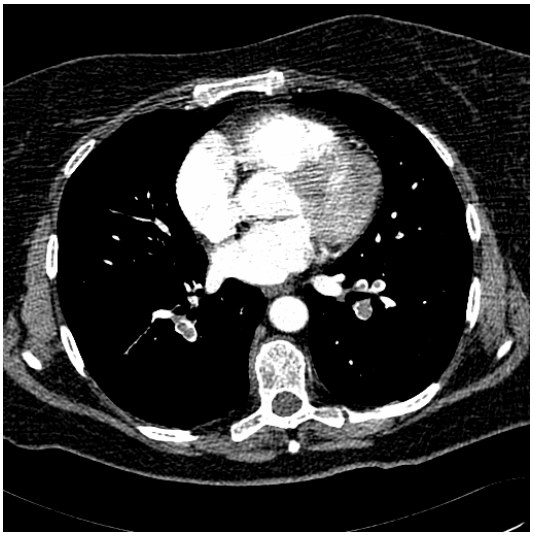
Ventilation-perfusion scintigraphy

By comparing the distribution of ^{99m}Technetium labeled albumin in the pulmonary vasculature with the distribution of radioactive aerosol in the lung airspace, mismatches can be defined. A high probability lungscan is defined as at least one mismatched perfusion defect that is segmental or larger [36;70].The specificity in the PIOPED study of a high probability scan result was 97% and the positive predictive value was 88%.

Helical computed tomography

A central partial intravascular filling defect surrounded by contrast medium, an eccentric or mural defect surrounded by contrast or a complete filling defect in a vessel are all signs of acute pulmonary embolism on spiral CT [60] (Picture 1). Specificity of spiral CT varies widely depending on collimation thickness. For 5 mm collimation scans, specificity ranges from 67 to 100%, while specificities of 94 to 100% are reported with 2 mm collimation [60]. Spiral CT has the additional advantage of providing an alternative diagnosis in a large proportion of patients suspected of pulmonary embolism [61].

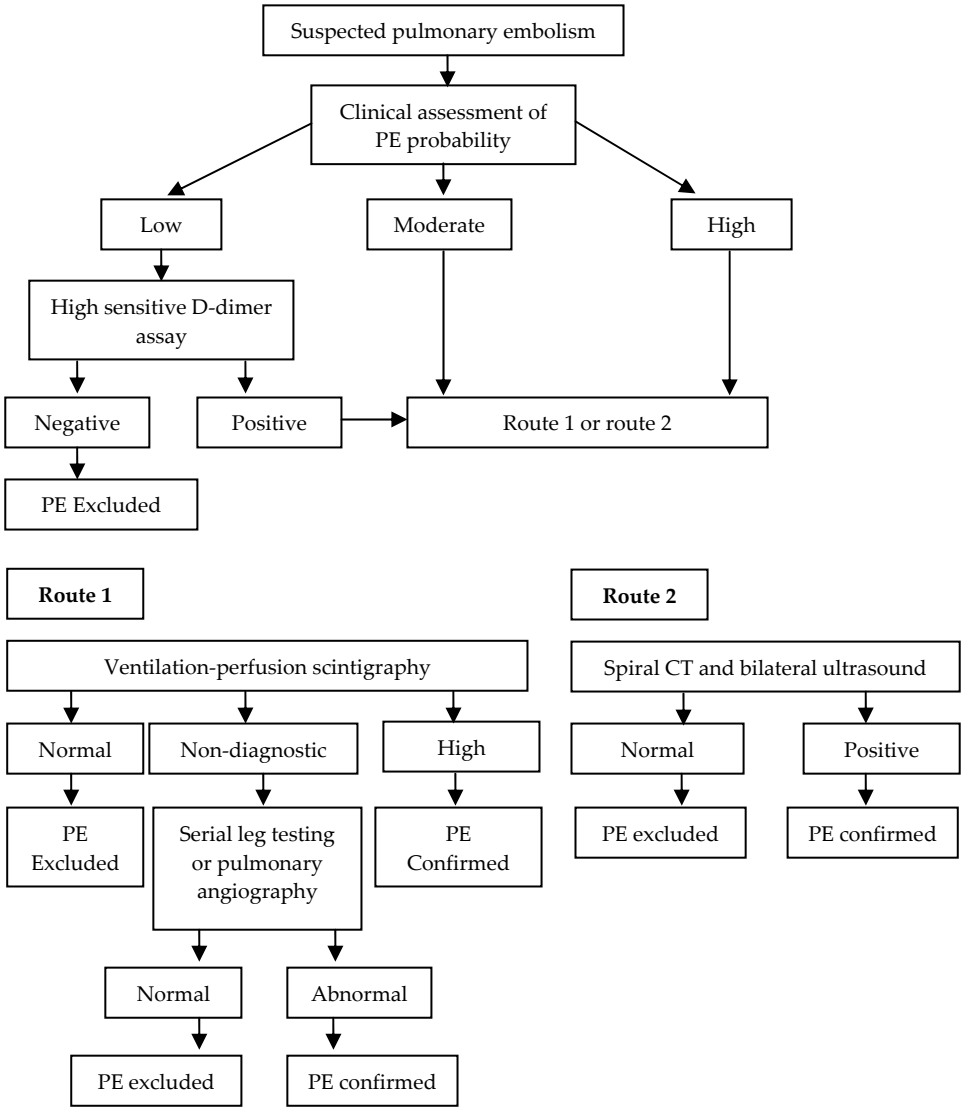
Picture 1: Central intravascular filling defects in the lower lobe pulmonary arteries bilaterally consistent with pulmonary embolism. The clot is surrounded by contrast medium



Serial leg testing

If in the diagnostic work-up of patients with suspected pulmonary embolism the result of a ventilation-perfusion scintigraphy is non-diagnostic, further tests should be performed. Serial leg testing has been used, since deep venous thrombosis and pulmonary embolism are both entities of the same disease. About three quarters of all patients who are diagnosed with pulmonary embolism do have deep venous thrombosis. Therefore the visualization of a deep venous thrombosis in a patient with clinical symptoms of pulmonary embolism is considered to be diagnostic for venous thromboembolism. Positive results of serial leg testing after non diagnostic ventilation-perfusion scan are found in 5 to 11% of patients and almost all within the first 5 days [58;71;72]. Furthermore, serial leg testing is used in some studies after a normal spiral CT. Positive ultrasound is found in 1 to 8% of patients with a normal spiral CT [45;65;73].

Recommended diagnostic algorithms



Reference List

1. Egeberg O. Inherited antithrombin deficiency causing thrombophilia. Thromb Diath Haemorrh 1965; 13:516-530.
2. Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wideman C. Deficiency of protein C in congenital thrombotic disease. J Clin Invest 1981; 68:1370-1373.
3. Broekmans AW, Veltkamp JJ, Bertina RM. Congenital protein C deficiency and venous thromboembolism. A study of three Dutch families. N Engl J Med 1983; 309:340-344.
4. Schwarz HP, Fischer M, Hopmeier P, Batard MA, Griffin JH. Plasma protein S deficiency in familial thrombotic disease. Blood 1984; 64:1297-1300.
5. Lensing AW, Prandoni P, Prins MH, Buller HR. Deep-vein thrombosis. Lancet 1999; 353:479-485.
6. Tait RC, Walker ID, Perry DJ et al. Prevalence of antithrombin deficiency in the healthy population. Br J Haematol 1994; 87:106-112.
7. Miletich J, Sherman L, Broze G, Jr. Absence of thrombosis in subjects with heterozygous protein C deficiency. N Engl J Med 1987; 317:991-996.
8. Tait RC, Walker ID, Reitsma PH et al. Prevalence of protein C deficiency in the healthy population. Thromb Haemost 1995; 73:87-93.
9. van den Belt AGM, Prins MH, Huisman MV, Hirsh J. Familial thrombophilia: a review analysis. Clin Appl Thromb Hemost 1996; 2:227-236.
10. Sanson BJ, Simioni P, Tormene D et al. The incidence of venous thromboembolism in asymptomatic carriers of a deficiency of antithrombin, protein C, or protein S: a prospective cohort study. Blood 1999; 94:3702-3706.
11. Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. Lancet 1995; 346:1133-1134.
12. Koster T, Rosendaal FR, de Ronde H, Briet E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. Lancet 1993; 342:1503-1506.
13. Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. N Engl J Med 1994; 330:517-522.
14. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: pathogenesis, clinical syndromes, and management. Blood 1996; 87:3531-3544.
15. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med 1995; 332:912-917.
16. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood 1995; 85:1504-1508.
17. Turkstra F, Karemaker R, Kuijer PM, Prins MH, Buller HR. Is the prevalence of the factor V Leiden mutation in patients with pulmonary embolism and deep vein thrombosis really different? Thromb Haemost 1999; 81:345-348.
18. Eichinger S, Weltermann A, Mannhalter C et al. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. Arch Intern Med 2002; 162:2357-2360.
19. Rosendaal FR, Doggen CJ, Zivelin A et al. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost 1998; 79:706-708.
20. Emmerich J, Rosendaal FR, Cattaneo M et al. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism--pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study Group for Pooled-Analysis in Venous Thromboembolism. Thromb Haemost 2001; 86:809-816.

21. Martinelli I. Risk factors in venous thromboembolism. Thromb Haemost 2001; 86:395-403.
22. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000; 343:1846-1850.
23. 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.
24. Goldhaber SZ, Haire WD, Feldstein ML et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341:507-511.
25. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002; 347:1143-1150.
26. Konstantinides S, Geibel A, Olschewski M et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. Circulation 1997; 96:882-888.
27. Grifoni S, Olivotto I, Cecchini P et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000; 101:2817-2822.
28. Konstantinides S, Geibel A, Olschewski M et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002; 106:1263-1268.
29. Douketis JD, Crowther MA, Stanton EB, Ginsberg JS. Elevated cardiac troponin levels in patients with submassive pulmonary embolism. Arch Intern Med 2002; 162:79-81.
30. Giannitsis E, Muller-Bardorff M, Kurowski V et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000; 102:211-217.
31. ten Wolde M, Tulevski II, Mulder JWM et al. Brain Natriuretic Peptide (BNP) as a predictor of adverse outcome in patients with pulmonary embolism. Circulation. In press.
32. Schulman S, Granqvist S, Holmstrom M et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. N Engl J Med 1997; 336:393-398.
33. Kearon C, Gent M, Hirsh J et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999; 340:901-907.
34. Ridker PM, Goldhaber SZ, Danielson E et al. Long-Term, Low-Intensity Warfarin Therapy for the Prevention of Recurrent Venous Thromboembolism. N Engl J Med 2003.
35. Kearon C, Ginsberg JS, Kovacs M, Anderson DR, Wells P. Low-Intensity (INR 1.5-1.9) Versus Conventional-Intensity (INR 2.0-3.0) Anticoagulation for Extended Treatment of Unprovoked VTE: A Randomized Double Blind Trial. Blood 100[11], 150a. 2002. Ref Type: Abstract
36. 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; 263:2753-2759.
37. 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; 98:891-899.
38. 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.
39. Kearon C. Diagnosis of pulmonary embolism. CMAJ 2003; 168:183-194.
40. Kruip MJ, Slob MJ, Schijen JH, van der HC, 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.

41. Perrier A, Desmarais S, Miron MJ et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999; 353:190-195.
42. Bernier M, Miron MJ, Desmarais S, Berube 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. J Thromb Haemost. 2004 Jul;2(7):1110-7.
43. 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.
44. ten Wolde M, Hagen PJ, Mac Gillavry MR et al. Non-invasive diagnostic work-up of patients with suspected pulmonary embolism:preliminary results of a management study. Thromb.Haemost. 7(suppl):OC153. 2001.
45. Anderson DR, Wells P, Kovacs M et al. Use of spiral computerized tomography (CT) to exclude the diagnosis of pulmonary embolism in the emergency department. Thromb.Haemost. 7(suppl):OC156. 2001 BC. Ref Type: Abstract
46. Stein PD, Athanasoulis C, Alavi A et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation 1992; 85:462-468.
47. Bookstein JJ. Segmental arteriography by pulmonary embolism. Radiology 1969; 93:1007-1012.
48. van Beek EJ, Bakker AJ, Reekers JA. Pulmonary embolism: interobserver agreement in the interpretation of conventional angiographic and DSA images in patients with nondiagnostic lung scan results. Radiology 1996; 198:721-724.
49. Quinn MF, Lundell CJ, Klotz TA et al. Reliability of selective pulmonary arteriography in the diagnosis of pulmonary embolism. AJR Am J Roentgenol 1987; 149:469-471.
50. Wagner HN SDMJeal. Diagnosis of massive pulmonary embolism in man by radioisotope scanning. N Engl J Med 1964; 271:377-384.
51. van Beek EJ, Kuyer PM, Schenk BE, Brandjes DP, ten Cate JW, Buller HR. A normal perfusion lung scan in patients with clinically suspected pulmonary embolism. Frequency and clinical validity. Chest 1995; 108:170-173.
52. Miron MJ, Perrier A, Bounameaux H et al. Contribution of noninvasive evaluation to the diagnosis of pulmonary embolism in hospitalized patients. Eur Respir J 1999; 13:1365-1370.
53. 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.
54. Kruit WH, 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; 230:333-339.
55. van Beek EJ, Kuijer PM, Buller HR, Brandjes DP, Bossuyt PM, ten Cate JW. The clinical course of patients with suspected pulmonary embolism. Arch Intern Med 1997; 157:2593-2598.
56. de Groot MR, van Marwijk KM, 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; 82:1588-1592.
57. Miniati M, Monti S, Pratali L et al. Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. Am J Med 2001; 110:528-535.
58. Hull RD, Raskob GE, Ginsberg JS et al. A noninvasive strategy for the treatment of patients with suspected pulmonary embolism. Arch Intern Med 1994; 154:289-297.
59. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold technique--comparison with pulmonary angiography. Radiology 1992; 185:381-387.

60. Ghaye B, Remy J, Remy-Jardin M. Non-traumatic thoracic emergencies: CT diagnosis of acute pulmonary embolism: the first 10 years. Eur Radiol 2002; 12:1886-1905.
61. Mullins MD, Becker DM, Hagspiel KD, Philbrick JT. The role of spiral volumetric computed tomography in the diagnosis of pulmonary embolism. Arch Intern Med 2000; 160:293-298.
62. Raptopoulos V, Boiselle PM. Multi-detector row spiral CT pulmonary angiography: comparison with single-detector row spiral CT. Radiology 2001; 221:606-613.
63. Schoepf UJ, Holzknecht N, Helmberger TK et al. Subsegmental pulmonary emboli: improved detection with thin-collimation multi-detector row spiral CT. Radiology 2002; 222:483-490.
64. Remy-Jardin M, Tillie-Leblond I, Szapiro D et al. CT angiography of pulmonary embolism in patients with underlying respiratory disease: impact of multislice CT on image quality and negative predictive value. Eur Radiol 2002; 12:1971-1978.
65. 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.
66. Lee AY, Hirsh J. Diagnosis and treatment of venous thromboembolism. Annu Rev Med 2002; 53:15-33.
67. van Beek EJ, Reekers JA, Batchelor DA, Brandjes DP, Büller HR. Feasibility, safety and clinical utility of angiography in patients with suspected pulmonary embolism. Eur Radiol 1996; 6:415-419.
68. Nilsson T, Carlsson A, Mare K. Pulmonary angiography: a safe procedure with modern contrast media and technique. Eur Radiol 1998; 8:86-89.
69. Hudson ER, Smith TP, McDermott VG et al. Pulmonary angiography performed with iopamidol: complications in 1,434 patients. Radiology 1996; 198:61-65.
70. Hull RD, Hirsh J, Carter CJ et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. Chest 1985; 88:819-828.
71. Ginsberg JS, Brill-Edwards PA, Demers C, Donovan D, Panju A. D-dimer in patients with clinically suspected pulmonary embolism. Chest 1993; 104:1679-1684.
72. 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.
73. 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.

Safety of a diagnostic algorithm, combining clinical probability, D-dimer testing and spiral computed tomography in patients with clinically suspected pulmonary embolism; a prospective management study (Christopher)

THE CHRISTOPHER STUDY GROUP

UNDER REVISION JAMA

Abstract

Background:

Clinical decision rules, D-dimer testing and spiral computed tomography have improved the diagnostic work-up of patients with suspected pulmonary embolism.

Using an optimized and simplified algorithm involving all three methods the safety of excluding pulmonary embolism by either the combination of an unlikely clinical decision rule and a normal D-dimer test, or a normal spiral computed tomography was assessed.

Methods:

Consecutive patients with suspected pulmonary embolism were categorized in unlikely or likely using a validated clinical decision rule. Pulmonary embolism was considered excluded in the unlikely group if the D-dimer test was normal. All others underwent computed tomography. Anticoagulants were withheld from patients without pulmonary embolism and they were followed to assess the three-month incidence of venous thromboembolism.

Results:

Of the 3503 eligible patients, 3306 (94%) were included. A clinical decision rule indicating pulmonary embolism unlikely and a normal D-dimer test occurred in 1057 patients (32.0 percent), with a three-month incidence of venous thromboembolism of 0.5 percent (95 percent confidence interval, 0.2 to 1.1 percent). Computed tomography confirmed pulmonary embolism in 674 patients (prevalence 20.4 percent). In 1505 patients computed tomography excluded pulmonary embolism with a three-month incidence of venous thromboembolism of 1.3 percent (95 percent confidence intervals, 0.7 to 2.0 percent). The algorithm was completed and allowed a management decision in 97.9 percent of patients.

Conclusions:

A diagnostic algorithm ruling out pulmonary embolism by a clinical decision rule, indicating pulmonary embolism unlikely, combined with a normal D-dimer or by a normal computed tomography is efficient, safe and widely applicable.

Introduction

The main challenge in the diagnostic work up of patients with clinically suspected pulmonary embolism (PE) is to adequately and rapidly distinguish the approximately 25 percent who have the disease and require anticoagulant treatment from the 75 percent who do not [1;2].

In recent years the introduction of new methods has further improved the diagnostic process of PE. The first is the combination of a low clinical probability and a normal D-dimer test. Several management studies have shown that with this approach PE can be safely ruled out in 20 to 40 percent of patients, without the need for additional imaging [3-5]. A retrospective analysis suggested that the clinical utility of the Wells score could be further increased by dichotomizing the clinical probability in PE "likely" and "unlikely"[3].

The second advancement is spiral computed tomography (CT) that has emerged as a prominent imaging technique, both for the exclusion and confirmation of PE as well as the detection of alternative diagnoses [6-10]. However, the important missing piece of information is whether it is safe to withhold anticoagulation after a CT result has ruled out PE[11;12].

Hence, an efficient strategy would be to consider PE excluded in those with an unlikely clinical probability score and a normal D-dimer test, and a CT in all other patients as the sole imaging method to make management decisions.

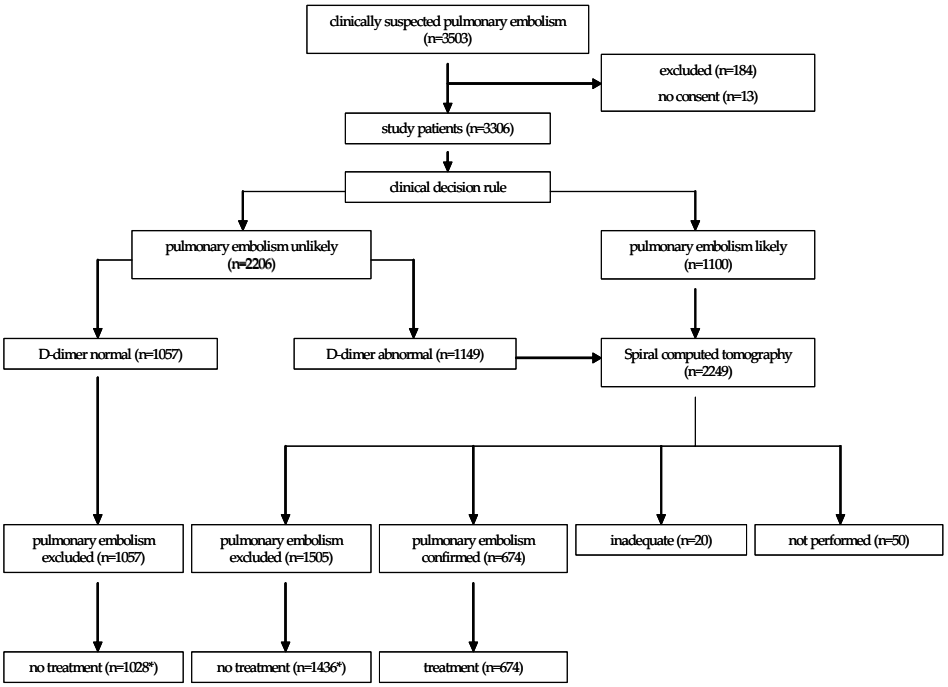
Therefore, we performed a prospective study in a large cohort of consecutive patients with clinically suspected PE to evaluate the safety and efficiency of this novel management strategy.

Methods

Study participants

Consecutive patients with clinically suspected PE were potentially eligible for the study. 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 below 18 years, allergy to intravenous contrast agents, previous participation in the study or hemodynamic instability. Five academic and seven general hospitals participated. The Institutional Review Boards of all participating hospitals approved the study protocol and informed consent was obtained from all participants.

Figure 1. Diagnostic flowchart with number of patients and diagnostic tests performed



* without patients receiving anticoagulants for other reasons than pulmonary embolism

Study design

This prospective management study of a diagnostic algorithm consisted of sequential application of a clinical decision rule, D-dimer test and CT within 24 hours (Figure 1). Patients were followed for a period of three months to document the occurrence of symptomatic venous thromboembolism.

Clinical decision rule and D-dimer

Patients with clinically suspected PE were evaluated by an attending physician using a validated clinical decision rule (Table 1) [3]. For the present study, PE was considered unlikely if the clinical decision rule score was ≤ 4 points, and PE was likely in case of a clinical decision rule score >4 points. In patients with a clinical decision rule indicating PE 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,

Table 1: Clinical decision rule according to Wells et al.

	points
Clinical signs and symptoms of deep vein thrombosis (DVT)(minimum of leg swelling and pain with palpation of the deep veins)	3.0
Heart rate >100/minute	1.5
Immobilisation (> 3 days) or surgery in the previous 4 weeks	1.5
Previous PE or DVT	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the last 6 months or palliative)	1.0
Alternative diagnosis less likely than PE	3.0

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

Mannheim, Germany). A D-dimer concentration of ≤ 500 ng/ml was defined as normal. If the D-dimer was normal, the diagnosis of PE was considered excluded and anticoagulant treatment was withheld. Patients who either had a clinical decision rule indicating PE unlikely but an abnormal D-dimer or those who had a clinical decision rule indicating PE likely, underwent CT.

Radiological evaluation

CT was performed using either single-slice or multi-slice detector systems. Patients were examined during suspended inspiration. The single-slice CT parameters were 3 mm slice thickness with a 2 mm reconstruction interval at 120 kV/140 mAs, 120-140 mL of non-ionic contrast material containing 350 mg I per mL with an injection speed of 3.0 mL/s and an injection delay of 16 s. Multi-slice CT parameters were 1.25 mm slice thickness with a 1.2 mm reconstruction interval at 120 kV/120 mAs, 80-100 mL of non-ionic contrast material containing 350 mg I 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. PE was diagnosed if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least two adjacent slices. The decision of the presence or absence of PE was made by a trained attending radiologist. These patients received low molecular weight heparin 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 CT could not be performed or who had a non-conclusive CT scan was left to the discretion of the attending physician.

Follow-up

Follow-up consisted of a hospital visit or telephone interview at three months. In addition, patients were instructed to contact the study centre or their general practitioner immediately in case of complaints suggestive of DVT or PE. At each visit information was obtained on complaints suggestive for venous thromboembolism and use of anticoagulants. In case of clinically suspected DVT or PE, appropriate objective tests (compression ultrasound for suspected DVT, ventilation-perfusion scintigraphy or 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 three months follow-up, defined as fatal PE, non-fatal PE or DVT. An independent adjudication committee, whose members were unaware of the patient's allocation within 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 [13]. Deaths were classified as due to PE in case of confirmation by autopsy, in case of an objective positive test for PE prior to death or if PE could not be confidently excluded as the cause of death.

Statistical analysis

Two primary analyses were defined that concerned the incidence of symptomatic venous thromboembolism confirmed by objective testing in the group of patients in whom anticoagulant treatment was withheld based on 1) a classification of PE unlikely by clinical decision rule and a normal D-dimer and 2) a CT that excluded PE. Additional analyses were performed for fatal PE in these groups, as well as for the patients with a normal CT and an alternative diagnosis on CT separately. Based on the assumption of a 1 percent incidence of venous thromboembolism in both patient groups and the aim to keep the upper limit of the 95% confidence interval below 2.5%, we calculated that approximately 1000 patients would have to be included in each group (type I error 0.05, two-sided; type II error 0.20). Since we expected that approximately 30% of patients would have a classification of PE unlikely by clinical decision rule and a normal D-dimer, a total study

population of 3300 patients was needed. Exact 95% confidence intervals (CI) were calculated around the observed incidences using StatXact software, version 5. Descriptive parameters were calculated using SPSS software, version 11.5 (SPSS, Inc., Chicago, Illinois).

Results

Study patients

Between October 2002 and September 2004 a total of 3503 patients with clinically suspected PE 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), and other reasons (n=41). In addition, 13 patients refused consent. The baseline demographic and clinical characteristics of the 3306 study patients are presented in Table 2.

Results of diagnostic algorithm

Of the 3306 included patients, 2206 (66.7%) had a clinical decision rule indicating PE unlikely, and were tested for D-dimer concentrations (Figure 1). D-dimer tests were normal in 1057 (32.0%) patients and in these patients PE was considered excluded. Of the 2249 patients with abnormal D-dimer concentrations (n= 1149) or a clinical decision rule indicating PE likely (n=1100), 2199 underwent CT. In 50 patients a CT was indicated but not performed. Multi-slice CT was performed in 1939 patients and single-slice CT in 260 patients. CT excluded PE in 1505 (45.5% of the total study population). Of these patients, 702 had an alternative diagnosis visualized by CT, for an overall prevalence of 21.2%; pneumonia (n=212), pleural effusion (n=163), malignancy (n=50) or other diagnoses (n=277)). PE was confirmed in 674 patients (overall prevalence of PE 20.4 %). CT was inconclusive in 20 patients (0.9%). Hence, the diagnostic algorithm could be completed according to the protocol in 3256 patients (98.1 %) and allowed a management decision in 3236 patients (97.9 %).

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

Characteristic	Value
Age in years, mean (SD+)	53.0 (18.4)
Female sex, n (%)	1896 (57.4)
Outpatients, n (%)	2701 (81.7)
Duration of complaints in days, median (IQR^)	2 (1-5)
Paralysis, n (%)	91 (2.8)
Immobilisation or recent surgery, n (%)	608 (18.4)
Previous VTE, n (%)	480 (14.5)
COPD with treatment, n (%)	341 (10.3)
Heart failure with treatment, n (%)	243 (7.3)
Malignancy, n (%)	474 (14.3)
Oestrogen use, n (%)*	438 (23.1)
Clinical symptoms of DVT, n (%)	190 (5.7)
Heart rate (beats per minute >100), n (%)	867 (26.2)
Hemoptysis, n (%)	176 (5.3)

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

Patients with clinical decision rule indicating PE unlikely and normal D-dimer

Of the 1057 patients with the combination of a clinical decision rule, indicating PE unlikely and normal D-dimer, 29 patients (2.7 %) were treated with oral anticoagulants during follow-up for various reasons other than venous thromboembolism. Three of the 1028 remaining patients returned with symptomatic venous thromboembolic events confirmed by objective tests (2 non-fatal PE, 1 DVT), during the three months follow-up. In 26 patients the protocol was violated and a CT or a ventilation-perfusion scan was performed while not indicated. PE was diagnosed in two. Therefore, the incidence of venous thromboembolism was 5 of 1028 (0.5%; 95% CI: 0.2 to 1.1%). Two patients were lost to follow-up (0.2%). In a 'worst case' scenario, in which these two patients would have

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

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

VTE: Venous Thromboembolic Events

presented with (fatal) venous thromboembolic events, the incidence of venous thromboembolism would have been 7/1028 (0.7%; 95% CI: 0.3 to 1.4%). Eight of the 1057 patients died (0.8%), none as a result of fatal PE (Table 3).

Patients in whom CT excluded PE

Of the 1505 patients, in whom CT excluded PE, 69 (4.6%) received anticoagulants during follow-up for various reasons other than venous thromboembolism. Of the 1436 remaining patients, who did not receive anticoagulant treatment, 18 experienced venous thromboembolic events during the 3-month follow-up (1.3 %; 95% CI: 0.7 to 2.0%). Eleven of these had non-fatal symptomatic thromboembolic events confirmed by objective tests (3 PE and

Table 4: Deaths related to pulmonary embolism

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

CAPD: Continuous Ambulatory Peritoneal Dialysis

8 DVT). Of the other 7 patients, fatal PE was proven by autopsy in 2 and considered to be 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 had a (fatal) venous thromboembolic event the incidence of venous thromboembolism would have been 19 of 1436 (1.3%; 95% CI: 0.8 to 2.1%). Among the patients who did not receive anticoagu-lants, similar incidences of venous thromboembolic events were observed in those with a normal spiral CT (9/764; 1.2% [95% CI: 0.5 to 2.2%]) and those with an alternative diagnosis on CT (9/672; 1.3% [95% CI: 0.6 to 2.5%]) (Table 3). Also, similar incidences in venous thromboembolic events were observed in untreated patients who underwent multi-slice CT (14/1266; 1.1% [95% CI: 0.6 to 1.9%]) and single-slice CT (4/170; 2.4% [95% CI: 0.6 to 5.9%]). The overall mortality rate in patients in whom CT excluded PE, was 8.6% (129 patients).

Patients with PE confirmed by CT

Of the 674 patients in whom CT had demonstrated PE, 20 patients (3.0%) had a recurrent venous thromboembolic event despite anticoagulant treatment. This included 11 fatal PE, 3 non-fatal PE and 6 DVT. One patient was lost to follow-up. The overall mortality was 8.2% (55 patients).

Discussion

This large cohort study in 3306 consecutive patients with clinically suspected PE clearly demonstrates that the evaluated diagnostic algorithm can efficiently and safely rule out the diagnosis of PE. No further diagnostic testing was necessary in a third of our patients with an unlikely clinical probability score in combination with a normal D-dimer test (3-month incidence of venous thromboembolism 0.5%; 95% CI: 0.2 to 1.1%). All other patients could be safely managed by spiral CT alone (3-month incidence of venous thromboembolism in those with normal spiral CT 1.3%; 95% CI: 0.7 to 2.0%). This applies both to patients with a normal spiral CT (3-month incidence of venous thromboembolism 1.2%; 95% CI: 0.5 to 2.2%) as well as to those without PE in whom an alternative diagnosis was obtained (3-month incidence of venous thromboembolism 1.3%; 95% CI: 0.6 to 2.5%). Furthermore, the tested diagnostic algorithm could be completed in 98.1% of the eligible patients and allowed a management decision in 97.9%.

Several management studies have documented the safety of a low clinical probability in combination with a normal D-dimer concentration for the exclusion of PE [3-5;14]. In order to improve the simplicity and utility, Wells et al. reduced the score from forty to seven items

and proposed to change the clinical probability model from the original three (low, moderate, high) to two categories, i.e. PE unlikely and PE likely [3]. The present study prospectively validates the safety of this simplified score in combination with the D-dimer test, which has the potential to increase the number of patients in which PE can be excluded by approximately 50% [3;14].

Despite the initial concern that the sensitivity of CT for PE is lower than that of the traditional gold standard (catheter pulmonary angiography), the observed risk of subsequent symptomatic venous thromboembolism in those in whom PE was excluded by CT compares favourably with the risk reported after a normal pulmonary angiogram (3-month incidence of venous thromboembolism 1.3%; 95%CI: 0.7 to 2.0% versus 1.7%; 95%CI: 1.0 to 2.7 %, respectively)[15]. Furthermore, CT has the advantage of identifying an alternative explanation for the presenting symptoms in an additional 20% of patients. These characteristics make CT superior to other imaging techniques and obviate the need for other diagnostic testing.

Taken together, compared to other validated diagnostic algorithms the combination of two non-invasive tests followed by CT if indicated is as safe, less complex and easy to use and may reduce unnecessary radiation exposure [2;9;10].

Several methodological aspects of our study require comment. First, the absence of PE 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, provided a (near) complete follow-up [16], which was achieved in the present study.

Second, while a randomized controlled study design would have allowed a direct comparison to another validated strategy, we preferred to perform a cohort study in a wide variety of patients and clinical settings with rigorous investigation and independent adjudication of outcomes in order to obtain precise point estimates of the rate of subsequent venous thromboembolism after normal tests.

Third, what is the external validity of our findings? The baseline clinical characteristics and the incidence of PE are fully comparable with those observed in other population based studies [5;10;12]. Together with the low proportion of patients excluded and the enrolment of consecutive patients, we believe that our conclusions are valid for all patients with suspected PE.

Fourth, we allowed using both single and multi-slice CT. No apparent difference in the subsequent rate of venous thromboembolism was observed in those in whom PE was excluded, which appears to be in agreement with previous observations [11]. Only 10% of

our patients underwent single slice CT, thus precluding a firm conclusion. However, multi-slice CT is gradually replacing single-slice CT.
In conclusion, the evaluated simplified diagnostic management strategy, using clinical decision rule, D-dimer and spiral CT can safely replace current more complex diagnostic algorithms in the work-up of patients with clinically suspected PE. This rapid and widely applicable strategy can be easily introduced in daily clinical practice.

Source Information

The writing committee of the Christopher Study, in alphabetical order: Arne van Belle, M.D., Harry R. Buller, M.D., Menno V. Huisman, M.D., Peter M. Huisman, M.D., Karin Kaasjager,M.D., Pieter Willem Kamphuisen, M.D., Mark H.H. Kramer, M.D., Marieke J.H.A. Kruip, M.D., Johanna M. Kwakkel-van Erp, M.D., Frank W.G. Leebeek, M.D., Mathilde Nijkeuter, M.D., Martin H. Prins, M.D., Maaike Sohne, M.D., Lidwine W. Tick M.D, takes responsibility for the content of this article.

Appendix

Adjudication committee: M.H. Prins, H. ten Cate.
The following institutions and investigators participated in the study: Meander Medical Center, Amersfoort: C.J.M.Halkes, B.Heggelman, M.Nix. Academic Medical Center Amsterdam: P.Bresser, D.R.Kool, S.S.K.S.Phoa, B.Rekke. Rijnstate Hospital, Arnhem: H.M.H Grandjean, F.O.H.W. Kesselring, J.J.Mol, E.F.Ullmann. Amphia Hospital, Breda: C. van Guldener, J.Y.Mijnsbergen, M.F.A.M. Sturm. Spaarne Hospital, Haarlem: C.de Swart, P.M. Kuijer, J.G. Schrama, A.v.d. Velde. General Hospital, Hilversum: M.M. van der Eerden, P.J.H.Janssen, R.Jansen, S.Lobatto. Leiden University Medical Center, Leiden: E.A.Compier, H.C.J.Eikenboom, A.de Roos. Academic Hospital, Maastricht: G.Snoep. Diakonessen Hospital, Meppel: H.de Korte, C.B.Kos, L.Laterveer, W.C.J.van Veldhuizen. St. Radboud University Medical Center, Nijmegen: S.J.H.Bredie, C.E.van Die, Y.F.Heijdra, J.W.M.Lenders. Erasmus Medical Center, Rotterdam: K-S.G.Jie, A.H.Kars, A.H.van den Meiracker, P.M.T.Pattynama. Medical Center Rijnmond Zuid, Rotterdam: J.M.de Borst, A.A.van Houten, H.T.Teng.

Reference List

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

2. 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.
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; 83:416-420.
4. Kruip MJ, Slob MJ, Schijen JH, et al. 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-invasive diagnostic work-up of patients with 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: a systematic 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 multi-center management study. Am J Med 2004; 116:291-299.
13. Buller HR, Davidson BL, Decousus H et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003; 349:1695-1702.
14. 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.
15. 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.
16. Kruip MJ, Leclercq MG, van der Heul C, et al. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med 2003; 138:941-951.

Accuracy of clinical decision rule, D-dimer and spiral computed tomography in patients with malignancy, previous venous thromboembolism, COPD, heart failure or older patients with suspected pulmonary embolism

MAAIKE SÖHNE, MARIEKE KRUIP, MATHILDE NIJKEUTER, LIDWINE TICK, HANNEKE KWAKKEL, STIJN HALKES, MENNO HUISMAN, HARRY BÜLLER

SUBMITTED

Abstract

Background:

The diagnostic work-up of patients with suspected pulmonary embolism has been optimized and simplified by the use of clinical decision rules, 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 clinical decision rule, D-dimer test and s-CT was evaluated in patients with malignancy, previous venous thromboembolism, COPD, heart failure and older patients. Pulmonary embolism was ruled out by either an unlikely clinical decision rule and a normal D-dimer or a s-CT negative for pulmonary embolism. The safety of these tests was assessed by the three month incidence rate of symptomatic venous thromboembolism in those without pulmonary embolism 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 clinical decision rule 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 to rule out one patient from pulmonary embolism with the studied strategy was highest in cancer patients and in elderly (approximately 10).

Conclusion:

It appears safe to rule out pulmonary embolism by either the combination of an unlikely clinical decision rule and a normal D-dimer or a negative s-CT in various subgroups of patients with suspected pulmonary embolism. However, the clinical usefulness of the clinical decision rule 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 prevalence of PE among those who present with a clinical suspicion of this disease [1;2]. As a consequence of this low prevalence, the diagnostic yield of imaging tests is low. Since 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), COPD or heart failure or older patients [7-10]. For example, higher prevalences of PE in cancer patients or in the elderly can decrease the negative predictive value and thus the safety, while co-morbidity may reduce the efficiency due to 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 which 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, heart failure or 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 clinical decision rule (CDR), D-dimer assay and spiral 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 with an age over 75 years were included in this analysis. 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 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 [17]. PE was considered unlikely if the CDR score was ≤ 4 points and PE was likely in case of a CDR score >4 points. In patients with a clinical decision rule indicating PE 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 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.

S-CT was performed using either single-slice or multi-slice detector systems according to the protocol as described in the original study[16]. Patients with confirmed PE on s-CT received low molecular weight heparin 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.

Follow-up

Follow-up consisted of a hospital visit or telephone interview at three months. In addition, patients were instructed to contact the study centre 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 venous thrombo-embolism and use of anticoagulants. In case of clinically suspected DVT or PE, appropriate objective tests (compression ultrasound for suspected DVT, ventilation-perfusion

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 three months follow-up, defined as fatal PE, non-fatal PE or DVT. An independent adjudication committee, whose members 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 [18]. Deaths were classified as due to PE in case of confirmation by autopsy, in case of an objective positive test for PE prior to death or if PE could not be confidently excluded as the cause of death.

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 venous thromboembolism confirmed by objective testing in the group of patients in whom anticoagulant treatment was withheld based on 1) a classification of PE unlikely by clinical decision rule and a normal D-dimer or 2) a s-CT scan that excluded PE were calculated. 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, Illinois).

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 and 82% of them were outpatients [16]. The three subgroups of patients with malignancy, with previous VTE or 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 1).

Table 1: Baseline characteristics of the overall study population and the different clinical subgroups with suspected pulmonary embolism

	Overall study population	Malignancy	Previous VTE	COPD	Heart failure	Age >75 yrs
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 yrs(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 prevalence	674 (20)	130 (27)	129 (27)	62 (18)	40 (17)	131 (27)

The proportion of outpatients was approximately 70% in all subgroups, except for those patients with previous VTE where this figure was 89% (Table 1). The prevalence of confirmed PE varied from 16.5% in those with heart failure to 27.4% in those with cancer.

Results of the combination of clinical decision rule and D-dimer 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 2). 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 D-dimer consequently was higher. The incidence of venous thromboembolic events during the three months of follow-up in the various studied subgroups was similar and comparable to the overall study population.

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 3). In the remaining 31% of the performed s-CT scans PE was confirmed, therefore 3.3 scans have to be done to detect one PE. Five patients with a s-CT result negative for PE returned with symptomatic venous thromboembolic events (1 DVT, 1 non-fatal PE and 3 fatal PE) during the three months of follow-up. Two of the patients with fatal PE died suddenly during immobilization because of severe pain and weakness on day 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

Table 2: Diagnostic performance of an unlikely clinical decision rule in combination with a normal D-dimer in the overall study population and the different clinical subgroups with suspected pulmonary embolism

	Total study population	Malignancy	Previous VTE	COPD	Heart failure	Age >75 yrs
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 normal n (%)	1142 (35)	55 (12)	128(27)	90 (26)	45 (19)	52 (11)
CDR unlikely and normal d-dimer 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 1 negative	3.1	10	5.1	4.4	5.7	10.6

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 3).

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).

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 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 three months of follow-up, this appeared to be comparable to the overall study-population. The number of s-CTs needed to have one CT indicating the presence of PE varied from three to five with the lowest diagnostic yield in those with heart failure.

Table 3: Diagnostic performance of spiral computed tomography in the overall study population and in the different clinical subgroups with suspected pulmonary embolism

	Total study population	Malignancy	Previous VTE	COPD	Heart failure	Age >75 yrs
Performed CT scans n	2199	417	378	258	193	422
PE ruled out by 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 CT n (%)	674 (31)	129 (31)	129(34)	62 (24)	40 (21)	131 (31)
Inconclusive CT n	20	2	3	0	0	2
VTE incidence during FU after 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)
Number needed to test to find one positive CT	3.2	3.3	2.9	4.2	4.8	3.2

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% confidence intervals of the VTE incidences are sometimes wide due to the relative small numbers of patients in each subgroup.

What are the clinical interpretations of these findings?

First, 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 whether or not to use these tests. For the subgroups of patients with previous VTE, COPD or heart failure the number needed to test is close to that in the overall study population (4.4 to 5.7 versus 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 this low diagnostic yield of these 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, since a CT scan can at least be prevented 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 number needed to test 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 prevalence of PE in the malignancy subgroup was 27% (Table 1). If the s-CT would have been performed directly in all these patients, 3.7 scans had to be

performed to find one positive. With the use of CDR and D-dimer the prevalence 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 3). 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 only includes 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 a s-CT negative for PE appears safe for subgroups of suspected PE patients with malignancy, previous VTE, COPD, heart failure or elderly. Judgment 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 number needed to test to rule out one PE, but also on the clinical setting.

Reference List

1. Lee AY, Hirsh J. Diagnosis and treatment of venous thromboembolism. Annu Rev Med 2002; 53:15-33.
2. 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.
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; 83:416-420.
4. Kruip MJ, Slob MJ, Schijen JH, van der HC, 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.
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; 2:1110-1117.
6. Kruip MJ, Leclercq MG, van der HC, Prins MH, Buller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med 2003; 138:941-951.
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; 131:417-423.
8. ten Wolde M, Kraaijenhagen RA, Prins MH, Buller HR. The clinical usefulness of D-dimer testing in cancer patients with suspected deep venous thrombosis. Arch Intern Med 2002; 162:1880-1884.
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; 109:357-361.
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; 114:276-282.

11. Kelly J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. Arch Intern Med 2002; 162:747-756.
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; 138:307-314.
13. Musset D, Parent F, Meyer G et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet 2002; 360:1914-1920.
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; 116:291-299.
15. Perrier A, Roy PM, Sanchez O et al. Multidetector-row computed tomography in suspected pulmonary embolism. N Engl J Med 2005; 352:1760-1768.
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. J Thromb Haemost 2005; 3: supplement 1(abstract)
17. 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.
18. Buller HR, Davidson BL, Decousus H et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003; 349:1695-1702.

Alternative clinical diagnoses with spiral computed tomography in patients with suspected pulmonary embolism

M. SÖHNE, J.C. VAN RIJN, O.M.VAN DELDEN, A.A. SMIT,
V.E.A.GERDES, J.B. REITSMA, H.R BULLER, P. BRESSER

SUBMITTED

Abstract

Spiral computed tomography is increasingly used as the first-line imaging test in the diagnostic work-up of patients with suspected pulmonary embolism, not only to confirm the presence of pulmonary embolism (PE), but also to provide an alternative explanation for the signs and symptoms in those patients without PE.

Frequencies of the different alternative diagnosis were assessed in 99 consecutive patients with suspected PE who underwent s-CT. The diagnoses made in the emergency department were compared to the diagnoses and radiological abnormalities after systematic reading of the s-CT by a radiologist and pulmonologist.

The radiological abnormalities seen at the systematic s-CT analysis supported an alternative diagnoses in 46 of the 76 patients without PE (61%), of which 28 were considered to have probable therapeutic consequences. The most frequent diagnoses were pneumonia (17% of those without PE) and congestive heart failure (9%). Compared to the given alternative diagnoses at the emergency department, differences were observed in 21 patients (49%) of which six patients had a pneumonia diagnosed with systematic s-CT reading, while the emergency diagnoses were different.

S-CT appears to be useful in confirming alternative diagnoses in patients with suspected PE. The diagnoses given after systematic reading of the s-CT compared to the diagnoses of the attending physician at the emergency department do vary in about half of the patients with an alternative diagnoses; however whether this is clinically or therapeutically relevant remains uncertain.

Introduction

The clinical manifestations of pulmonary embolism (PE) are non-specific, which makes diagnosing or excluding the disease difficult. Approximately 75% of the patients presenting with signs and symptoms suggestive of PE do not have the disease confirmed by objective testing [1-3]. In a large number of these patients, complementary diagnostic testing is needed to confirm or rule out an alternative diagnosis.

In current practice, contrast-enhanced spiral computed tomography (s-CT) has emerged as the preferred imaging tool in diagnosing PE. It is increasingly used as the first-line imaging test in the diagnostic process, not only to confirm the presence of PE, but also because of the possibility to directly provide an alternative explanation for the signs and symptoms in those patients without PE [4,5]. However, the proportion of patients in which an alternative diagnosis is suggested varies in the different studies (26% to 75%) [5-8] and more importantly little is known about whether these diagnoses may have therapeutic consequences.

The purpose of the present study was to assess the frequency and clinical relevance of alternative diagnoses in consecutive patients in whom PE was ruled out by s-CT. Furthermore, the proportion of alternative diagnoses which indeed may have a therapeutic consequence was determined. Finally, the difference between the initial conclusions reached in the emergency department with regard to alternative diagnoses was compared to the outcome of a later systematic reading of the s-CT by a radiologist and pulmonologist.

Methods

Study population

This study was part of a large diagnostic management study in 12 teaching hospitals in the Netherlands evaluating a new diagnostic strategy including clinical decision rule (CDR), D-dimer test and s-CT [9]. Patients were included between November 2002 and August 2004.

The present study included outpatients with a clinical suspicion of acute pulmonary embolism in whom s-CT was performed according to the studied strategy, seen at the Academic Medical Center, Amsterdam. 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 the used iodinated contrast, had a life expectancy of less than three months or if there was an inability to obtain follow-up. The study protocol was approved by the Institutional Review Board.

S-CT-protocol

S-CT was performed with a multi-detector row s-CT scanner (Mx 8000; Philips) with a collimation of 4x1 mm, a pitch of 1.25, a scan time of 0.5 second, 120 kV and 140-160 mAs. S-CT was performed using 100 ml of iodinated contrast (Visipaque 320® Nycomed, Oslo, Norway) administered at a rate of 4 mL/sec with a power injector using a bolus tracking protocol. All patients underwent caudocranial imaging during single breath hold. The z-axis covered the thorax from the diaphragm to the apex of the lung. Central intraluminal filling defects or totally occluded vessels were considered as positive for PE.

Study design

The s-CT images were initially assessed by the on-call radiology resident and patients were treated by the attending physician based on the s-CT report in combination with the clinical signs and symptoms. The final diagnoses and treatment if applicable were recorded in the routine patient files. Patients in whom PE was initially ruled out received no anticoagulant therapy. The s-CT images were later systematically reviewed by an independent panel consisting of a radiologist and a pulmonologist, according to a predefined list of possible radiological CT-abnormalities. The frequencies of the different abnormalities were scored for patients with PE and those without. The readers were blinded to the results of the previous CT-reading. After assessment of the s-CT images and completing the predetermined list with radiological findings, a most likely clinical diagnosis was given. These diagnoses were compared with the clinical diagnoses reached by the attending physician at the emergency department who based the diagnoses on patient examination and the s-CT result provided by the on-call radiologist.

Results

Patient characteristics

A total of 99 patients were included with a mean age of 55 years (interquartile range 41 to 69 years) and 44% were male. Pulmonary embolism was present in 23 patients (prevalence 23%). Nine of the 99 included patients (9%) had a history of chronic obstructive pulmonary disease (COPD) and a similar proportion had a history of congestive heart failure.

None of the patients in whom PE was initially ruled out experienced venous thromboembolic complications during the three months of follow-up.

Table 1. Alternative diagnoses given by the attending physician at the emergency department and of those given after systematic reading of the spiral computed tomography

Alternative diagnoses	No. of patients diagnosed at emergency department n (%)	No. of patients diagnosed after systematic consensus reading n (%)
Infection		
Pneumonia	13 (17)	19 (25)
Bronchitis	3 (4)	7 (9)
Viral pleuritis	5 (7)	1 (1)
Congestive heart failure	7 (9)	4 (5)
Malignancy (metastasised)	3 (4)	3 (4)
Other		
Sarcoidosis	1 (1)	1 (1)
Exacerbation small airway disease/ COPD	3 (4)	3 (4)
Possible pericarditis	1 (1)	0 (0)
Bronchogenic cyst	0 (0)	1 (1)
Smokers lung	0 (0)	3 (4)
Pleural fluid (no cause seen)	5 (7)	4 (5)
Atypical chest pain/no diagnosis	33 (43)	30 (39)
Total	76 (100)	76 (100)

Diagnoses at the emergency department

Of the 76 patients in whom PE was excluded an alternative diagnosis was made by the attending physician in the emergency department in 43 patients (57%; 95% CI: 45% to 68%). These were based on the initial reading of the s-CT and the clinical presentation of the patient and are listed in Table 1. The two most frequent diagnoses to explain the patient's symptoms were pneumonia (17%) and congestive heart failure (9%). In two patients a prior known malignancy was considered the cause of signs and symptoms. In one patient, previously unknown sarcoidosis was discovered as a new diagnosis. Of the 43 alternative diagnoses 27 (pneumonia, congestive heart failure, malignancy, sarcoidosis and exacerbation of COPD) would have therapeutic consequences (36%; 95% CI: 25% to 47%).

Diagnoses after systematic consensus reading of s-CT

The radiological findings at s-CT with the systematic evaluation, in combination with clinical information, supported an alternative diagnosis in 46 of the 76 patients without PE (61%; 95% CI: 49% to 72%) (Table 1). The great majority of diagnoses concerned pneumonia (25%), whereas bronchitis was the second most frequent diagnosis (9%). In 28

patients the alternative diagnosis would have therapeutic consequences (37%; 95 CI%: 26% to 48%).

Radiological abnormalities with systematic CT scan evaluation

The radiological abnormalities for the patients with PE and for those without are given in Table 2. It is shown that except for consolidation all other findings are present in similar proportions in the group with or without PE. Besides consolidation the most frequently present radiological finding was lymphadenopathy (approximately 30% in both groups). Emphysema and pleural fluid were other abnormalities with a high prevalence.

Comparison of the two readings

Comparison of the clinical diagnoses given at the emergency department by the attending physicians and the diagnoses based on the systematically reviewed s-CT scan and clinical information showed a different diagnosis in 21 patients (49%).

In six patients a pneumonia was diagnosed based on the systematic reading of the s-CT scan, while the initial diagnoses at the emergency department in these patients consisted

Table 2. Frequencies of the radiological abnormalities in patients with or without pulmonary embolism

	PE patients (%) n=23	**No PE patients (%) n=76**
Consolidation	16 (70)	29 (38)
Atelectasis	3 (13)	11 (15)
Groundglass density	3 (13)	9 (12)
Mosaic pattern	1 (4)	3 (4)
Nodules	4 (17)	14 (18)
Emphysema	5 (22)	17 (22)
Bulla	2 (9)	5 (7)
Cysts	1 (4)	6 (8)
Bronchiectasies	3 (13)	16 (21)
Pleural fluid	8 (35)	18 (24)
Cardiomegaly	1 (4)	5 (7)
Pericardial fluid	0	4 (5)
Aneurysm aorta	0	1 (1)
Lymphadenopathy	7 (30)	24 (32)
Pleural thickening	4 (17)	13 (17)
Linear abnormalities	6 (26)	20 (26)
Coronary and/or aortic atherosclerosis	1 (4)	9 (12)

of viral pleuritis, pleural fluid, emphysema, muscle pain and cardiac chest pain. In six other patients systematic s-CT reading showed no clinical diagnosis, while the attending physician treated the patient for congestive heart failure or an exacerbation of COPD. Furthermore, bronchitis increased from three to seven patients with systematic s-CT reviewing and viral pleuritis decreased from five patients diagnosed by the attending physician to one patient diagnosed after reviewing the s-CT.

Discussion

This study shows that s-CT provided an alternative clinical diagnosis that may have therapeutic consequences in approximately 37% of the patients in whom PE was ruled out by s-CT. The most frequently observed diagnosis was pneumonia, which was seen in one third of the patients with an alternative diagnosis. Our proportion of alternative diagnoses of 37% is comparable with the studies by van Strijen and collegues and Remy-Jardin et al which found percentages of alternative diagnoses of 26% and 44% respectively [6;10]. Pneumonia was present in 17% and 25% in their studies compared to 17% in our study. However, the study by Kavanagh et al. reported a proportion of significant additional findings of 75% which is in contrast with our observation [7]. This can be explained by the fact that their percentage included more diseases and radiological abnormalities, such as emphysema which explained a major part of the difference. The proportion of emphysema was similar in our study.

A comparison of the clinical diagnoses given by the attending physician in the emergency department and those given after systematic consensus reading showed a difference in diagnoses in 21 of the 46 patients with an alternative diagnosis. In a modest proportion (about a quarter) of these patients the differences might have a possible therapeutic effect. In particular in those six patients with pneumonia at systematic reading that had not been concluded by the attending physician as well as in those patients with congestive heart failure or an exacerbation of COPD diagnosed at the emergency department while systematic s-CT reading did not provide evidence for these diagnoses. However, these latter categories are diagnoses often made based on the full clinical picture at presentation and physical examination and not specifically on s-CT abnormalities.

Another remarkable observation in this study was the similarity of the proportions of the different radiological abnormalities in those with and without PE when the s-CT scan was systematically read (Table 2). Only the presence of consolidation was different between the PE and the non-PE patients. This further suggests that besides the specific abnormality

seen on s-CT, clinical information and the absence of PE likely influenced the conclusion of an alternative diagnosis.

Two aspects of the present study require comment.

One of our main objectives was to evaluate whether systematic reading of the s-CT would show an important change of clinically relevant diagnoses compared to the diagnoses given by the attending physician in an acute setting. Being very conservative this would be the case for those six patients with pneumonia at systematic reading but without this diagnosis in the acute setting, although it is unknown whether all of these patients needed antibiotic therapy. Probably a better design would have been to obtain the systematic reading within 24 hours rather than after several months as was done in the present study, and to include follow-up of these patients as the gold standard for outcome. Another limitation is the moderate sample size of this study. Therefore, firm conclusions on subcategories of alternative diagnoses cannot be drawn.

In conclusion, s-CT appears to be useful to confirm alternative diagnoses in patients with suspected PE, although clinical information and examination remain important as well. There are some differences between diagnoses made by the attending physician in the acute setting compared to diagnoses made when the s-CT was systematically examined, however the clinical relevance and therapeutic consequences appear to be modest.

Reference List

1. 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.
2. Stein PD, Hull RD, Saltzman HA, Pineo G. Strategy for diagnosis of patients with suspected acute pulmonary embolism. Chest 1993; 103:1553-1559.
3. 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; 98:891-899.
4. Schoepf UJ, Goldhaber SZ, Costello P. Spiral computed tomography for acute pulmonary embolism. Circulation 2004; 109:2160-2167.
5. 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.
6. Remy-Jardin M, Remy J, Baghaie F, Fribourg M, Artaud D, Duhamel A. Clinical value of thin collimation in the diagnostic workup of pulmonary embolism. AJR Am J Roentgenol 2000; 175:407-411.
7. Kavanagh EC, O'Hare A, Hargaden G, Murray JG. Risk of pulmonary embolism after negative MDCT pulmonary angiography findings. AJR Am J Roentgenol 2004; 182:499-504.
8. Richman PB, Courtney DM, Friese J et al. Prevalence and significance of nonthromboembolic findings on chest computed tomography angiography performed to rule out pulmonary embolism:

a multicenter study of 1,025 emergency department patients. Acad Emerg Med 2004; 11:642-647.
9. 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. J Thromb Haemost 2005; 3: supplement 1(abstract)
10. 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.

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 BOSSUYT, FRANK W.G. LEEBEEK, HARRY 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%)

Conclusion:

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

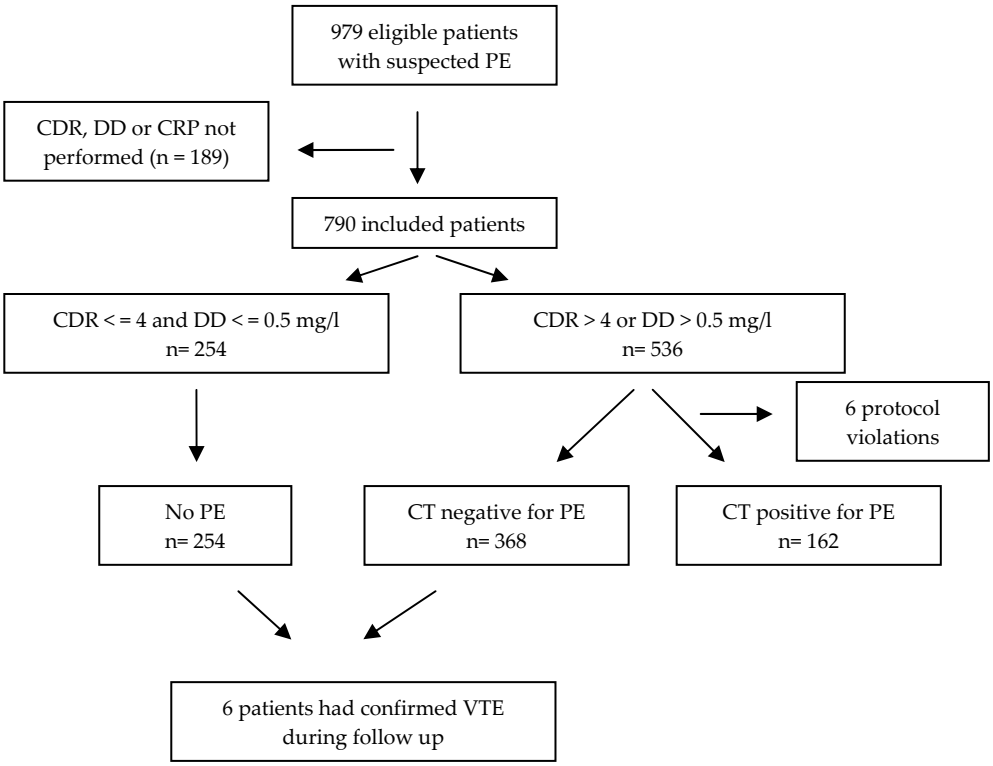
A multiple reference standard was used to evaluate the diagnostic accuracy of CRP. Patients were classified as having pulmonary embolism in case of a positive helical CT or in case of positive testing for venous thromboembolism during follow-up. All other patients were classified as not having pulmonary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

Figure 1 Flow chart of diagnostic management strategy



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)

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 28% (95% CI: 24 to 31%) (Table 2). Figure 2 shows the discriminative power of CRP when used as the sole test in the diagnostic work-up of suspected pulmonary

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

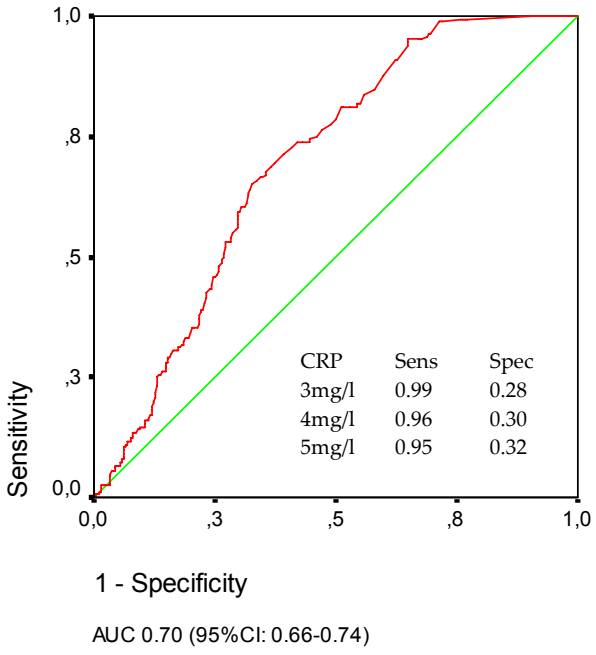
	All patients n= 790	**CDR unlikely* n= 510**	**CDR likely* n= 280**
PE prevalence n(%)	164 (21%)	61 (12%)	103 (37%)
CRP			
Sensitivity	99% (96%-100%)	98% (91%-100%)	99% (95%-100%)
Specificity	28% (24%-31%)	33% (29%-37%)	14% (9%-19%)
Negative predictive value	99% (96%-100%)	99% (96%-100%)	96% (80%-100%)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

CDR unlikely = 4 or less points; CDR likely = more than 4 points

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.

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



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 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%).

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.

Reference List

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 HC, 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. J Thromb Haemsot 2005; 3: supplement 1 (abstract).
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.

Chapter 7

D-Dimer test in cancer patients with suspected acute pulmonary embolism

MARCELLO DI NISIO, MAAIKE SÖHNE,
PIETER.W.KAMPHUISEN, HARRY R. BÜLLER

J THROMB AND HAEMOST. 2005 JUN; 3 (6) : 1239-42

Abstract

Background:

The safety of a d-dimer (DD) measurement in cancer patients with clinically suspected pulmonary embolism (PE) is unclear.

Objectives:

To assess the accuracy of the DD test in consecutive patients with clinically suspected PE with and without cancer.

Methods:

The diagnostic accuracy of DD (Tinaquant D-dimer; Roche Diagnostica, Germany) was first retrospectively assessed in an unselected group of patients referred for suspected PE (n=350). Subsequently, the predictive value of the DD was validated in a group of consecutive in- and out-patients with clinically suspected PE prospectively enrolled in a management study (n=519). The results of the DD test in cancer patients were assessed according to the final diagnosis of PE and the 3-month clinical follow-up.

Results:

In the first study group, DD showed a sensitivity and a negative predictive value (NPV) of 100% and 100% in patients with cancer and 97% and 98% in those without malignancy, respectively. In the validation cohort, the sensitivity and NPV of DD were both 100% (95% CI, 82%-100% and 72%-100%, respectively), whereas in patients without malignancy the corresponding estimates were 93% (95% CI, 87%-98%) and 97% (95% CI, 95%-99%), respectively. The specificity of DD was low in patients with (21%) and without cancer (53%).

Conclusion:

A negative DD result safely excludes the diagnosis of PE in patients with cancer. Because of the low specificity, when testing hundred patients with suspected PE, a normal DD concentration safely excludes PE in 15 patients with cancer and in 43 patients without cancer.

Introduction

Pulmonary embolism (PE) might be the first manifestation of an underlying occult malignancy or represent a complication of a known malignancy [1]. Since the majority of preventable deaths associated with PE can be ascribed to a missed diagnosis and anti-coagulation is associated with a risk of bleeding, it is crucial to exclude or confirm the diagnosis of PE to avoid unnecessary anticoagulation or promptly start such treatment if appropriate [2,3].

Only 25% of patients suspected for PE have a diagnosis confirmed by objective testing [4]. For this reason, several non-invasive diagnostic tests, such as d-dimer (DD), have been developed to limit the number of patients requiring an invasive and costly test [5]. The use of DD aims at safely excluding rather than confirming the presence of PE since elevated DD concentrations are not specific for PE and are observed in many other circumstances, including advanced age, pregnancy, trauma, inflammatory states, and cancer [6-8]. As a consequence, false positive results are common in hospital inpatients, particularly in patients with infections and cancer. Although the DD test has been investigated in various algorithms to exclude PE [5], the safety and diagnostic accuracy of DD in cancer patients has not been established. Both the cancer and its treatments can reduce the accuracy due to more frequently abnormal results than in patients without cancer [9]. A safe exclusion of PE in patients with overt malignancy is extremely important, since in these patients PE is associated with a high mortality and anticoagulant therapy greatly increases the risk of major bleeding [10].

Recently, two studies investigated the diagnostic accuracy of the DD test in cancer patients with clinically suspected deep venous thrombosis (DVT) reaching divergent conclusions on the predictive value and clinical utility of DD in this setting [11,12].

The aim of our study was first to retrospectively determine the predictive value of DD in patients referred for clinically suspected PE and compare the performance of the DD test in patients with and those without cancer. Subsequently, the accuracy of the DD test was validated in a prospective cohort of patients with suspected PE.

Methods

Patients

The initial group consisted of an unselected sample of in- and outpatients referred to the thrombosis unit for clinically suspected acute PE. Only data from patients whose initial DD

test results and final PE diagnosis were recorded in the initial database were included. Patients whose cancer status was not confirmed on chart review were excluded from the analysis. The diagnosis of PE was excluded in case of: 1) normal spiral computed tomography (CT) scan and normal ultrasonography, 2) alternative diagnosis made by spiral CT, 3) normal pulmonary angiography, or 4) normal ventilation-perfusion (V/Q) lung scan. In addition to these tests, another requirement was that no episode of venous thromboembolism (VTE) during a 3 month clinical follow-up had occurred.

To validate the results, the predictive value of DD was further evaluated in a cohort of consecutive in- and outpatients evaluated at the thrombosis units of 3 teaching hospitals in the Netherlands for clinically suspected acute PE [13]. Exclusion criteria were any objective testing for a clinically suspected episode of VTE in the previous 7 days, age less than 18 years, pregnancy, treatment with vitamin K antagonists or therapeutic doses of heparin for more than 24 hours before inclusion, indication for thrombolysis, follow-up not possible or if written informed consent could not be obtained. Cancer status was recorded at presentation. Patients were considered to have active cancer if they were receiving treatment for cancer or if they had received treatment for cancer in the past 6 months. Patients in whom the diagnosis of cancer was made after study enrolment were not considered to have active cancer at presentation.

The cut-off value for the DD test (Tinaquant D-dimer; Roche Diagnostica, Mannheim, Germany) was 0.5 μg/ml, with DD values below or equal considered normal and value above the cut-off abnormal.

In the validation group, the diagnosis of PE was excluded if: 1) clinical probability estimate <20% combined with a normal DD, 2) normal perfusion scintigraphy, 3) non-high probability V/Q scan in combination with a normal result on serial leg ultrasonography on days 1, 3 or 4 and 7 or normal pulmonary angiography [13]. All patients were followed up for 3 months for possible subsequent thromboembolic events with objective testing performed in all suspected cases. All deaths were classified by the adjudication committee using clinical reports of treating and/or family physicians and, if available, autopsy reports. Death was attributed to PE (i.e. confirmed by objective testing as well as in those cases in which PE could not be ruled out as the possible contributing factor), cardiovascular disease, malignancy, or other causes.

Statistical Analysis

To compare the performance of the DD assay in patients with cancer and those without cancer, the sensitivity, specificity, the positive and negative predictive values, and the negative likelihood ratio were determined separately in the two patient groups. The

number of patients to be tested with DD to exclude a diagnosis of PE was also determined. The 95% confidence interval for the negative likelihood ratio was calculated using the profile maximum likelihood method.

Results

In the first study population, the diagnosis of PE was confirmed in 85 (24%) of the 350 in- and out-patients with an initial suspicion of PE. A diagnosis of active cancer was made in 35 patients and all the 12 PE cases had an abnormal DD result, while the test gave 21 false positive results in the 23 cancer patients for whom PE was excluded. The sensitivity and the NPV among cancer patients were therefore 100% (100% [95% confidence interval (CI), 74%-100%] and 100% [95% CI, 16%-100%], respectively), whereas the specificity and positive predictive value (PPV) were lower (9% [95% CI, 0%-20%] and 36% [95% CI, 20%-53%] respectively). In the group of patients without cancer, the sensitivity, specificity, NPV, and PPV of the DD were 97% (95% CI, 94%-100%), 44% (95% CI, 38%-50%), 98% (95% CI, 96%-100%), and 34% (95% CI, 28%-41%), respectively.

Table 1. Baseline characteristics of patients with and without cancer in the validation cohort

Characteristic	Patients with cancer (N=72)	Patients without cancer (N=447)
Age (years, median)	60	48**
Males (%)	56	40*
Outpatients, n (%)	33 (46)	317 (71)
History of Arterial disease§ (%)	6.9%	13.9%
Symptoms of DVT (%)	15.3	11.7
Use of oral contraceptives (%)	1.4	13.5**
Hormone therapy (%)	5.6	1.6**
History of VTE (%)	8.3	11.7
Surgery in the past 3 months (%)	30.6	15.5**
Trauma past 3 months (%)	-	3.6
Family history of VTE (%)	2.8	9.0*
Patients with PE, n (%)	19 (26)	83 (19)
D-dimer, mg/ml (range)	1.70 (0.12-36.6)	0.63 (0.01-95.0)**

*p<0.05
**p<0.01
§Cardiovascular disease, cerebral vascular disease, peripheral arterial disease.
DVT=deep venous thrombosis; PE=pulmonary embolism; VTE=venous thromboembolism

The validation cohort

From the original study group of 631 patients, a DD test was performed at presentation in 519 patients (82%) who represent the validation set [13]. A diagnosis of PE was confirmed in 102 patients (20%). The baseline characteristics and the distribution of the PE risk factors in patients with and without cancer are presented in Table 1. A total of 72 patients were diagnosed with cancer including tumors of the lungs and respiratory tract (10), gastrointestinal system (19), breast cancer (8), urinary and reproductive systems (18), or other tumor types (17). As compared to patients without cancer, those with active cancer were older, more frequently males, more likely to have undergone surgery in the previous three months, and they used more often hormone therapy, but less oral contraceptives. A positive family history of VTE was more common among patients without cancer. The median DD level in patients with and without cancer was 1.70 μg/ml (0.12 μg/ml to 36.6 μg/ml) and 0.63 μg/ml (0.01 μg/ml to 95.0 μg/ml), respectively ($p<0.001$).

Of the 72 patients with active cancer, PE was diagnosed in 19 patients (26%) and excluded in 53. There were no false negative DD results among cancer patients with PE, whereas the test was negative in only 11 of the 53 patients without PE. The sensitivity, the NPV, and the negative likelihood ratio were 100% (95% CI, 82%-100%), 100% (95% CI, 72%-100%), and 0 (95% CI, 0-0.5%), respectively whereas the specificity and PPV were 21% (95% CI, 10%-32% and 31% (95% CI, 20%-43%), respectively (Table 2).

Of the 447 patients without malignancy, 83 (19%) had a diagnosis of PE and 77 of these patients had an abnormal DD result. Among the remaining 364 patients in this group, DD result was normal in 193. The sensitivity (93% [95% CI, 87%-98%)]) and NPV (97% [95% CI, 95%-99%]) were lower than in the group with cancer, but comparable to the values reported in the literature [6] (Table 2).

Table 2. Diagnostic accuracy of DD test in patients with and without cancer

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Negative Likelihood Ratios
Patients with cancer	100 (82-100)	21 (10-32)	100 (72-100)	31 (20-43)	0 (0-0.5)
Patients without cancer	93 (87-98)	53 (48-58)	97 (95-99)	31 (25-37)	0.14(0.06-1.34)

Data in parentheses are the 95% confidence interval.

In cancer patients with suspected PE, 6 patients have to be tested with DD to find one true negative result whereas in patients without cancer and with suspected PE one in every two patients will have a true negative DD result. In other words, when 100 patients are tested with DD, a normal DD result can safely rule out the presence of PE in 15 patients with active cancer and in 43 patients without cancer. During the 3-month follow-up, there were 6 (8.3%) and 9 (2.0%) deaths among patients with and without cancer, respectively. Among the 6 cases in the cancer group the diagnosis of PE was excluded in 5 patients and confirmed in 1 by the initial diagnostic work-up. The DD was abnormal in all these 6 patients. In the group of patients without malignancy PE was excluded in 6 (4 abnormal and 2 normal DD results) and confirmed in 3 (all abnormal DD results).

Discussion

While plasma DD measurement is increasingly accepted as a first-line test in patients with clinically suspected PE, the accuracy of this test in cancer patients is limited.

The results of the present study suggest that a negative DD is useful in the diagnostic work-up for the exclusion of PE in this high risk group of patients given a NPV of 100% (95% CI, 72%-100%) and a sensitivity of 100% (95% CI, 82%-100%). The specificity and PPV of DD were low both in cancer and non cancer patients. The clinical utility of the DD to confirm PE is limited due to the non specificity of a positive DD result.

Patients with cancer who develop VTE have a reduced life expectancy and the mortality risk after an acute PE is 4-8 fold higher as compared to patients without cancer [1;14]. This might be due to a more aggressive course of malignancies associated with VTE [14;15]. With anticoagulant treatment the rates of recurrent PE and death can be decreased from 26% to 2-9% over 3-6 months [2]. The implementation of non invasive tools such as the DD test could help to avoid invasive and costly examinations in the diagnostic work-up of suspected PE.

Recently, two studies evaluated the diagnostic accuracy of DD in cancer patients with suspected DVT [11;12] with conflicting results regarding the predictive value of DD in this context. In the first study, the value of the SimpliRED DD assay was retrospectively assessed in 1068 consecutive outpatients with suspected DVT included in three prospective studies [11]. As compared to patients without cancer, the NPV of the DD test was significantly lower in cancer patients (78.9% versus 96.5%, p=0.008) and the authors concluded that a normal DD result could not safely exclude the diagnosis of DVT in patients with concomitant malignancy. In the second study, 1739 consecutive outpatients with suspected DVT were evaluated with a diagnostic strategy including the SimpliRED

DD test and compression ultrasonography[12]. The NPV of the DD test was found to be 97% in both cancer and non-cancer patients. Moreover, the combination of a normal DD test and ultrasonogram results at referral could safely exclude the diagnosis of DVT and safely withhold anticoagulant therapy in patients with malignancy [12]. The discrepancy in the findings of these two studies might be partially explained by the different reference tests used, differences in the populations included as well as in the design characteristics of the studies. The evidence on the role of DD for the diagnosis of DVT in cancer patients remains scarce and unclear.

To our knowledge, this is the first study that investigated the use of DD for the diagnosis of PE in patients with malignancy. Given the morbidity and mortality associated with PE, a test with a high NPV and a low number of false-negative results is mandatory. The 100% NPV of DD in the present study, suggests that this assay can be used to safely exclude the presence of PE in cancer patients, although these results need to be confirmed in a larger sample. Moreover, the validation group represented the 82% of the original study population for whom a DD test result was available. Almost all of the patients (109 out of 112) in whom a DD result was not obtained had a clinical probability of more than 20% and the attending physician decided not to perform the DD test in these cases since the DD result would have not influenced the management decisions. The exclusion of part of the patients with a high clinical probability could have resulted in selection bias, since inclusion of only patients with a low to moderate clinical probability may lead to an overestimation of the NPV of the DD. In clinical practice, however, the most often used algorithm in the diagnostic work-up to exclude PE involves the combination of a normal DD test in combination with a low or low-moderate clinical probability score. Our results support the usefulness of a normal DD result only in this group of patients. The safety of excluding PE in cancer patients with a high clinical probability has still to be established.

When screening 100 patients with clinically suspected PE, the number of patients in whom PE could be excluded based on a negative DD test result was 15 in the presence of cancer as compared to 43 patients without a malignancy. This difference was due to the lower specificity of the assay in cancer patients (21%) in comparison to non cancer patients (53%) which led to the higher number of false positive DD results in the presence of cancer.

In conclusion, a negative DD result safely excludes the diagnosis of PE in patients with cancer. Whether the combination of DD with other imaging techniques, such as the CT scan or serial leg ultrasonography, might improve the diagnostic work-up warrants further investigation.

Reference List

1. Lee AYY: Epidemiology and management of venous thromboembolism in patients with cancer. Thromb Res 2003, 110:167-172.
2. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE: Antithrombotic therapy for venous thromboembolic disease. Chest 2004, 126:401S-428S.
3. Levine MN, Raskob GE, Beyth RJ, Kearon C, Schulman S: Hemorragic complications of anticoagulant treatment. Chest 2004, 126:287S-310S.
4. 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.
5. Kruip MJHA, Leclercq MGL, 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. Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, Biel RK, Bharadia V, Kalra NK: D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism. Ann Intern Med 2004, 140:589-602.
7. Brown MD, Lau J, Nelson RD, Kline JA: Turbidimetric d-dimer test in the diagnosis of pulmonary embolism: a metaanalysis. Clin Chem 2003, 49:1846-1853.
8. Brown MD, Rowe BH, Reeves MJ, Bermingham JM, Goldhaber SZ: The accuracy of the enzyme-linked immunosorbent assay d-dimer test in the diagnosis of pulmonary embolism: a meta-analysis. Ann Emerg Med 2002, 40:133-144.
9. Kelly J, Rudd A, Lewis RR, Hunt BJ: Plasma d-dimers in the diagnosis of venous thromboembolism [abstract]. Arch Intern Med 2002, 162:747-756.
10. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S: Hemorrhagic complications of anticoagulant treatment. The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004, 126:287S-310S.
11. Lee AYY, Julian JA, Levine MN, Weitz JI, Kearon C, Wells PS, Ginsberg JS: 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, 131:417-423.
12. ten Wolde M, Kraaijenhagen RA, Prins MH, Buller HR: The clinical usefulness of d-dimer testing in cancer patients with suspected deep venous thrombosis. Arch Intern Med 2002, 162:1880-1884.
13. Ten Wolde M, Hagen PJ, MacGillavry MR, Pollen IJ, Mairuhu ATA, Koopman MMW, Prins MH, Hoekstra OS, Brandjes DPM, Postmus PE, Buller HR: Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism: results of a management study. J Thromb Haemost 2004, 2:1110-1117.
14. Kakkar AK: An expanding role for antithrombotic therapy in cancer patients. Cancer Treatment Reviews 2003, 29:23-26.
15. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA: Prognosis of cancers associated with venous thromboembolism. New Engl J Med 2000, 343:1846-1850.

Diagnostic strategy using a modified clinical decision rule and D-dimer test to rule out pulmonary embolism in elderly in-and outpatients

MAAIKE SÖHNE, PIETER W. KAMPHUISEN,
PATRICIA J.W.B. VAN MIERLO, HARRY R. BÜLLER

THROMBOSIS AND HAEMOSTASIS 2005; 94:206-210

Abstract

Background:

Excluding or confirming pulmonary embolism remains a diagnostic challenge. In elderly patients pulmonary embolism is associated with substantial co-morbidity and mortality, and many elderly patients with suspected pulmonary embolism are inpatients. The safety and efficacy of the combination of a clinical probability (CDR) and D-dimer test in excluding pulmonary embolism in this group is unclear.

Methods:

We retrospectively analysed data of two prospective studies of consecutive in-and outpatients with suspected pulmonary embolism. The patients were categorized into three age groups: <65 years, 65-75 years and >75 years. The sensitivity, negative predictive value and the proportion of patients with the combination of a non-high CDR score according to Wells (≤4) and a normal D-dimer result were calculated for each group.

Results:

In 747 consecutive patients with suspected pulmonary embolism, sensitivity and negative predictive value of a non-high CDR and a normal D-dimer result in outpatients (n=538) of all age categories (<65 years, 65-75 years and >75 years) were both 100%. These tests were however less reliable for inpatients(n=209), irrespective of their age (sensitivity 91% [CI: 79-98%], negative predictive value 88% [CI: 74-96%]. The proportion of both in-and outpatients >75 years with a non-high CDR and a normal D-dimer concentration was only 14%, whereas this was 22% in patients 65-75 years and 41% among in-and outpatients <65 years, respectively.

Conclusion:

In elderly outpatients the combination of a non-high CDR and a normal D-dimer result is a safe strategy to rule out pulmonary embolism. However, in inpatients this algorithm is not reliable to safely exclude pulmonary embolism. In addition, the proportion of patients >65 years in which this strategy excludes pulmonary embolism is markedly lower compared to younger patients.

Introduction

Pulmonary embolism is associated with a substantial morbidity and mortality if untreated [1;2], whereas anticoagulant treatment is associated with an increased bleeding risk [3;4]. It is therefore important to reliably exclude or confirm the presence of this disease. Several diagnostic strategies are available, but pulmonary embolism still remains a diagnostic challenge, especially in elderly patients. Compared to younger patients, clinical symptoms in elderly patients are more often non-specific due to frequent co-morbidity[5;6]. In addition, the diagnostic yield of ventilation/perfusion(V/Q) scanning further decreases with advancing age [7].

Several studies recently showed that pulmonary embolism can be safely ruled out in outpatients by the combined use of a low clinical probability score and a normal plasma D-dimer concentration [8-10]. With these simple and fast tests, in approximately 30 percent of the referred patients further diagnostic tests to rule out pulmonary embolism can be left out. The safety of this diagnostic strategy in inpatients with suspected pulmonary embolism is less clear. There are no studies with substantial numbers of patients that evaluated the reliability of this algorithm in hospitalised patients [11].

In most studies evaluating a clinical probability score in the exclusion of pulmonary embolism, the low probability category was analysed. To further optimise the clinical utility, a non-high clinical probability score according to Wells has recently been advocated, which combines low and moderate scores [12] (Table 1). With a non-high clinical

Table 1: Clinical decision rule (Wells).

	points
Clinical signs and symptoms of deep vein thrombosis (DVT)(minimum of leg swelling and pain with palpation of the deep veins)	3.0
Heart rate greater than 100/minute	1.5
Immobilization or surgery in the previous four weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the last six months or palliative)	1.0
An alternative diagnosis is less likely than PE	3.0

Score ≤ 4: non-high
Score > 4: high

probability score, the number of patients in which pulmonary embolism can be excluded may be higher than when a low probability score as cut-off is used.

It is at present unclear whether this strategy of a non-high clinical probability in combination with a normal D-dimer test is also effective and safe in elderly patients with a clinical suspicion of pulmonary embolism. D-dimer levels increase with age [13-15], and older patients more often have pre-existing co-morbidity, which may further elevate the D-dimer concentration [14;16;17].

In the present sub-study of two large prospective studies on consecutive in- and outpatients with suspected pulmonary embolism [18] we investigated whether the combination of a non-high clinical probability and a normal D-dimer concentration is a safe and effective strategy in excluding pulmonary embolism in both elderly in- and outpatients.

Methods

Study population

From 1999 to 2001 consecutive in- and outpatients with a clinical suspicion of acute pulmonary embolism were eligible for inclusion. Outpatients were referred by their general practitioners. Patients were excluded if they were younger than 18 years of age, were pregnant, had received vitamin K antagonists or heparin in a therapeutic dose for more than 24 hours, had already undergone objective testing for venous thromboembolism, had an indication for thrombolysis or if written informed consent could not be obtained. For the statistical analysis all included patients were categorized into three different age groups: younger than 65 years, between 65 and 75 years, and patients older than 75 years.

Diagnostic methods

Upon referral, the attending physician completed the simplified clinical decision rule (CDR) according to Wells [12]. The CDR consists of seven questions regarding specific signs and risk factors for pulmonary embolism along with an alternative explanation of the complaints that is at least as likely as pulmonary embolism [12]. A score less than or equal to 4 indicated a non-high probability of having pulmonary embolism; a score above 4 indicated a high probability. After performing the clinical score, plasma D-dimer concentration was measured using a quantitative rapid immunoturbidimetric D-dimer assay (Tinaquant D-dimer, Roche Diagnostica, Mannheim, Germany). The cut-off value for a positive test was 0.5 mg/l. D-dimer measurements were performed by technologists who were unaware of patients' clinical status.

Data on the final diagnosis of pulmonary embolism for each patient were derived from two subsequent diagnostic follow-up studies. In both studies, the reference standard for the confirmation of pulmonary embolism was V/Q scan in combination with compression ultrasound or a pulmonary angiography. Those with normal test results did not receive anticoagulant therapy. All patients had a follow-up of three months to document the accuracy and safety of the diagnostic method. Each patient was contacted by telephone after 6 weeks and scheduled for a hospital visit after three months.

Outcome

The primary (safety) outcome measure was the incidence of symptomatic and objectively confirmed venous thromboembolism during the three months of follow-up in three age categories of in- and outpatients with a CDR score ≤ 4 and a D-dimer concentration ≤ 0.5 mg/L. Suspected pulmonary embolism was confirmed with a high probability V/Q scan result, a non-high V/Q scan result in combination with an abnormal ultrasound of the lower limbs or a positive pulmonary angiography. Suspected deep vein thrombosis was confirmed with compression ultrasound. All deaths were classified by the adjudication committee using clinical reports of treating and/or family physician and, if available, autopsy reports. Death was attributed to pulmonary embolism (i.e. confirmed by objective testing as well as cases in which embolism could not be ruled out as the possible contributing factor); other cardiovascular diseases; malignancy; or other causes. In this retrospective analysis, sensitivity, specificity and negative predictive values were calculated for the different age groups. Exact 95% confidence intervals were calculated using Confidence Interval Analysis (CIA, version 1.0; Gardner MJ). To calculate whether there was a difference in the sensitivities and the negative predictive values of the different age groups the Armitage test for trend was performed.

The secondary outcome measure was the clinical utility in excluding pulmonary embolism of the combination of tests in patients between 65 and 75 years and older than 75 years as compared to patients younger than 65 years. Furthermore, the proportion of in- and outpatients in which further diagnostic tests like a V/Q scan or angiography could be left out because of a non-high probability clinical score and a normal D-dimer result was calculated.

Results

During the study period a total of 1290 consecutive patients with suspected pulmonary embolism were screened. 431 (33%) patients were excluded. The main reasons for exclusion were: refusal or inability to provide consent (160); anticoagulant treatment for more than 24 hours (112); already objective diagnostic testing for VTE performed (39) and age under18 years or pregnancy (17).

The study population consisted of 859 patients. D-dimer results were available for 747 (87%) patients. In the remaining 112 (13%) patients no D-dimer test was performed, because of the impossibility to obtain blood or refusal of the attending physician, since a V/Q scan was thought necessary even if the D-dimer result would be negative. Therefore, 747 patients were included in the present analysis of which 30% were older than 65 years of age.

The prevalence of pulmonary embolism in the overall study-population was 21% (160 patients). Of all patients with pulmonary embolism, the diagnosis was confirmed with a high probability lung scan in 85%, with pulmonary angiography in 7% and with compression ultrasound in combination with a non-high probability V/Q scan in 8%. The mean age of the patients with pulmonary embolism was 62 years (range 14-95) while those without pulmonary embolism had a mean age of 52 years (range 17-92). The prevalence of pulmonary embolism increased with age: 18% in patients younger than 65 years, 28% in those between 65-75 years and 31% in patients older than 75 years (Table 2).

Of all included patients, 234 (31%) had a combination of a CDR score ≤ 4 and a D-dimer concentration ≤ 0.5 mg/L. The incidence of confirmed pulmonary embolism during follow-

Table 2: Prevalences of pulmonary embolism for the different D-dimer (DD) and CDR categories.

	Prevalence of pulmonary embolism (%)				
Age (yrs)	**DD≤0.5 mg/l CDR≤ 4**	**DD≤0.5 mg/l CDR> 4**	**DD>0.5 mg/l CDR≤ 4**	**DD>0.5 mg/l CDR> 4**	**Total prevalence (%)**
<65	1	4	28	39	18
65-75	8	0	38	36	28
>75	7	0	31	46	31
All ages (n)	2 (234)	4 (53)	30 (314)	40 (146)	21 (747)

Table 3: Sensitivity, specificity and negative predictive value for the combination of a negative D-dimer result and a non-high CDR.

Age (yrs)	Total number of patients	Number of patients with d-dimer ≤ 0.5 mg/l and CDR ≤ 4	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)
< 65	527	194 (37%)	98 (93-100)	44 (40-49)	99 (96-100)
65-75	113	25 (22%)	94 (79-99)	28 (19-40)	92 (74-100)
>75	107	15 (14%)	97 (84-100)	19 (11-30)	93 (68-100)

up in these 234 patients was 2.1% (95% CI 0.7-4.9%). All these episodes of were confirmed by a high probability V/Q scan on the initial day of referral. The overall sensitivity and negative predictive value of the combination of a non-high CDR score and a low D-dimer concentration in patients with suspected pulmonary embolism in this study population were 97% (95% CI 93-99%) and 98% (95% CI 95-99%), respectively.

Of the patients with a pulmonary embolism despite a non-high CDR and a low D-dimer concentration, two were younger than 65 years, two were 65-75 years, and one patient was older than 75 years. One of these patients died due to pulmonary embolism. Therefore, the sensitivity of the combined test results for the three different age groups was 98% (95% CI 93-100%) in the youngest group, and 94% (95% CI 79-99%) and 97% (95% CI 84-100%) (p-value for trend 0.58) in the categories of patients between 65-75 years and patients older than 75 years, respectively (Table 3). The negative predictive values for the three age categories were 99%, 92% and 93%, respectively (p-value for trend 0.02). The specificity of the combination of a non-high CDR and a low D-dimer concentration was low and further decreased with advanced age: 44, 28 and 19%, respectively(p value for trend <0.001) (Table 3).

The proportion of patients with a combination of a non-high CDR score and a normal D-dimer concentration varied with age. This combination was present in 37% of the patients younger than 65 years, in 22% of the patients between 65-75 years, and in only 14% of the patients >75 years (p-value <0.001). These results were mainly caused by the low prevalence of normal D-dimer levels among the elderly. Only 17% of the patients >75 years had a D-dimer ≤ 0.5 mg/l, whereas 22% of the patients between 65-75 years and nearly half of the young patients had normal D-dimer levels (p<0.001). Age did not have a clear influence on the CDR score. The CDR score of ≤ 4 was present in 74% of the patients younger than 65 years, and in 72% and 71% of the patients between 65 and 75 years and >75 years, respectively.

Subgroups of in- and outpatients

Of the total population, 72% consisted of outpatients. This percentage varied from 77% in the young patients to 59% in patients older than 75 years. The sensitivity and negative predictive value of the combination of a CDR ≤ 4 and a normal D-dimer test were clearly lower among inpatients compared to outpatients in all age groups. Overall sensitivity and negative predictive value in outpatients were 100% (95% CI 97-100) and 100% (95% CI 98-100), respectively, whereas these were 91% (95% CI 79-98) and 88% (95% CI 74-96) among inpatients (Table 4).

The proportion of patients younger than 65 years with a non-high probability test and a normal D-dimer concentration was almost 50% lower among inpatients compared to outpatients (22% for inpatients and 41% for outpatients). This difference was mainly caused by a lower prevalence of a normal D-dimer result among the hospitalised patients. In elderly patients, the percentage of in- and outpatients that could be excluded with these tests was not different: 22% of the patients between 65-75 years and 14% of patients above the age of 75 years (Table 4).

Discussion

This study investigated the safety and clinical utility of the combination of a non-high CDR score and a low D-dimer concentration in elderly patients and among subgroups of in- and outpatients. Pulmonary embolism in the elderly is associated with a high morbidity and mortality[19]. It is therefore of the utmost importance to test the reliability of simple and non-invasive tests for the exclusion of pulmonary embolism in this patient category. It has previously been demonstrated that the assessment of a clinical probability for pulmonary embolism using a CDR is reliable in elderly patients, although age reduces the negative

Table 4: Results of the combination of a negative D-dimer result and a non-high CDR score for inpatients and outpatients separately.

	Inpatients					Outpatients				
Age group	N	% of pts with CDR ≤ 4 and low d-dimer	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	NPV (%) (95% CI)	N	% of pts with CDR ≤ 4 and low d-dimer	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	NPV (%) (95% CI)
< 65 years	123	22%	92 (75-99)	26 (17-36)	93 (76-99)	404	41%	100 (95-100)	50 (45-55)	100 (98-100)
65-75 years	40	22%	82 (48-98)	24 (10-44)	77 (40-97)	73	22%	100 (84-100)	31 (19-45)	100 (79-100)
>75 years	44	14%	90 (56-99)	15 (5 -32)	83 (36-100)	63	14%	100 (85-100)	22 (11-38)	100 (66-100)
All ages	207	20%	91 (79-98)	23 (17-30)	88 (74-96)	540	36%	100 (97-100)	45 (40-50)	100 (98-100)

predictive value [20]. In our study, the negative predictive value of the modified CDR according to Wells in combination with a normal D-dimer measurement was high in elderly outpatients with suspected pulmonary embolism, but we confirm that this negative predictive value is somewhat lower compared to the younger patients. The sensitivity and negative predictive value were 97% and 93%, respectively for patients older than 75 years, 94% and 92%, respectively for patients between 65-75 years, and 98% and 99% for younger patients. The confidence intervals in the elderly patient groups though were wide, due to the relatively small numbers of patients in these high age categories.

The percentage of in- and outpatients who had a combination of a non-high CDR score and a low D-dimer concentration was 37% among patients <65 years and only 14% in patients older than 75 years. Consequently, seven patients older than 75 years have to undergo these non-invasive diagnostic tests to exclude a pulmonary embolism in one patient. This result might in part be explained by the higher prevalence of co-morbidity, like cancer, rheumatoid arthritis or infection in the older patients, as these conditions increase the D-dimer concentrations. It should be mentioned that increasing age itself also is associated with higher D-dimer levels [21]. In order to decrease the number of tests that have to be performed in elderly patients, a higher cut-off level for the D-dimer might be more cost-effective. Increasing the cut-off value of the D-dimer increases however the false-negative results and lowers safety of this diagnostic test [22]. Hence, the combination of a non-high CDR score and a D-dimer level <0.5 mg/L is the preferred strategy to exclude acute pulmonary embolism in the elderly outpatients, like in younger patients, but the diagnostic yield will be lower than in these younger patients.

For inpatients, the negative predictive value of a normal D-dimer concentration and a non-high CDR was lower compared to outpatients (88% and 100%, respectively). This difference between in- and outpatients was present in all three age categories. However, the results of inpatients were based on relatively small groups, especially in the elderly patients, and therefore the confidence intervals were wide. Nevertheless, all five failures of the strategy were inpatients. Therefore, further evaluation in larger groups of inpatients of all ages is necessary to show whether the combination of a non-high CDR score and a low D-dimer concentration is a safe strategy to rule out pulmonary embolism in hospitalised patients. Presently, the safe exclusion of pulmonary embolism in inpatients of all ages by the combination of a CDR and D-dimer remains to be established.

In 13% of the patients, no D-dimer concentration was measured and this group was excluded from our analyses. This could have resulted in a selection bias. However, the prevalence of pulmonary embolism in this group was not higher compared to the total

study population. Moreover, the mean age and age distribution, as well as the percentages of patients with specific signs and symptoms that form the basis of the CDR, were largely comparable with the total study population.

In summary, the combination of a normal D-dimer measurement and a CDR score according to Wells ≤ 4 is a safe method to exclude pulmonary embolism in elderly outpatients. Due to a low number of normal D-dimer results, the proportion of outpatients older than 75 years in which pulmonary embolism can be ruled out with this strategy is markedly lower compared to younger patients. In inpatients of all ages this algorithm seems less reliable to safely exclude pulmonary embolism.

Reference List

1. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:401S-428S.
2. BARRITT DW, JORDAN SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960; 1:1309-1312.
3. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S. Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:287S-310S.
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; 348:423-428.
5. 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; 109:357-361.
6. Ceccarelli E, Masotti L, Barabesi L, Forconi S, Cappelli R. Pulmonary embolism in very old patients. Aging Clin Exp Res 2003; 15:117-122.
7. 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; 109:357-361.
8. 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.
9. Kruip MJ, Slob MJ, Schijen JH, van der HC, 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.
10. 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.
11. Kruip MJ, Leclercq MG, van der HC, Prins MH, Buller HR. Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med 2003; 138:941-951.
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. Mari D, Mannucci PM, Coppola R, Bottasso B, Bauer KA, Rosenberg RD. Hypercoagulability in centenarians: the paradox of successful aging. Blood 1995; 85:3144-3149.
14. Hager K, Platt D. Fibrin degeneration product concentrations (D-dimers) in the course of ageing. Gerontology 1995; 41:159-165.
15. Pieper CF, Rao KM, Currie MS, Harris TB, Chen HJ. Age, functional status, and racial differences in plasma D-dimer levels in community-dwelling elderly persons. J Gerontol A Biol Sci Med Sci 2000; 55:M649-M657.
16. Becker DM, Philbrick JT, Bachhuber TL, Humphries JE. D-dimer testing and acute venous thromboembolism. A shortcut to accurate diagnosis? Arch Intern Med 1996; 156:939-946.
17. Raimondi P, Bongard O, de Moerloose P, Reber G, Waldvogel F, Bounameaux H. D-dimer plasma concentration in various clinical conditions: implication for the use of this test in the diagnostic approach of venous thromboembolism. Thromb Res 1993; 69:125-130.
18. 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.
19. Siddique RM, Siddique MI, Connors AF, Jr., Rimm AA. Thirty-day case-fatality rates for pulmonary embolism in the elderly. Arch Intern Med 1996; 156:2343-2347.
20. 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; 109:357-361.
21. Righini M, de Moerloose P, Reber G, Perrier A, Bounameaux H. Should the D-dimer cut-off value be increased in elderly patients suspected of pulmonary embolism? Thromb Haemost 2001; 85:744.
22. Righini M, de Moerloose P, Reber G, Perrier A, Bounameaux H. Should the D-dimer cut-off value be increased in elderly patients suspected of pulmonary embolism? Thromb Haemost 2001; 85:744.

Part II

Two

Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism

M. TEN WOLDE, M.SÖHNE, E.QUAK, M.R.MAC GILLAVRY, H.R.BÜLLER

ARCH INTERN MED. 2004;164:1686-1689

Abstract

Background:

Echocardiographically assessed right ventricular dysfunction is increasingly used to guide more aggressive therapy in hemodynamically stable patients with acute pulmonary embolism (PE). However, the prognostic value of right ventricular dysfunction in these patients is still unclear.

Methods:

We systemically reviewed the literature to assess the prevalence of echocardiographic right ventricular dysfunction and the association with adverse outcomes in patients with PE who had this condition. The methodologic quality of each study was scored. Absolute risks of the outcome events were calculated for each study separately and positive predictive values of PE related mortality were determined for normotensive patients.

Results:

Seven studies were included. All had methodological shortcomings, but they suggested an at least 2-fold increased risk of PE related mortality in patients with right ventricular dysfunction, the prevalence of which varied from 40% to 70%. However, this seems to be less convincing in hemodynamically stable patients. The only 2 studies that allowed for an estimation of the accuracy in normotensive patients, showed low positive predictive values of echocardiographic right ventricular dysfunction for PE related in-hospital mortality (positive predictive value, 4% and 5% in the 2 studies).

Conclusion:

It remains unclear whether echocardiographic right ventricular dysfunction is a prevalent and reliable predictor of adverse outcomes in hemodynamically stable patients with acute PE.

Introduction

Before the introduction of anticoagulants, patients with pulmonary embolism (PE) had a poor prognosis. The chance of dying as a result of their disease was around 25% [1-3]. Currently, hemodynamically stable patients with PE are routinely treated with a course of heparin and vitamin K antagonists as secondary prophylaxis, and the prognosis has considerably improved, with PE related mortality rates ranging from 1.5 to 7% [4-7]. To further reduce this rate, patients with a high risk of recurrent (fatal) PE could be treated more aggressively, i.e. with thrombolytic agents or embolectomy. For the selection of these high risk patients, a tool is needed that accurately predicts adverse outcomes at the time of presentation.

In 1993 Goldhaber and colleagues [8] suggested a correlation between echocardiographic right ventricular dysfunction and poor outcome in patients with acute PE. They observed in a randomised controlled trial of heparin vs thrombolysis, that all patients with recurrent PE, some of whom died, showed right ventricular hypokinesis on echocardiography. Since then several studies have evaluated the importance of echocardiographic right ventricular dysfunction as a predictor of mortality, suggesting that 40% to 60% of unselected patients with PE may have echocardiographic right ventricular dysfunction [7,9-11]. The majority of these patients were hemodynamically stable.

Recently, the first randomised, double-blind, placebo-controlled trial was published of thrombolysis and heparin vs heparin alone as initial treatment in patients with acute PE and concomitant pulmonary hypertension and/or (echocardiographic or electrocardiographic) right ventricular dysfunction [12]. Remarkably, the in-hospital PE related mortality was very low in both the thrombolysis and heparin only groups (1.7% and 1.4%, respectively) and, moreover, the prevalence of echocardiographic right ventricular dysfunction in this highly selected patient category was only 31%. This raises the question of whether echocardiographically assessed right ventricular dysfunction is of clinical importance in hemodynamically stable patients with PE. We, therefore, performed a systematic review to establish whether echocardiographically assessed right ventricular dysfunction is a prevalent and reliable prognostic marker in patients with acute PE, in particular in those who are hemodynamically stable.

Methods

Literature search and data sources

Two reviewers (MtW and EQ) searched the OVID, MEDLINE, EMBASE, PUBMED, COCHRANE and WEB of SCIENCE databases, by combining the keywords 'pulmonary embolism', 'right ventricular dysfunction', and 'echocardiography'. Furthermore, abstracts were searched from the databases of relevant congresses. The same 2 reviewers independently selected trials suitable for inclusion in the analysis on the basis of the three criteria outlined in the following paragraph. For inclusion, all three criteria needed to be met. Disagreement between reviewers was resolved by discussion and consensus.

Criteria for considering studies for this review

1. Studies had to be prospective cohort studies or randomised controlled trials in patients with clinically suspected acute PE. Initial treatment had to be either heparin or thrombolysis, followed by vitamin K antagonists for a minimum of 3 months.
2. All patients, with objectively proven PE, had to undergo echocardiography to assess right ventricular function at baseline. Transthoracic echocardiography had to comprise assessment of right ventricular size, right ventricular wall motion by different views, pulmonary artery systolic pressure, tricuspid regurgitation, right ventricular wall thickness or paradoxical septal movement [13,14].
3. Patients needed to be clinically followed up for a minimum of 14 days or during the period of their in-hospital stay.

Analysis

All studies were scored for their methodological quality by evaluating the following criteria [15]: proper formation of an inception cohort (i.e. were patients included consecutively and was the diagnosis of PE objectively confirmed by established methods?), description of referral pattern, completeness of follow-up, a priori definition of outcomes, blind outcome assessment and adjustment for other prognostic factors.

Outcome measures were absolute risks of all cause short-term mortality (i.e. occurring within the in-hospital period or 14 days) and all cause long-term mortality (defined by a minimum follow-up of 3 months) and mortality due to PE (short-term and long-term), in patients with and without right ventricular dysfunction. Positive predictive values were calculated in patients who were normotensive, since this was be the population of interest. If no clinical or statistical heterogeneity was observed, pooled estimates of absolute risks of the outcome events were calculated.

Table 1. Quality assessment of studies on the prognosis of patients with pulmonary embolism and echocardiographic right ventricular dysfunction

	Study type	Proper formation of inception cohort	Description of referral pattern	Completeness of follow-up	Objectivity of outcome criteria	Assessment of blind outcome	Adjustment for extraneous prognostic factors
Goldhaber et al. 1993[8]	RCT	-	-	+	-	Not Reported	+*
Ribeiro et al. 1997[9]	PCS	+	-	+	+	Not Reported	+*
Kasper et al. 1997[10]	PCS	-	-	+	-	Not Reported	-
Goldhaber et al. 1999[7]	Registry	-	+	+	-	Not Reported	+*
Grifoni et al. 2000[11]	PCS	+	+	+	-	Not Reported	+
Grifoni et al. 2001[18]	PCS	-	-	+	Not Reported	Not Reported	+
Jerjes-Sanchez 2001[19]	PCS	-	-	+	Not Reported	Not Reported	-

RCT= Randomised Controlled Trial, PCS= Prospective Cohort Study, * = No adjustment for type of therapy (e.g. thrombolysis or placement of vena cava filter)

Results

The computer search yielded 62 references, of which 9 articles met our inclusion criteria [7-11,16-19]. Two of these articles reported on previously published cohorts [16,17], hence these studies were excluded from further analysis.

Methodological quality of the studies

Table 1 presents the results of the quality assessment of the 7 included studies.

In 3 studies it is unknown whether consecutive patients were included [8,10,18] whereas in three studies the diagnosis of PE was not always confirmed by established methods but by a suggestive echocardiogram and/or a (high) clinical suspicion of PE [7,10,19] Thus, only two studies had a proper inception cohort.

Most of the studies did not describe to which type of department (e.g. coronary care unit) or type of hospital (e.g. tertiary care clinic) patients were referred, making it difficult to analyse the referral pattern.

Follow-up was completed in all studies. Short-term follow-up was defined as the in-

hospital period or an observation period of less than 14 days. The long-term follow-up varied among the studies from 3 months 7 to longer than 6 months [18] to 1 year [9,10] or more [19].
Apart from the study by Ribeiro et al., in none of the studies was it explicitly stated how the outcome criterion PE related mortality was assessed and whether it was defined a priori. Moreover, none of the studies reported whether an independent committee, blinded to the cardiac status of the patient, assessed the outcome measurement.
Adjustment for other risk factors influencing mortality was not performed in the studies by Kasper et al [10] and Jerjes-Sanchez et al.[19] The other studies did evaluate the influence of extraneous prognostic factors. However, despite the fact that the Goldhaber et al. and Ribeiro et al.[9] did adjust for possible confounders by multivariate analyses, they did not control for treatment type, e.g. thrombolysis or placement of a caval filter.

Echocardiography criteria for right ventricular dysfunction

In the majority of studies, right ventricular dysfunction was defined as right ventricular hypokinesis as assessed by a qualitative evaluation of the right ventricular wall motion [7-9,19]. In the study by Kasper et al [10], right ventricular dysfunction was defined as follows: dilatation of the right ventricular cavity (apical, subcostal or transoesophageal 4 chamber view), or right ventricular end diastolic diameter greater than 30 mm (precordial view); or when 2 of the following items were satisfied: (1) tricuspid regurgitation velocity greater than 2.8m/s, (2) tricuspid regurgitation velocity greater than 2.5 m/sec in the absence of inspiratory collapse of the inferior vena cava; (3) dilation of the right pulmonary artery (>12 mm/m2); (4) right ventricular wall thickness greater than 5 mm or (5) loss of inspiratory collapse of the inferior vena cava. Grifoni and colleagues considered (acute) right ventricular dysfunction to be present when 1 or more of the following criteria were met: right ventricular dilation (end-diastolic diameter >30 mm or right ventricular/left ventricular end-diastolic diameter ratio > 1 in 4-chamber view); or paradoxical septal systolic movements or pulmonary hypertension (defined as Doppler pulmonary acceleration time <90 milliseconds or presence of a right ventricular-atrial gradient > 30 mm Hg). In addition, right ventricular wall hypertrophy (free wall thickness > 7 mm) needed to be absent. Thus, among the different studies, no uniform criteria were used to assess the presence of right ventricular dysfunction.

Patient characteristics

Table 2 summarizes the baseline clinical characteristics and overall outcomes of the included studies. A large degree of heterogeneity was observed in the included patients

Table 2. Clinical characteristics of all patients with pulmonary embolism

	Nr of patients	Mean age (y)	Hemodynamic status	Thrombolytic Treatment No. (%)	Patients with confirmed PE and available echocardiography, No.	Patients with RVD No. (%)	Total mortality No. (%)		Mortality due to PE No. (%)	
							*Short term**	*Long term*	*Short term*	*Long term*
Goldhaber 1993[8]	101	59	Stable	46 (46)	101	NDA	2 (2)	NDA	2 (2)	NDA
Ribeiro 1997[9]	157	>65	Not reported	37 (24)	126	70 (56)	10 (8)	19 (15) ‡	9 (7)	9 (7)
Kasper 1997[10]	317	59	Not reported	49 (15)	164	72 (44)	29 (9)	30 (9) ‡	13 (4)	14 (4)
Goldhaber 1999[7]	2454	62	2182 stable 169 no symptoms	49 (15)	1135	454 (40)	280 (11)	426 (17) †	NDA	179 (7)
Grifoni 2000[11]	209	65	162 Normotensive 19 hypotensive 28 shock	31 (15)	207	110 (53) (normotensive: 65 [40])	17 (8)	NDA	13 (6)	NDA
Grifoni 2001[18]	117	63	Not reported	NDA	117	48 (41)	NDA	12 (10) V	NDA	3 (3)
Jerjes-Sanchez 2001[19]	40	47	Large/massive PE 24 normotensive	40 (100)	40	28 (70)	5 (13)	5 (13) β	4 (10)	NDA

PE = Pulmonary embolism, RVD = Right ventricular dysfunction, * follow-up during in-hospital period or <14 days, † 3 months follow-up, ‡ 1 year follow-up, V > 6 months follow-up, β >1 year follow-up

with regard to their hemodynamic status. The percentage of patients receiving thrombolytic therapy varied from 100% in the study by Jerjes-Sanchez et al [19] to 15% in the studies by Goldhaber et al [7], Grifoni et al [18], and by Kasper et al [10]. One fourth of the patients in the study by Ribeiro and colleagues [9] received thrombolytic therapy, whereas half of the patients (by definition) in the randomised trial by Goldhaber et al[8] received this treatment. Also, variation was observed in the proportion of included patients with objectively proved PE who underwent echocardiography, which varied from 46% to 100%. The prevalence of right ventricular dysfunction in patients with PE ranged from 40% to 70%. Finally, the studies varied with respect to their overall outcomes: short-term all cause and PE related mortality rates ranged from 2% to 13% and from 2% to 10%, respectively.

Right ventricular dysfunction and outcomes

As a result of the observed heterogeneity of the included studies - with respect to their methodological quality, the echocardiographic criteria of right ventricular dysfunction and the patient characteristics - pooling of the results and performance of statistical analysis to obtain one overall estimate of the studied outcome measures was not meaningful. We will therefore describe the different studies separately.

Table 3 gives the outcomes of the included studies stratified for the presence or absence of right ventricular dysfunction are given. Six studies, including at total of 1773 patients, showed that patients with right ventricular dysfunction had at least a two fold higher risk of dying in the short term as compared with patients without right ventricular dysfunction [7-11,19]. The absolute difference ranged from 4% [8] to 18% [19]. This increase is supported by the multivariate analysis in the study by Ribeiro et al [9], which showed a relative risk of 6.0 (95% confidence interval: 1.1-111.5) [9]. The absolute differences in all-cause mortality rates between patients with and without right ventricular dysfunction remained higher after a longer duration of follow-up in most studies. The Goldhaber et al study [7] and the study by Ribeiro and colleagues [9] reported adjusted risk estimates for long-term total mortality; these multivariate analyses showed an odds ratio for 3 months follow-up of 2.0 (95% confidence interval: 1.3-2.9) and a relative risk for 1 year follow-up of 2.4 (95% confidence interval 0.9-8.7), respectively.

When deaths related to PE are considered, 5 studies (638 patients) [8-11,19] showed that more patients died in the group having right ventricular dysfunction than in the group without it. The absolute difference in short-term PE related mortality rate ranged from 4% [8] to 14% [19]. For patients who completed long-term follow-up (3 studies, 407 patients [9,10,18]), this

Table 3. Mortality in patients with pulmonary embolism with and without right ventricular dysfunction

	No. of patients		Total mortality, No. (%)				Mortality related to PE, No. (%)			
			Short-term		*Long-term*		*Short-term*		*Long-term*	
	RVD Present	RVD Absent	RVD Present	RVD Absent	RVD Present	RVD Absent	RVD Present	RVD Absent	RVD Present	RVD Absent
Goldhaber 1993[8]	46	55	2 (4)	0	NDA	NDA	2 (4)	0	NDA	NDA
Ribeiro 1997[9]	70	56	10 (14)	0	15 (21)	4 (7)	9 (13)	0	9 (13)	0
Kasper 1997[10]	87*	230*	16 (18)	13 (6)	16 (18)	14 (6)	11 (13)	2 (1)	11 (13)	3 (1)
Goldhaber 1999[7]	NDA	NDA	16†	8†	21†	15†	NDA	NDA	NDA	NDA
Grifoni 2000[11]	110 (65‡)	99 (97‡)	14 (13)	3 (3)	NDA	NDA	13 (12) (3‡ [5])	0	NDA	NDA
Grifoni 2001[18]	48	69	NDA	NDA	4 (8)	8 (11)	NDA	NDA	3 (3)	0
Jerjes-Sanchez 2001[19]	28	12	5 (18)	0	NDA	NDA	4 (14)	0	NDA	NDA

NDA=No data available, * Pulmonary embolism was not objectively confirmed in all patients, † Percentage estimated from the Kaplan Meier curve, ‡ Normotensive patients

difference varied from 3% [18] to 13% [9,10]. The two studies that allow an estimation in normotensive patients showed an absolute difference in the short-term PE related mortality of 4% [8] and 5% [11]. In these studies the specificity of echocardiographic right ventricular dysfunction for in-hospital mortality was 56% and 61%, whereas the positive predictive value was 4% and 5%, respectively.

Discussion

The prognosis of acute PE ranges from good - for which in special cases avoiding therapy might even be safe [20]- to a poor outcome, despite aggressive treatment [21]. A bad prognosis seems to be associated with the severity of hemodynamic impairment. In the MAPPET registry [22] the rate of death due to PE in patients with cardiac arrest, cardiogenic shock and arterial hypotension was 60%, 23% and 14%, respectively. If this correlation between ventricular function and mortality is extrapolated to patients with sub clinical hemodynamic impairment (e.g. hemodynamically stable patients with right ventricular dysfunction) a higher rate of fatal PE would be expected in these patients as compared with those without such a dysfunction. The aim of this review was to assess the prevalence

of echocardiographic right ventricular dysfunction and to evaluate the predictive potential for adverse outcomes in patients with acute PE who have this condition.

On the basis of the currently available literature, the prevalence of right ventricular dysfunction ranges from 40% in normotensive patients to 70% in patients with large PE. The short-term as well as long-term mortality related to PE seems higher in patients with right ventricular dysfunction than in those without it; absolute differences range from 4% to 14% and 3% to 13%, respectively (Table 3). Only 2 studies allow for estimation in normotensive patients. In these studies, absolute differences with regard to short-term PE related mortality were the lowest: 4% and 5%. In addition, the specificity and positive predictive value of right ventricular dysfunction for PE related in-hospital mortality in hemodynamically stable patients were low (specificity: 61% and 56%, positive predictive value 4% and 5%, respectively). Thus, the predictive potential of echocardiographic right ventricular dysfunction might be less reliable in hemodynamically stable patients.

The preceding conclusions have to be interpreted with great caution because they are based on studies with some potentially relevant methodological shortcomings. (1) In the majority of studies it was not clear whether consecutive patients were included, how they were referred or whether all patients definitely had PE. As a consequence the risk of selection and referral bias cannot be excluded. This in particular may affect the prevalence of right ventricular dysfunction. (2) In none of the studies was it reported whether an independent blinded committee assessed the outcome criteria. Consequently, outcomes might be preferentially attributed to fatal PE because of diagnostic suspicion bias. (3) Most of the studies did not adjust for type of treatment or other important prognostic factors. Therefore, the risk exists that patients with right ventricular dysfunction preferentially received a treatment that is associated with fewer or possibly more adverse outcomes. (4) The results apply to a patient population, which is not clearly defined with regard to its hemodynamic status. This is relevant because there is consensus that patients with hemodynamically unstable PE should receive thrombolytic therapy, whereas the controversy centres on the question of lytic therapy in hemodynamically stable patients with right ventricular dysfunction.

At present, risk stratification is based on clinical signs and symptoms. In patients with hypotension and circulatory collapse, thrombolysis is the therapy of choice [23,24]. Some experts advocate a broadening of the indication for thrombolytic therapy [25,26], whereas others believe that exposure to thrombolysis will result in unnecessary deaths and intracranial hemorrhage [27,28]. Throughout the literature many experts have called for a randomised trial of heparin vs thrombolysis in patients with PE and echocardiographic

right ventricular dysfunction [29-31]. Meanwhile, such a trial has been carried out, and no treatment difference was observed in clinically relevant outcomes such as recurrent fatal or non-fatal PE [12]. As is evident from this review, no definitive data are available on the prognostic significance of echocardiographic right ventricular dysfunction in hemodynamically stable patients with PE. For this group evidence is required because hemodynamically unstable patients already have an indication for more aggressive therapy. Therefore, one step back would be needed, i.e. a methodologically rigorous trial to conclusively answer the question regarding the prognostic significance of echocardiographic right ventricular dysfunction in hemodynamically stable patients with acute PE, before it can be advocated that these patients should be exposed to thrombolysis or other forms of more aggressive therapy. An additional requirement would be a uniformly accepted definition of the criteria for echocardiographically detected right ventricular dysfunction. At present the variety in criteria hampers the proper evaluation of the prognostic significance.

In conclusion, the prognostic importance of right ventricular dysfunction in patients with acute PE remains unclear because most of the available studies are of insufficient methodological quality. They suggest that right ventricular dysfunction predicts adverse outcomes, however this predictive potential seems less strong in hemodynamically stable patients with acute PE. It needs to be convincingly shown that the risk of aggressive therapy outweighs the potentially small gain in absolute benefit, as measured by PE related mortality.

Reference List

1. Barker NW, Nygaard KK, Walters W, Priestly JT. A statistical study of postoperative venous thrombosis and pulmonary embolism. I. Incidence in various types of operations. Proceedings of the staff meetings of the mayo clinic 1940; 15:769-773.
2. Short DS. A survey of pulmonary embolism in a general hospital. British Medical Journal 1952; 790-796.
3. Barrit DW, Jordan S.C. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960; 1309-1312.
4. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998; 279:458-462.
5. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, et al. The clinical course of pulmonary embolism. N Eng J Med 1992; 326:1240-1245.
6. van Beek EJ, Kuijer PM, Buller HR, Brandjes DP, Bossuyt PM, Ten Cate JW. The clinical course of patients with suspected pulmonary embolism. Archives of Internal Medicine 1997; 157:2593-2598.
7. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the

International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999; 353:1386-1389.
8. Goldhaber SZ, Haire WD, Feldstein ML, Miller M, Toltzis R, Smith JL, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341:507-511.
9. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. American Heart Journal 1997; 134:479-487.
10. Kasper W, Konstantinides S, Geibel A, Tiede N, Krause T, Just H. Prognostic significance of right ventricular afterload stress detected by echocardiography in patients with clinically suspected pulmonary embolism. Heart 1997; 77:346-349.
11. Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000; 101:2817-2822.
12. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N.Engl.J.Med. 2002; 347:1143-1150.
13. Cheriex EC, Sreeram N, Eussen YF, Pieters FA, Wellens HJ. Cross sectional Doppler echocardiography as the initial technique for the diagnosis of acute pulmonary embolism. Br.Heart J. 1994; 72:52-57.
14. McConnell MV, Solomon SD, Rayan ME, Come PC, Goldhaber SZ, Lee RT. Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. Am.J.Cardiol. 1996; 78:469-473.
15. Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 1994; 272:234-237.
16. Wolfe MW, Lee RT, Feldstein ML, Parker JA, Come PC, Goldhaber SZ. Prognostic significance of right ventricular hypokinesis and perfusion lung scan defects in pulmonary embolism. Am.Heart J. 1994; 127:1371-1375.
17. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis [see comments]. Circulation 1999; 99:1325-1330.
18. Grifoni S, Olivotto I, Pieralli F, Cecchini P, Camaiti A, Zanobetti M, et al. Long-term clinical outcome of patients with pulmonary embolism with or without right ventricular dysfunction. Thrombosis and Haemostasis, supplement 2001; Abstract.
19. Jerjes-Sanchez C, Ramirez-Rivera A, Arriaga-Nava R, Iglesias-Gonzalez S, Gutierrez P, Ibarra-Perez C, et al. High dose and short-term streptokinase infusion in patients with pulmonary embolism: prospective with seven-year follow-up trial. J.Thromb.Thrombolysis. 2001; 12:237-247.
20. Stein PD, Hull RD, Raskob GE. Withholding treatment in patients with acute pulmonary embolism who have a high risk of bleeding and negative serial noninvasive leg tests. Am.J.Med. 2000; 109:301-306.
21. Hall RJ, Sutton GC, Kerr IH. Long-term prognosis of treated acute massive pulmonary embolism. Br.Heart J. 1977; 39:1128-1134.
22. Kasper W, Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser KD, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J.Am.Coll.Cardiol. 1997; 30:1165-1171.
23. Anonymous. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force

on Pulmonary Embolism, European Society of Cardiology. Eur Heart J JID - 8006263 2000; 21:1301-1336.
24. Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, et al. Antithrombotic therapy for venous thromboembolic disease. Chest 2001; 119:176S-193S.
25. Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser K, Rauber K, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. [see comments]. Circulation 1997; 96:882-888.
26. Goldhaber SZ. Pulmonary embolism thrombolysis: broadening the paradigm for its administration. Circulation 1997; 96:716-718.
27. Hamel E, Pacouret G, Vincentelli D, Forissier JF, Peycher P, Pottier JM, et al. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. Chest JID - 0231335 2001; 120:120-125.
28. Dalen JE. The uncertain role of thrombolytic therapy in the treatment of pulmonary embolism. Arch.Intern.Med. 2002; 162:2521-2523.
29. Davidson BL, Lensing AW. Should echocardiography of the right ventricle help determine who receives thrombolysis for pulmonary embolism? Chest 2001; 120:6-8.
30. Goldhaber SZ. Thrombolysis in pulmonary embolism: a large-scale clinical trial is overdue. Circulation JID - 0147763 2001; 104:2876-2878.
31. Agnelli G, Becattini C, Kirschstein T. Thrombolysis vs Heparin in the Treatment of Pulmonary Embolism: A Clinical Outcome-Based Meta-analysis. Arch.Intern.Med. 2002; 162:2537-2541.

Biomarkers in Pulmonary Embolism

MAAIKE SÖHNE, MARIJE TEN WOLDE, HARRY R BÜLLER

CURRENT OPINION IN CARDIOLOGY 2004 NOV;19(6): 558-62

Abstract

Purpose of review:

Controversy exists about the precise role of thrombolytic therapy in normotensive patients with pulmonary embolism. To resolve this controversy two major questions need to be addressed. Firstly, can a subgroup of normotensive pulmonary embolism patients with a high risk for adverse outcomes, such as in-hospital mortality or early recurrent venous thromboembolism, be identified? Secondly, is there convincing evidence that the benefits of more aggressive therapy counterbalance its risks?

Troponin I and T as well as brain natriuretic peptide (BNP) have recently been introduced as promising tools in the risk assessment of patients with pulmonary embolism.

Recent findings:

The studies in series of patients with pulmonary embolism showed prevalences of elevated cardiac biomarkers of 16 to 84%. Positive predictive values for in-hospital mortality varied from 6 to 44%, whereas negative predictive values for uneventful outcome were above 93% in all studies.

Summary:

Although a correlation between elevated biomarkers and in-hospital mortality in pulmonary embolism patients is present in most of the studies, the positive predictive value appears to be insufficiently to extend the indication for thrombolytic therapy to all patients with elevated biomarkers. Future research is necessary to show whether combining different biomarkers with echocardiography is more useful.

Introduction

At present several strategies are available for the treatment of patients presenting with symptomatic pulmonary embolism. Oral vitamin K antagonists, initially combined with (low molecular weight) heparin, is the standard of treatment for the great majority of these patients. However, more aggressive therapies are available, such as thrombolysis and catheter guided embolectomy. Controversy exists about the precise role of these latter therapies. The decision to treat a patient more aggressively should ideally depend on a positive assessment of the benefit-risk ratio.

Patients with clear signs of shock are obviously high risk patients, with a high morbidity and mortality rate. It is therefore generally accepted that these patients should be considered for thrombolytic therapy or embolectomy. However, these patients represent only a small minority of all consecutive patients with pulmonary embolism (usually less than 5%). The majority of patients with acute pulmonary embolism are hemodynamically stable and with standard anticoagulant therapy the cardiovascular mortality rate in these patients varies from 2 to 10% during the first three months of follow up[1-4]. The current controversy focuses on the extension of the indication of thrombolytic therapy to a subgroup of the normotensive patients at high risk for recurrent thromboembolic disease. The two major challenges for resolving this controversy are identification of the subgroup by simple, rapid and non invasive methods and convincing evidence that more aggressive treatment indeed improves the benefit-risk ratio.

In recent years, echocardiographically assessed right ventricular dysfunction (RVD) has emerged as a tool to predict adverse outcomes, such as (cardiovascular) mortality. The in-hospital mortality rate for patients without RVD is less than 2%, while in those with RVD in-hospital mortality rises to more than 10% [3;4]. The results of most of the studies on RVD however, were obtained in patient populations that were not clearly defined with regard to their hemodynamic status. Nevertheless, the only two series in normotensive patients reveal that RVD may be present in a substantial proportion of these patients (approximately 40%) and the follow up data suggest a correlation between RVD and pulmonary embolism related mortality in the first weeks after presentation [2;5]. In most centres right sided echocardiography is readily available. What is lacking however, is evidence whether the initiation of more aggressive therapy in patients with echocardiographically assessed RVD improves overall prognosis in the hemodynamic stable population.

Another emerging field to identify the subgroup with a high risk for recurrent disease is

the use of (bedside) biomarkers. Troponin I and T, as well as brain natriuretic peptide (BNP) are excreted from the myocardiac cells and their clinical usefulness has been firmly established in the risk stratification of patients with acute coronary syndromes and the diagnosis of left ventricular failure, respectively [6-8]. These so called cardiac biomarkers as well as the measurement of myoglobin have recently also been introduced as promising tools in the risk stratification of patients with pulmonary embolism.
The results of the studies with these biomarkers in patients with pulmonary embolism will be discussed as well as their usefulness in guiding therapeutic decisions.

Pathophysiology of biomarkers

The cardiac myocytes can excrete several biomarkers when they are stretched or injured, e.g troponin I and T, BNP and myoglobin. The cardiac troponins are released upon myocardial ischemia and are very sensitive and specific for damage to the myocardium. The likely explanation for the release of troponins in pulmonary embolism is the development of micro-infarctions through the abrupt increase of pulmonary artery pressure with an elevation in right ventricular wall tension. Troponin levels are elevated within 12 hours of the onset of pulmonary embolism [9].
While the release of troponins only occurs with degradation of the cardiac myocyte, the secretion of BNP is stimulated upon stretch of mainly the ventricular mycocytes. It is therefore hypothesized that BNP is released in an earlier stage of pulmonary embolism associated myocardial strain.
Myoglobin is a third biomarker that increases with myocardial damage. It has been suggested to be elevated, similarly to BNP, before any detectable rise of cardiac troponin levels occurs [10].

Prevalences of elevated biomarker concentrations

The six studies that have been performed with troponin I and the four studies with troponin T use different assays with varying cut-off values, even for the same assay. It is therefore not surprising that the prevalences of elevated troponins in patients presenting with acute pulmonary embolism vary. In addition, patient selection, in particular the presence or absence of hemodynamic compromise, varied among the studies which further contributes to the differences in prevalences.
In two studies using the same assay (MEIA) and cut-off value (0.4 ng/ml) the prevalences

Table 1: Prevalences and positive predictive values for in-hospital mortality and all serious adverse outcomes in patients with pulmonary embolism

References	N	Bio-marker	Test used	Cut-off	Prevalen-ces of elevated troponins	In-hospital mortality	PPV for in-hospital mortality (95% CI)	All serious adverse outcomes	PPV for serious adverse outcomes
Douketis et al. 1998 [11]	24	cTnI	MEIA (Abbott)	>0.4 ng/ml	21%	n.a	n.a	n.a	n.a
Mehta et al. 2003 [12]	38	cTnI	MEIA (Abbott)	>0.4 ng/ml	47%	5.3%	6% (1-24)	18%*	33% (13-59)
Yalamanchili et al. 2004 [13]	147	cTnI	MEIA (Abbott)	≥2.0 ng/ml	16%	12%	33% (16-55)	n.a	n.a
Kucher et al. 2003 [22]	91	cTnI	MEIA (Abbott)	>0.06 ng/ml	31%	5%	14% (4-33)	23%†	64% (44-81)
Konstantinides et al. 2002 [9]	106	cTnI	Advia (Bayer)	≥0.07ng/ml	41%	6.6%	14% (5-28)	18%†	37% (23-53)
Meyer et al. 2000 [20]	36	cTnI	ACS (Bayer)	>0.15 ng/ml	39%	n.a	n.a	n.a	n.a
Giannitsis et al. 2000 [21]	56	cTnT	tropT (Roche)	>0.1 ng/ml	32%	16%	44% (22-69)	n.a	n.a
Konstantinides et al. 2002 [9]	106	cTnT	Elecsys (Roche)	≥0.04 ng/ml	37%	6.6%	13% (4-27)	18%†	41% (26-58)
Pruszczyk et al. 2003 [14]	64	cTnT	ECLIA (Roche)	>0.01 ng/ml	45%	12.5%	28% (13-47)	23%†	44% (26-62)
Janata et al. 2003 [24]	106	cTnT	Elecsys (Roche)	>0.09 ng/ml	n.a	5%	34% (10-59)	n.a	n.a

PPV = positive predictive value cTnI = troponin I cTnT = troponin T
* cardiogenic shock
† including death

of elevated troponin I varied from 21% to 47% (Table 1) [11;12]. In the study by Yalaman-chili and colleagues, who used a cut-off value of 2.0 ng/ml with this assay, the prevalence of increased troponin I was 16% [13].

A single study compared the prevalence of elevated troponin levels in pulmonary embolism patients relative to patients presenting with suspected pulmonary embolism in whom the diagnosis was subsequently ruled out. In this study 16% of the pulmonary embolism patients and 3% of those without this disease had an elevated troponin I level($p<0.001$) [13].

For troponin T the prevalences of elevated levels varied from 32% to 45% (Table 1) [14].

BNP elevations above the cut-off value of 90 pg/ml were found in approximately 40% of the patients in two studies using the same assay (Table 2) [15;16]. In a study where BNP concentrations were divided in tertiles, the cut-off value was 21.7 pmol/l for the highest group [17]. Finally, in the two studies using proBNP the observed prevalences were 58% and 84% [18;19].

In a recent study in 46 patients with major acute pulmonary embolism 46% were found to have myoglobin levels exceeding the cut-off value [10].

Correlation of right ventricular dysfunction and elevated biomarkers

The study by Mehta et al. showed that 67% of the patients with increased troponin I had RVD compared to 15% of the patients with normal concentrations [12]. This percentage was lower in the study by Yalamanchili et al., where the proportion of RVD in the elevated troponin I group was 47% [13]. In another study, 50% of the patients with high levels of troponin I (above 1.5 ng/ml) had RVD, whereas this was 43% of those with moderately increased troponin I (0.04-1.5 ng/ml) and 10% in those with normal concentrations [9]. Thus,

Table 2: Prevalences and positive predictive values of brain natriuretic peptide (BNP) for in-hospital mortality in patients with pulmonary embolism

References	N	Biomarker	Test used	Cut-off	Prevalences of elevated (pro)-BNP	In hospital mortality	PPV for in-hospital mortality (95% CI)	All serious adverse outcomes	PPV for serious adverse outcomes (95% CI)
Kucher et al. 2003 [15]	73	BNP	Triage (Biosite Diagnostics)	90 pg/ml	44%	7%	13% (4-29)	27%†	53% (35-71)
Kruger et al. 2004 [16]	50	BNP	Triage (Biosite Diagnostics)	90 pg/ml	40%	8%	12% (26-31)	n.a	n.a.
Ten Wolde et al. 2003 [17]	110	BNP	Shionoria (Cis bio-international)	21.7 pmol/L	33%	6%	17% (6-33)	n.a.	n.a
Kucher et al. 2003 [18]	73	proBNP	Elecsys (Roche)	500 pg/ml	58%	7%	12% (4-26)	27%†	45% (30-61)
Pruszczyck et al. 2003 [19]	79	proBNP	Elecsys (Roche)	153-334 pg/ml	84%	19%	23% (13-35)	30%	36% (25-49)

* age and sex specific values according to manufacturer
† including death

in patients with elevated troponin levels the presence of RVD in the different studies varied between 40-70%. In patients with pulmonary embolism and normal troponin concentrations RVD was noted in 15-27% [12;20].

For BNP, the relation with RVD was documented by Kruger and colleagues [16]. Of their patients, 94% without RVD had BNP levels within the reference range, whereas BNP levels were elevated in 64% of patients with RVD. Similar proportions have been observed for proBNP [19].

Predictive significance of biomarkers in patients with acute pulmonary embolism

To resolve the controversy on the precise role of thrombolytic therapy in normotensive patients with symptomatic pulmonary embolism, the cardiac biomarkers can potentially be useful in different ways. A biomarker with a high positive predictive value for adverse outcomes, such as in-hospital mortality or clinical deterioration, can be useful in the decision to initiate thrombolytic therapy. High negative predictive values for an uneventful follow up on the other hand, can be utilized to refrain from more aggressive therapy.

The positive predictive values in the respective studies for in-hospital mortality for troponins and BNPs are shown in Tables 1 and 2. For troponin I and T these predictive values varied from 6-33% and from 13-44% respectively [9;12;13;21]. For BNP the highest positive predictive value was shown to be 23% [19].

The positive predictive values of troponin I and T and BNP for adverse outcomes other than mortality (cardiogenic shock, inotropic therapy, mechanical ventilation) are higher (Table 1 and 2). In the study by Kucher et al. the positive predictive value of BNP for adverse events, other than death, was 41%, while their predictive value for in-hospital mortality was 13% [15]. Another study with proBNP revealed predictive values of 23% for in-hospital mortality only, to 44% for all serious adverse events (including death) [19]. In a study with troponin I these values were 14% and 64%, respectively [22].

The other possible role for biomarkers in pulmonary embolism is to identify those patients who are at low risk for mortality or clinical deterioration. These patients should be treated with standard anticoagulant therapy and could be considered for out-of-hospital treatment.

The negative predictive values of normal concentrations of biomarkers for uncomplicated follow up are above 93% in all studies.

Conclusions and interpretation

The prevalences of elevated biomarkers in patients presenting with symptomatic pulmonary embolism were high in most studies (around 40-50%). Furthermore, elevated biomarker concentrations were significantly related to in-hospital mortality and other adverse events. However, in all studies, except the reports by Ten Wolde et al. and Pruszczyk et al. [14;17], the study populations were a mixture of hemodynamically stable and unstable patients. Therefore, the prevalence of elevated cardiac biomarkers in the subgroup of interest, i.e. those being hemodynamic stable at presentation, remain largely unknown and is likely to be lower (approximately 30-40%). The associated positive predictive values for in-hospital mortality and other adverse outcomes in this subgroup were 17 to 28%.

Are these predictive values, for example for in-hospital mortality, high enough to recommend aggressive treatment with thrombolytic therapy in patients with abnormal biomarkers?

Taking the data from one study with a high in-hospital mortality[14] to answer this question, the following can be calculated: in 1000 patients with hemodynamic stable pulmonary embolism and a prevalence of an elevated biomarker of 45%, with an expected in-hospital mortality of 12.5% and a positive predictive value of 28%, thrombolytic therapy would be given to 450 patients, of whom only 125 (i.e those who will die) may potentially benefit. The remaining 325 patients, who would otherwise survive, are only exposed to the risks of thrombolytic therapy.

With a more realistic in-hospital mortality in patients with a normal hemodynamic status of approximately 4%, the ratio of unnecessary aggressive treatment, which was one correctly treated patient and 2.5 patients receiving thrombolytic therapy for no reason, may shift to 1 versus 10. It is obvious that when other serious adverse outcomes (such as hypotension, shock and endotracheal intubation) are taken into account, the balance may become more favourable.

However, evidence whether thrombolytic therapy indeed prevents in-hospital mortality or other important outcomes is scarce. The only large randomized clinical study performed in normotensive patients, performed by Konstantinides et al [23], showed that in 256 normotensive patients with pulmonary embolism there was no significant difference between the heparin plus alteplase patients and the heparin plus placebo recipients with respect to mortality or the development of hypotension, shock or the need for endotracheal intubation during 30 days of follow-up. There was however a significant difference in the number of patients with worsening symptoms during follow-up (24 patients in the heparin

plus placebo group, 8 in the alteplase group). These symptoms were not defined, but these patients received rescue thrombolysis which might have prevented further clinical deterioration.

In conclusion, within the total population of patients with pulmonary embolism a subgroup of patients with increased risk for adverse outcomes can be identified by elevated cardiac biomarkers. However, deciding to give more aggressive treatment based on the elevation of one specific cardiac biomarker would result in the use of thrombolysis in a large number of patients. A substantial proportion of these patients would thus receive thrombolysis with no or minimal benefit, whereas the risk for major bleeding can not be neglected. Finally, whether thrombolytic therapy would really change the outcome in those at high risk remains to be demonstrated.

Hence, before cardiac biomarkers can be advocated for incorporation into today's clinical practice these unresolved questions need to be addressed..

Reference List

1. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998; 279:458-462.
2. Grifoni S, Olivotto I, Cecchini P et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000; 101:2817-2822.
3. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. Am Heart J 1997; 134:479-487.
4. Konstantinides S, Geibel A, Olschewski M et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. Circulation 1997; 96:882-888.
5. Goldhaber SZ, Haire WD, Feldstein ML et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341:507-511.
6. Antman EM, Tanasijevic MJ, Thompson B et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996; 335:1342-1349.
7. McDonagh TA, Robb SD, Murdoch DR et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998; 351:9-13.
8. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ 2002; 324:1498.
9. Konstantinides S, Geibel A, Olschewski M et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002; 106:1263-1268.
10. Pruszczyk P, Bochowicz A, Kostrubiec M et al. Myoglobin stratifies short-term risk in acute major pulmonary embolism. Clin Chim Acta 2003; 338:53-56.
11. Douketis JD, Crowther MA, Stanton EB, Ginsberg JS. Elevated cardiac troponin levels in patients with submassive pulmonary embolism. Arch Intern Med 2002; 162:79-81.

12. Mehta NJ, Jani K, Khan IA. Clinical usefulness and prognostic value of elevated cardiac troponin I levels in acute pulmonary embolism. Am Heart J 2003; 145:821-825.
13. Yalamanchili K, Sukhija R, Aronow WS, Sinha N, Fleisher AG, Lehrman SG. Prevalence of increased cardiac troponin I levels in patients with and without acute pulmonary embolism and relation of increased cardiac troponin I levels with in-hospital mortality in patients with acute pulmonary embolism. Am J Cardiol 2004; 93:263-264.
14. Pruszczyk P, Bochowicz A, Torbicki A et al. Cardiac troponin T monitoring identifies high-risk group of normotensive patients with acute pulmonary embolism. Chest 2003; 123:1947-1952.
15. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003; 107:2545-2547.
16. Kruger S, Graf J, Merx MW et al. Brain natriuretic peptide predicts right heart failure in patients with acute pulmonary embolism. Am Heart J 2004; 147:60-65.
17. ten Wolde M, Tulevski 2, Mulder JW et al. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. Circulation 2003; 107:2082-2084.
18. Kucher N, Printzen G, Doernhoefer T, Windecker S, Meier B, Hess OM. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. Circulation 2003; 107:1576-1578.
19. Pruszczyk P, Kostrubiec M, Bochowicz A et al. N-terminal pro-brain natriuretic peptide in patients with acute pulmonary embolism. Eur Respir J 2003; 22:649-653.
20. Meyer T, Binder L, Hruska N, Luthe H, Buchwald AB. Cardiac troponin I elevation in acute pulmonary embolism is associated with right ventricular dysfunction. J Am Coll Cardiol 2000; 36:1632-1636.
21. Giannitsis E, Muller-Bardorff M, Kurowski V et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000; 102:211-217.
22. Kucher N, Wallmann D, Carone A, Windecker S, Meier B, Hess OM. Incremental prognostic value of troponin I and echocardiography in patients with acute pulmonary embolism. Eur Heart J 2003; 24:1651-1656.
23. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002; 347:1143-1150.
24. Janata K, Holzer M, Laggner AN, Mullner M. Cardiac troponin T in the severity assessment of patients with pulmonary embolism: cohort study. BMJ 2003; 326: 312-313

Brain Natriuretic Peptide (BNP) as a predictor of adverse outcome in patients with pulmonary embolism

M. ten Wolde, I.I. Tulevski, J.W.M. Mulder, M. Söhne,
F. Boomsma , B.J.M. Mulder, H.R. Büller

Circulation 2003;107:2082-2084

Abstract

Background:

Despite effective treatment with anticoagulants, 2-7% of patients with pulmonary embolism will die as a result of their disease.

Methods:

We examined in 110 consecutive patients with pulmonary embolism whether plasma Brain Natriuretic Peptide (BNP), a novel marker of (right) ventricular dysfunction, is a predictor of fatal pulmonary embolism. The relationship between BNP concentration measured at presentation and clinical outcome was assessed by comparing the proportion of outcome events among tertiles. Positive and negative predictive values of BNP levels in the highest and lowest tertiles were calculated. The risk of death related to pulmonary embolism if the BNP level is above 21.7 pmol/L is 17% (95% CI: 6-33%). The negative predictive value for uneventful outcome of a BNP value below 21.7 pmol/L is 99% (95% CI 93-100%).

Conclusion:

This is the first study to show that plasma BNP levels seem to predict adverse outcome in patients with acute pulmonary embolism.

Introduction

Hemodynamically stable patients with pulmonary embolism are initially treated with heparin and subsequently with vitamin K antagonists. Although this therapy is very effective, still during 3 months of follow-up 2-7% of patients will die as a result of pulmonary embolism [1-4]. Mortality likely occurs in those patients with right ventricular dysfunction at presentation [5-7]. Brain Natriuretic Peptide (BNP) is a plasma neurohormone secreted in the cardiac ventricles in response to stretch and/or pressure increase [8]. BNP levels are known to correlate with left ventricular dysfunction and are used for the diagnosis of left ventricular failure [9;10]. We recently showed that BNP levels are also associated with right ventricular dysfunction in patients with pulmonary embolism [11]. Because right ventricular dysfunction in these patients is a likely marker for long term adverse outcome, we hypothesised that this may be predicted by high BNP levels at presentation.

Methods

Study population

Consecutive patients presenting with clinically suspected pulmonary embolism, referred for diagnostic work-up, were eligible for this study. Only patients with objectively confirmed pulmonary embolism on the basis of abnormal angiography, a high-probability scintigram, a non-high probability scintigram with abnormal ultrasonography of the legs or the presence of pulmonary embolism on spiral CT were included. Patients requiring thrombolytic therapy because of hemodynamic instability were excluded. The Institutional Review Boards approved the study protocol and participants gave informed consent. Since renal insufficiency can result in elevated BNP levels, we excluded patients with known renal insufficiency. Sixteen of the patients in this study were previously included in a study evaluating the relationship between echocardiographic right ventricular dysfunction and BNP levels [11].

Blood sampling

At presentation, blood was collected in citrated tubes and centrifuged for 15 minutes. Plasma was stored at – 80 °C and BNP concentrations were determined with an immuno-radiometric assay (Shionoria, Osaka, Japan) without knowledge of the clinical outcome. In healthy volunteers, the normal values (+/- 2SD) of BNP range between 0.4 and 4.6 pmol/L.

Outcome Events

All adverse events occurring during 3 months of follow-up were reviewed by a blinded and independent adjudication committee. Deaths were subcategorised as deaths definitely due to pulmonary embolism, possibly due to pulmonary embolism or other causes. The following outcomes were used for our analysis: deaths due to pulmonary embolism, deaths related to pulmonary embolism (i.e. those patients with pulmonary embolism as a definite as well as a possible cause of death) and all cause mortality.

Statistical Analysis

Patients were divided into tertiles on the basis of their BNP level. The chi square test was used to analyse the differences in proportions of outcome events. The positive and negative predictive values for death related to pulmonary embolism of a BNP level in the highest and lowest tertiles, respectively, were calculated. Their exact 95% confidence intervals were calculated using Confidence Interval Analysis (Gardner MJ, BMJ Books 1989, version 1.0). To evaluate the effects of other variables on mortality, multiple logistic regression analysis was performed using SPSS (SPSS for Windows, release 10.0.7). BNP was entered as a dichotomous variable using the 67th percentile as the cut-off value. P values <0.05 were considered statistically significant. Standard deviations were reported for a mean, whereas the interquartile range was given for a median.

Results

Study Population

Hundred-ten patients with confirmed pulmonary embolism were included. The mean (+/- SD) age was 58 (+/- 18). The median BNP level was 9.4 pmol/L (1.7 - 37.1 pmol/L). Eleven patients (10%) died during 3 months of follow-up. Seven deaths were related to pulmonary embolism of whom 5 deaths were definitely (3 of these patients died 2 days after presentation, whereas the others died on days 5 and 38) and 2 possibly due to pulmonary embolism (days 8 and 34). The remaining 4 deaths died because of cancer (38, 43, 76 and 87 days after presentation). None of the 5 patients who died as a consequence of pulmonary embolism had a history of heart failure. Of the 2 patients who possibly died of pulmonary embolism heart failure contributed to the cause of death. The 11 patients who died were older (mean age 66 +/- 15) and more often had cancer (36%) as compared with those who survived (mean age 56 +/- 18; 14% suffered from cancer), p=0.074 and 0.064, respectively. No differences between the deaths and survivors were observed with regard to the prevalences of chronic obstructive pulmonary disease and vascular disease including

cerebrovascular, coronary artery and peripheral artery disease. The median BNP in the patients who died was 71.6 pmol/L (47.4 - 117.1), compared with 8.7 pmol/L (1.5 - 29.3) in those who survived (p<0.001). The median BNP value in the 5 patients who died due to pulmonary embolism was 80.5 pmol/L (25.8 - 101.5; P=0.030 for the comparison with the median BNP level of the other patients).

Plasma BNP concentrations and clinical outcome

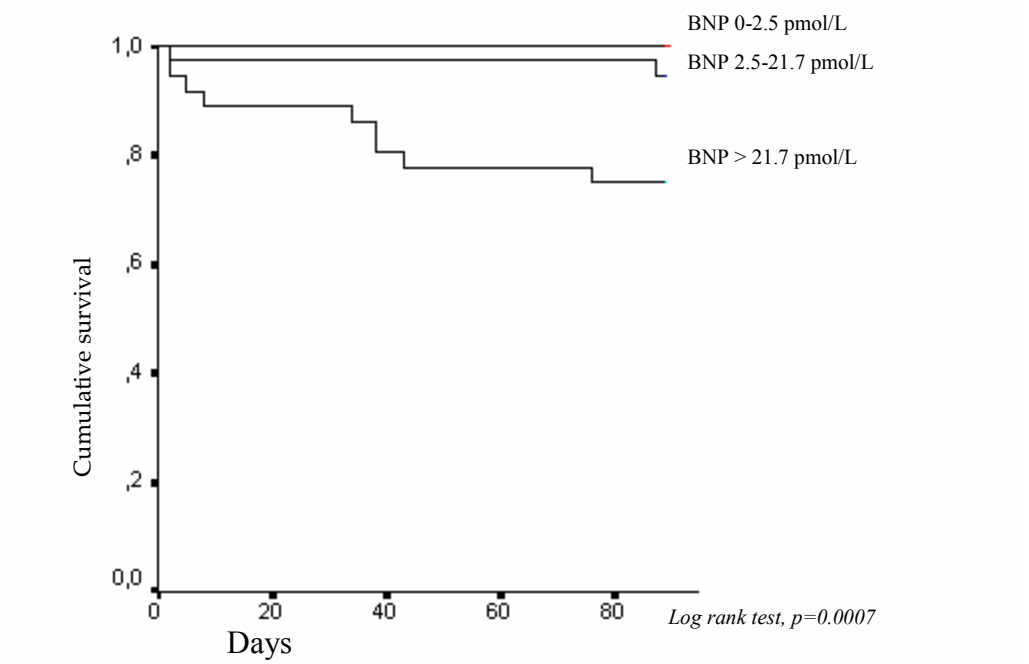
Patients with events had BNP levels at presentation belonging to the highest tertiles (Table 1). High BNP levels were associated with all cause mortality and death related to pulmonary embolism. Of the 36 patients in the highest tertile, 4 died of pulmonary embolism, whereas in another 2 patients pulmonary embolism was a possible cause of death. Hence, the positive predictive value for pulmonary embolism related death of a BNP level above 21.7 pmol/L was 17% (95% CI: 6-33%). The negative predictive value for an uneventful outcome of a value below 21.7 pmol/L was 99% (95% CI 93-100%). Survival was significantly worse in patients with BNP concentrations in the highest tertile(Figure 1). As shown by multiple logistic regression analysis, the odds ratio for the risk of all cause related to pulmonary embolism was 14.1 (95% CI: 1.5-131.1).

Table 1. Distribution of outcome events during 3 months follow-up among BNP tertiles in patients with pulmonary embolism

Concentration BNP (pmol/L)	Patients n	Death definitely due to PE n	Deaths related to PE n	All cause mortality n	Deaths due to other causes‡ n
0 - 2.5	37	0	0	0	0
2.5 - 21.7	37	1 (2.7%)	1* (2.7%)	2 (5.4%)	1 (2.7%)
> 21.7	36	4 (11.1%)	6† (16.7%)	9 (25%)	3 (8.3%)
P value		0.024	0.003	<0.001	0.067

*This death was definitely due to pulmonary embolism
† 4 of these deaths were definitely due to pulmonary embolism
‡ All these patients died as a consequence of cancer

Figure 1. Kaplan-Meier survival curve for 110 patients during 3 months after the diagnosis of pulmonary embolism. There were 0 deaths in the first tertile (BNP level 0-2.5 pmol/L), 2 deaths in the second (2.5-21.7 pmol/L), and 9 in the highest tertile.
BNP= Brain Natriuretic Peptide



Discussion

This analysis demonstrates that the BNP plasma concentration in patients with pulmonary embolism, measured at presentation, seems to predict adverse outcome during 3 months follow-up. Patients with pulmonary embolism are part of a clinically heterogeneous group, which ranges from patients with minimal pleuritic chest pain to those who are hemodynamically compromised. Attempts have been made to stratify patients in order to select those with a high risk of fatal pulmonary embolism, with the eventual aim to guide more aggressive therapy. Previous studies have shown that echocardiography, to assess right ventricular dysfunction, appears to be such a tool. However, the positive predictive value of echocardiographically assessed right ventricular dysfunction for pulmonary embolism related death in hemodynamically stable patients appears only 5% [7]. More recently, cardiac troponine T and I have been advocated as possible candidates for risk stratification. Konstantinides and colleagues found that 35% to 40% of patients with

pulmonary embolism has elevated levels of cardiac troponines which were associated with overall mortality and a complicated in-hospital course [12]. However, cardiac troponines are released as a consequence of myocardial injury, whereas the triggering factor for release of BNP is an increase in stretch or pressure of the ventricles which precedes right ventricular failure. Five percent of the patients in the study of Konstantinides were hemodynamically unstable and 28% of the patients suffered from syncope, which might have resulted in the high percentage of elevated troponines and (overall) mortality. The results of the present study are of particular interest, because only hemodynamically stable patients were included. These patients are currently treated with heparin and vitamin K antagonists, but might benefit from more aggressive treatment (e.g. thrombolysis) if their BNP level is high at presentation. Hemodynamically unstable patients already have an indication for thrombolytic therapy.

One of the limitations of this study is that causes of death might be incorrectly attributed to pulmonary embolism. We do not believe that this has affected our findings since an independent blinded committee adjudicated the outcome events. Another potential bias concerns the fact that in addition to angiography, other diagnostic methods were used to diagnose pulmonary embolism such as lung scintigraphy, spiral computed tomography, and compression ultrasonography of the legs. However, in the past 10 years these methods have been extensively investigated and are now generally accepted for the diagnosis of pulmonary embolism. In conclusion, our results indicate that high BNP levels, measured at presentation, are associated with mortality during 3 months of follow-up in patients with pulmonary embolism. It needs to be investigated whether BNP, troponine or a combination of both is the best predictor of adverse outcomes in hemodynamically stable patients with acute pulmonary embolism. If proven to be effective, this easy to perform blood test might be a simple tool to stratify patients for more aggressive therapy such as thrombolysis or percutaneous embolectomy.

Reference List

1. Douketis JD, Kearon C, Bates S et al. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998; 279:458-62.
2. Carson JL, Kelley MA, Duff A et al. The clinical course of pulmonary embolism. N Eng J Med 1992; 326:1240-1245.
3. van Beek EJ, Kuijer PM, Buller HR et al. The clinical course of patients with suspected pulmonary embolism. Arch Intern Med 1997; 157:2593-98.
4. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999; 353:1386-89.
5. Ribeiro A, Lindmarker P, Johnsson H et al. Pulmonary embolism: one-year follow-up with

echocardiography doppler and five-year survival analysis. Circulation 1999; 99:1325-30.
6. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A et al. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. Am Heart J 1997; 134:479-87.
7. Grifoni S, Olivotto I, Cecchini P et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000; 101:2817-22.
8. Boomsma F, van den Meiracker AH. Plasma A- and B-type natriuretic peptides: physiology, methodology and clinical use. Cardiovasc Res 2001; 51:442-49.
9. Cowie MR, Struthers AD, Wood DA et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997; 350:1349-53.
10. Hobbs FD, Davis RC, Roalfe AK et al. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ 2002; 324:1498.
11. Tulevski II, Hirsch A, Sanson BJ et al. Increased brain natriuretic peptide as a marker for right ventricular dysfunction in acute pulmonary embolism. Thromb Haemost 2001; 86:1193-96.
12. Konstantinides S, Geibel A, Olschewski M et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002; 106:1263-68.

Chapter 12

Brain natriuretic peptide in hemodynamically stable acute pulmonary embolism

MAAIKE SÖHNE, MARIJE TEN WOLDE, FRANS BOOMSMA,
JOHANNES B REITSMA, JAMES D DOUKETIS, HARRY R BÜLLER

SUBMITTED

Abstract

Background:

Controversy exists about the indication of thrombolytic therapy in the subgroup of hemodynamically stable patients with acute pulmonary embolism and right ventricular dysfunction. Brain Natriuretic Peptide (BNP) is excreted from the cardiac ventricles in response to cardiomyocyte stretch and can be measured with an easy to perform blood test.

The objective of this study was to determine the predictive value of elevated BNP levels for early recurrent venous thromboembolism with or without fatal outcome in hemodynamically stable patients with acute pulmonary embolism and to calculate the clinical consequences of initiating thrombolytic therapy based on BNP levels.

Methods:

A nested case-control study was performed within the framework of a large randomized controlled trial totalling 2213 hemodynamically stable patients with confirmed acute, symptomatic pulmonary embolism. Ninety patients experienced a (fatal) recurrent venous thromboembolism during the first 3 months of follow-up (cases); 297 patients with uneventful follow-up served as controls. Blood for BNP levels was obtained and assayed in a central laboratory.

Results:

Cases had significantly higher mean baseline BNP levels (p=0.0002). The odds ratio for every logarithmic unit increase in BNP concentration was 2.4 (95% CI: 1.5-3.7). A BNP cut-off level of 1.25 pmol/L (the optimal point on the ROC curve) was associated with a sensitivity and specificity of 60% and 62%, respectively. For every patient correctly receiving thrombolytic therapy at this cut-off, 16 patients will receive this therapy unnecessarily.

Conclusions:

BNP level at presentation is significantly associated with early (fatal) recurrent venous thromboembolism in hemodynamically stable patients with acute pulmonary embolism. However, this relationship appears clinically insufficient to guide the initiation of thrombolytic therapy.

Introduction

The standard initial treatment of hemodynamically stable patients with acute symptomatic pulmonary embolism is (low-molecular-weight) heparin [1]. Thrombolytic therapy is currently indicated only in patients with pulmonary embolism who are hemodynamically unstable, with systemic hypotension or cardiogenic shock [1].

Controversy exists about the optimal treatment of hemodynamically stable patients with right ventricular dysfunction, who comprise up to 40% of hemodynamically stable patients and who may be at increased risk for early recurrent venous thromboembolism and death [2;3]. Thrombolytic therapy might be indicated in these patients, based on the premise that early clot lysis will improve prognosis. Echocardiography is the currently used modality to identify patients with pulmonary embolism and right ventricular dysfunction in whom thrombolytic therapy would be considered. However, its use in an acute clinical setting is limited by a lack of rapid availability, high cost, and the potential for inter-observer variability in the interpretation of results [2;3].

Brain natriuretic peptide (BNP), a vasoactive hormone that is released from the cardiac ventricles in response to acute ventricular dilation, may be a biochemical means to identify patients with acute pulmonary embolism and right ventricular dysfunction that would obviate the need for echocardiography. BNP is measured by an easy-to-perform blood test that has shown promise in the risk stratification of patients with acute pulmonary embolism [4-7]. Four studies, totalling 335 patients, found that an elevated BNP was predictive for adverse outcomes, such as all cause mortality or the need for thrombolysis, cardiopulmonary resuscitation or mechanical ventilation [4-7]. Three of these studies, however, included hemodynamically unstable patients who are more likely to develop adverse events, thereby limiting the applicability of findings to hemodynamically stable patients. Therefore, we assessed the predictive value of elevated BNP for adverse outcomes, i.e. death due to pulmonary embolism and recurrent venous thromboembolism, in a large cohort of hemodynamically stable patients with pulmonary embolism. Furthermore, we calculated the potential clinical consequences of initiating thrombolytic therapy at different BNP cut-off levels.

Methods

Study population and design

A nested case-control study was performed within the framework of a large randomized controlled trial totalling 2213 hemodynamically stable patients with confirmed acute,

symptomatic pulmonary embolism [8]. This trial compared fondaparinux sodium (Arixtra, NV Organon and Sanofi-Synthélabo), a synthetic pentassacharide, with intravenous unfractionated heparin for the initial treatment of acute pulmonary embolism and revealed a similar efficacy and safety. All patients were followed up for three months. A predefined schedule for follow-up with regular contacts was used and at each contact, the patients was evaluated for symptoms and signs of recurrent venous thromboembolism and bleeding. The major exclusion criteria were: massive PE associated with hypotension (systolic blood pressure < 90 mmHg), cardiogenic shock or respiratory failure in whom thrombolytic therapy or surgical thrombectomy might be considered; uncontrolled hypertension; renal insufficiency (serum creatinine >2.0 mg/dL); an estimated life expectancy < 3 months [8].

The study outcomes were recurrent symptomatic and objectively confirmed venous thromboembolism and fatal pulmonary embolism. Patients were classified as cases if they had one of the study outcomes during the 3-month follow-up period; all other patients were potential controls. All the suspected recurrent venous thromboembolic events were assessed based on prespecified and validated objective criteria so that recurrent disease was reliably confirmed or excluded. Deaths were assessed based on autopsy data and other relevant clinical information. All clinical outcomes were adjudicated by a blinded independent committee without prior knowledge of patients' BNP levels.
For each case, three age and sex-matched controls were selected.

BNP measurement

Serum samples were obtained at baseline, before treatment was initiated. The samples were processed according to a standardized method and they were analysed in a central laboratory using the Shionoria BNP kit (Shionogi, Osaka, Japan; produced under licence CIS-bio International, France). This is a solid-phase sandwich immunoradiometric assay, using two different monoclonal antibodies. The lowest detectable concentration is 0.5 pmol/L. BNP concentrations were measured in serum instead of (most-often used) EDTA-plasma. In a series of samples simultaneously collected in serum and in EDTA-tubes, correlation was excellent (r = 0.998) with a line of identity of [EDTA-BNP] = 1.224 [serum-BNP] + 2.412 (unpublished data).
BNP measurements were performed by technologists who were unaware of patients' clinical status.

Study Objective

The primary study objective was to determine the predictive value of the BNP concentration at presentation in hemodynamic stable patients with proven pulmonary embolism for adverse events, defined as confirmed or possible fatal outcome pulmonary embolism and recurrent venous thromboembolism that occurred during the 3 month follow-up period.

Since congestive heart failure and, possibly, hypertension are associated with elevated BNP levels [9-12], we evaluated whether these factors were potential confounders in the association between elevated BNP and adverse outcomes.

Statistical analysis

Median and inter-quartile ranges for BNP were calculated in cases and controls, and the distributions were compared using the Mann-Whitney U test. Because of the matched design, conditional logistic regression was used to examine the strength of the association between BNP levels and subsequent adverse outcome. The log-transformed levels of BNP were used in the regression models, since this transformation led to a better fit of the data.

The influence of the presence of congestive heart failure or hypertension on the association between BNP and adverse outcome was examined by adding the appropriate interaction terms to the conditional logistic regression models. The different types of cases, i.e. the patients with fatal outcome and the patients with recurrent venous thromboembolism, were added as interaction term to the model as well to exclude the possible influence of the different types of cases on the association between BNP and combined adverse outcome.

A receiver operating characteristic (ROC) analysis was done to assess the clinical consequences of using different cut-off levels of BNP. We calculated positive and negative predictive fractions at the "optimal" cut-off point, where the sum of sensitivity and specificity was the highest, and at cut-off values where either sensitivity or specificity was at its highest value. Finally, the clinical consequences, i.e. numbers of false positive results and numbers of true positive results, at these different cut-off values were calculated. This was done for a hypothetical population of 1000 hemodynamically stable pulmonary embolism patients with an incidence of adverse outcomes as observed in the original study population.

Results

Study population

During the 3-month follow-up period, 98 patients had recurrent symptomatic venous

thromboembolism or died (possibly) due to pulmonary embolism. Eight patients (three with recurrent pulmonary embolism, three with recurrent deep venous thrombosis and two deaths) were excluded since baseline BNP samples were not available. Therefore, 90 cases were included in the analysis, consisting of 29 deaths and 61 episodes of objectively confirmed recurrent venous thromboembolism. Two hundred ninety-seven age- and gender-matched patients served as controls.

The baseline characteristics of cases and controls are shown in Table 1.

A history of congestive heart failure was more common in cases compared to controls (13% versus 5%, p= 0.005), whereas the proportion of patients with hypertension was not significantly different (37% versus 40%, p= 0.64). The median time interval to the adverse event, i.e. fatal or non fatal recurrent venous thromboembolism, was 21 days (inter-quartile range: 6-40 days).

Primary study objective

Cases, on average, had significantly higher baseline levels of BNP than controls (Table 1): the median BNP concentration was 2.45 pmol/L (inter-quartile range: 0.70- 10.40 pmol/L) in cases and 0.80 pmol/L (inter-quartile range: 0.50- 4.85 pmol/L) in controls (p=0.0002). Figure 1 shows the logarithmic (log) transformed baseline BNP concentrations for cases and controls.

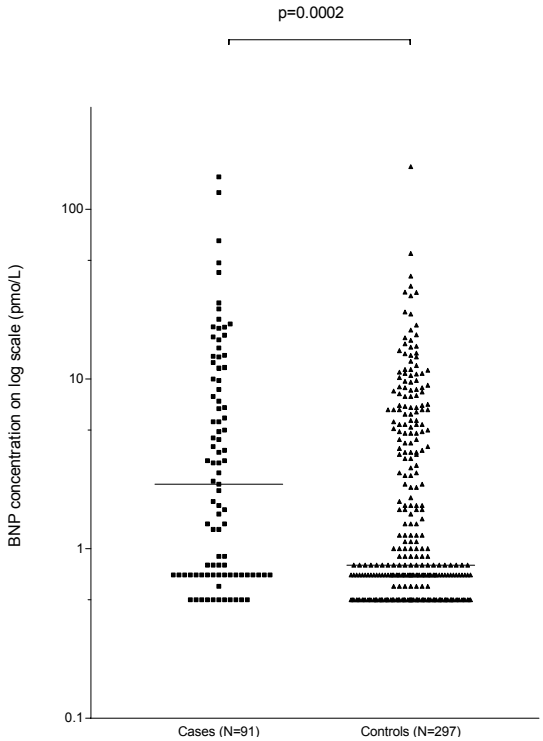
For every unit increase in the log-transformed concentration of BNP, conditional logistic regression analysis revealed an odds ratio of 2.4 (95% CI: 1.5 to 3.7) for an adverse event. Hence, a 10-fold increase in the BNP concentration more than doubles the odds of

Table 1. Baseline characteristics of the 387 study patients

	Cases	**Controls**
Number of patients	90	297
Mean age, years (interquartile range)	64 (54-75)	64 (53-75)
Male n (%)	41 (46%)	132 (44%)
Co-morbidity		
congestive heart failure	12 (13%)	14 (5%)
hypertension	34 (37%)	119 (40%)
Median BNP concentration (pmol/L)	2.45	0.8
(interquartile range)	(0.70-10.40)	(0.50-4.85)
Median time to event (days)	21	n.a

n.a = not applicable

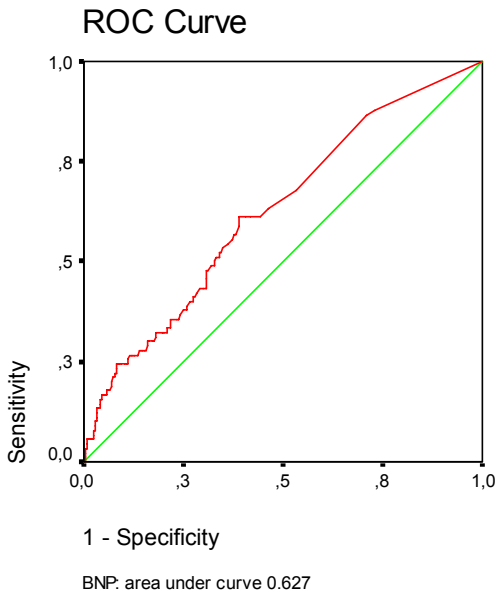
Figure 1 Baseline BNP concentrations of cases and controls on a logarithmic scale



= median BNP concentration

developing an adverse event. A history of congestive heart failure at presentation significantly modified the association between the (log) BNP concentration and adverse outcome (p-value for interaction =0.04). In patients without a history of heart failure, the odds ratio for (log) BNP was 2.8 (95% CI: 1.6 to 4.7), whereas in patients with heart failure, elevated BNP levels were not significantly associated with adverse outcomes (odds ratio = 1.6; 95% CI: 0.3 to 9.9). The presence of hypertension did not change the association between (log) BNP and adverse outcome (p-value for interaction = 0.30) and was, therefore, not included in the logistic regression analysis. The association between (log) BNP and adverse outcome was also not different for the two different components of the investigated adverse events (p-value for interaction p= 0.41).

Figure 2 ROC curve of BNP for patients without heart failure



The ROC curve for the patients without heart failure is presented in Figure 2. The area under the curve (AUC) was 0.63 (95% CI: 0.56-0.70). The sensitivity, specificity and positive predictive values for three different cut-off levels of BNP, i.e. at the highest sensitivity, at the optimal point in the ROC curve and at the cut-off with the highest specificity, are detailed in Table 2. At the optimal BNP cut-off level of 1.25 pmol/L, the sensitivity and specificity are both approximately 60%.

Value of BNP for therapeutic management

The potential consequences of initiating thrombolytic therapy based on the different cut-off values for patients without congestive heart failure are shown in Table 3. A BNP cut-off level of 1.25 pmol/L was associated with a sensitivity and specificity of 60% and 62%,

Table 2 Sensitivity, specificity and positive predictive values for different BNP cut-off concentrations

Cut off BNP (pmol/l)	0.55	1.25	15.50
sensitivity	88%	60%	15%
specificity	28%	62%	95%
positive predictive value	4.4%	5.7%	10.3%

Table 3 Clinical consequence of different BNP cut off concentrations in a hypothetical population of 1000 hemodynamically stable pulmonary embolism patients without heart failure and a presumed incidence of adverse events of 3.7% during three months of follow up

Cut off BNP (pmol/l)	0.55	1.25	15.50
Total number of positive test results/1000 patients	725	388	54
Number of cases correctly identified*/1000 patients	32	22	6
Number of cases missed †/1000 patients	5	15	31
Number of false positive test results/1000 patients	693	366	48

* patients with a BNP concentration above the cut-off level who will experience adverse outcome; the true positive results
† patients with a BNP concentration below the cut-off level who will experience adverse outcome; the false negative results

respectively, and a positive predictive value of 5.7%. Thus, for a hypothetical sample of 1000 hemodynamically stable patients with confirmed pulmonary embolism, this cut-off level would lead to a positive BNP test in 388 patients. It would correctly predict an adverse outcome in 22 of these patients and they may benefit from treatment with thrombolytic therapy. However, 15 patients from the expected 37 patients with an adverse outcome would have been missed. In contrast, a false positive BNP test would occur in 366 patients, with the potential that these patients might receive thrombolytic therapy without justification. Lowering the cut-off level of BNP associated with the highest sensitivity (88%) would increase the number of correctly predicted cases with an adverse outcome from 22 to 32. However, the number of false positive BNP results would increase from 366 to 693 patients. The inverse is observed when the threshold of BNP concentration is increased to the concentration with a specificity of 95%.

Discussion

The principal finding of this study is that in hemodynamically stable patients with acute pulmonary embolism, there is a significant association between the BNP concentration at presentation and the subsequent risk of early fatal or non fatal recurrent venous thromboembolism during the first three months of follow up. Every 10-fold increase in the BNP level is associated with a 2.4-fold increased risk of developing an adverse outcome, defined as recurrent venous thromboembolism or fatal pulmonary embolism. This association is strongest in patients without a history of congestive heart failure (OR = 2.8; 95% CI: 1.6 to 4.7), but was not statistically significant in patients with a history of heart

failure (OR = 1.6; 95% CI: 0.3 to 9.9). Our findings are in agreement with previous investigations and further supports an association between elevated BNP and adverse outcomes in hemodynamically stable patients [6].

Should BNP measurement therefore be advocated in the triage of patients presenting with pulmonary embolism to guide thrombolytic therapy? We applied the observed accuracy indices of BNP to a hypothetical population of 1000 hemodynamically stable patients with confirmed pulmonary embolism. When using the BNP cut-off level with the highest sensitivity, only 5 of 37 patients who are destined to develop an adverse outcome would have been missed (Table 3). However, as a consequence of a high sensitivity of this BNP cut-off level, 693 patients with positive BNP levels would also receive thrombolytic therapy although they would not develop an adverse outcome. These 693 patients would be unlikely to benefit from thrombolytic therapy, but would be exposed to a 4-fold higher risk of major bleeding compared to conventional anticoagulant therapy [13]. With a conservative estimate of the risk of major bleeding of 2% [14] and a rate of intracranial bleeding of 0.5% to 0.8% [14;15], this would mean 17 major haemorrhages, of which at least three would be intracranial. To achieve a favourable benefit-to-risk ratio, thrombolytic therapy would have to prevent more deaths than the associated increase in the number of intracranial bleeds. This entails that thrombolysis has to reduce pulmonary embolism related mortality by at least 30%. The currently available studies provide no evidence for such a benefit of thrombolytic therapy over heparin [14].Hence, we believe that BNP measurement should not routinely be used in hemodynamically stable patients with pulmonary embolism to decide on more aggressive therapy.

There are potential limitations of this study. Firstly, there is the potential for biased results in this, as in any, retrospective case-control study. However, our findings are likely to be valid because blood samples for BNP were measured in all patients using a single assay in a centralized laboratory, and clinical outcomes were objectively adjudicated by an independent committee without knowledge of BNP levels. Secondly, the results of this study were obtained in the framework of a large randomized clinical trial with the potential of patient selection. Although a patient selection bias cannot be excluded, it is unlikely as the baseline clinical characteristics as well as the incidences of clinical relevant outcomes of the study population are comparable with those obtained in population-based studies and intervention trials involving comparable patients with acute pulmonary embolism [16-19]. Thus, we believe that our findings are applicable to the wide range of hemodynamically stable patients with pulmonary embolism. A third limitation of our study is that for the calculation of the clinical consequences only patients without heart failure were

considered. As a consequence, the results of this study are only applicable to hemodynamically stable patients without heart failure. Whether BNP can also predict adverse outcome in patients with a history of heart failure cannot conclusively be answered, but is unlikely to be better than calculated for those without heart failure.

In summary, although BNP is associated with adverse outcome in hemodynamically stable patients with acute pulmonary embolism, this relationship appears clinically insufficient to guide the initiation of thrombolytic therapy. It remains to be determined whether BNP in combination with other prognostic markers, such as troponin and right ventricular dysfunction on spiral CT, further improves the prognostic significance.

Reference List

1. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax 2003; 58:470-483.
2. Grifoni S, Olivotto I, Cecchini P et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000; 101:2817-2822.
3. Goldhaber SZ, Haire WD, Feldstein ML et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341:507-511.
4. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003; 107:2545-2547.
5. Kucher N, Printzen G, Doernhoefer T, Windecker S, Meier B, Hess OM. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. Circulation 2003; 107:1576-1578.
6. ten Wolde M, Tulevski II, Mulder JW et al. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. Circulation 2003; 107:2082-2084.
7. Pruszczyk P, Kostrubiec M, Bochowicz A et al. N-terminal pro-brain natriuretic peptide in patients with acute pulmonary embolism. Eur Respir J 2003; 22:649-653.
8. Buller HR, Davidson BL, Decousus H et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003; 349:1695-1702.
9. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. Eur Heart J 2003; 24:1735-1743.
10. Maisel AS, McCord J, Nowak RM et al. Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J Am Coll Cardiol 2003; 41:2010-2017.
11. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK. Reliability of N-terminal proBNP assay in diagnosis of left ventricular systolic dysfunction within representative and high risk populations. Heart 2004; 90:866-870.
12. Maisel AS, Krishnaswamy P, Nowak RM et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161-167.
13. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999; 353:1386-1389.

14. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis Compared With Heparin for the Initial Treatment of Pulmonary Embolism. A Meta-Analysis of the Randomized Controlled Trials. Circulation 2004.
15. Agnelli G, Becattini C, Kirschstein T. Thrombolysis vs heparin in the treatment of pulmonary embolism: a clinical outcome-based meta-analysis. Arch Intern Med 2002; 162:2537-2541.
16. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. Ann Intern Med 2004; 140:175-183.
17. 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.
18. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998; 279:458-462.
19. Prandoni P, Carnovali M, Marchiori A. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. Arch Intern Med 2004; 164:1077-1083.

Chapter 13

The prevalence and prognostic significance of elevated cardiac troponins in patients with submassive pulmonary embolism

JAMES D. DOUKETIS, OSCAR LEEUWENKAMP, PETER GROBARA, MARILYN JOHNSTON, MAAIKE SÖHNE, MARIJE TEN WOLDE, HARRY BÜLLER

J THROMB HAEMOST 2005 MAR; 3(3):508-13

Abstract

Background:

Although the incidence and prognostic significance of elevated cardiac troponins are known in patients with massive pulmonary embolism (PE), few studies have addressed this issue in patients with hemodynamically-stable submassive PE, who comprise the majority of patients presenting with PE. This prospective cohort study was therefore, designed to determine the incidence and prognostic significance of elevated cardiac troponins in patients with submassive PE.

Methods:

Consecutive patients with acute, symptomatic submassive PE that was confirmed by objective diagnostic testing were studied. All patients received treatment with either unfractionated heparin or fondaparinux followed by a coumarin derivative and underwent clinical follow-up for 3 months. Cardiac troponin I (cTnI) levels were measured within 24 hours of clinical presentation. An elevated cTnI was defined as >0.5 μg/L and indicated myocardial injury. Major myocardial injury, that is associated with myocardial infarction, was defined by a cTnI > 2.3 μg/L. The clinical outcomes were recurrent venous thromboembolism and all-cause death.

Results:

In 458 patients with submassive PE, the incidence of cTnI >0.5 μg/L was 13.5% (95% confidence interval [CI]: 10.4-16.7), and the incidence of cTnI >2.3 μg/L was 3.5% (95% CI: 2.0-5.6). An elevated cTnI >0.5 μg/mL was associated with an increased risk of all-cause death (odds ratio [OR] = 3.5; 95% CI: 1.0-11.9), but did not appear to confer an increased risk of recurrent venous thromboembolism (OR = 1.1; 95% CI: 0.2-4.9).

Conclusion:

In patients who present with submassive PE, an elevated cTnI occurs in about 1 in 7 patients and is associated with a 3.5-fold increased risk of all-cause death.

Introduction

Cardiac troponins, which include cardiac troponin I (cTnI) and cardiac troponin T (cTnT), are biochemical markers of myocardial injury that are widely used in patients presenting with undifferentiated chest pain or dyspnea. Elevated cardiac troponins are helpful in diagnosing an acute coronary syndrome, whereas serially negative troponins reliably exclude this condition [1-3]. Elevated cardiac troponins occur also in patients with non-ischemic myocardial injury who have congestive heart failure, myocarditis or infiltrative cardiomyopathy [4], and in patients with chronic renal insufficiency [5].

Massive pulmonary embolism (PE), defined as PE that is associated with systemic hypotension, cardiogenic shock or respiratory failure [6], is another condition that is associated with elevated cardiac troponins, and likely results from myocardial injury due to acute right ventricular dilation and strain caused by vascular obstruction in the pulmonary arteries [7]. Elevated cardiac troponins occur in at least one-third of patients with massive PE, and this finding confers a 30-fold increased risk of death [8]. Because cardiac troponin assays are highly sensitive to any myocardial injury, it is biologically plausible that elevated cardiac troponins also occur in patients with submassive PE, who represent 80-85% of all patients presenting with PE [9]. However, the prevalence and prognostic importance of elevated cardiac troponins patients with submassive PE is unclear [10,11]. Addressing this issue is clinically relevant for two reasons. First, if the prevalence of elevated cardiac troponins in patients with submassive PE is relatively high, this will suggest that PE should be considered in the differential diagnosis of all patients presenting with undifferentiated chest pain or dyspnea and elevated cardiac troponins. Second, if elevated cardiac troponins are predictors of recurrent venous thromboembolism or death, this finding might justify more aggressive therapy or closer clinical surveillance in patients who are newly diagnosed with submassive PE.

We, therefore, undertook a prospective cohort study to determine the prevalence and prognostic significance of an elevated cTnI in patients presenting with submassive PE.

Patients and Methods

Study Design

We undertook a prospective cohort study that was nested within a randomized controlled trial. The randomized trial was investigating a new anticoagulant for the initial treatment of submassive PE [12].

Patients

The study population was derived from a randomized trial that was investigating the synthetic pentassacharide, fondaparinux sodium (Arixtra, NV Organon and Sanofi-Synthélabo), in 2184 consecutive patients with acute, symptomatic, submassive PE. Clinical centers involved in this trial were asked to participate in the cardiac troponin sub-study. In clinical centers that agreed to participate in this sub-study, all patients in the randomized trial, irrespective of treatment allocation, had cTnI testing within 24 hours of clinical presentation and additional documentation of cardiovascular risk factors that was not required as part of the randomized trial. Patients were excluded from the randomized trial if they had massive PE associated with hypotension (systolic blood pressure <90 mmHg), cardiogenic shock or respiratory failure in whom thrombolytic therapy or surgical thrombectomy might be considered or a life expectancy <3 months. The other patient exclusion criteria are described elsewhere [12].

Diagnosis of PE

The diagnosis of PE was based on one or more of the following objective criteria: at least one segmental or two subsegmental ventilated areas in the lung without perfusion on ventilation-perfusion lung scan; an intraluminal filling defect in an interlobar or more proximal pulmonary artery on spiral computed tomography of the chest; an intraluminal filling defect of ≥2 mm on pulmonary angiography; or an indeterminate ventilation-perfusion lung scan and confirmed lower limb deep vein thrombosis on venous ultrasound or venography [12].

Anticoagulant Therapy

Patients were randomly allocated to receive initial treatment with either intravenous unfractionated heparin, administered to achieve a target activated partial thromboplastin time of 1.5-2.5 times the control value, or subcutaneous once-daily fixed-dose fondaparinux (5.0 mg for body weight <50 kg; 7.5 mg for body weight 50-100 kg; 10.0 mg for body weight >100 kg). Patients received a coumarin derivative, administered to achieve a target international normalized ratio of 2.0-3.0, for at least 3 months. The duration of patient follow-up was 3 months.

Study Outcomes

Elevated cTnI. All patients had a 4.5 mL sample of whole blood drawn into a heparinized glass tube for measurement of cTnI. All blood samples were processed at each clinical center using a standardized method, and were analyzed in a central laboratory

(Hemostasis Reference Laboratory, Hamilton, ON) using the quantitative immunofluroresence AxSYM assay for cTnI (Abbott Laboratories, Abbott Park, IL). The analytical sensitivity for this cTnI assay is 0.3 μg/L, and represents the lowest measurable concentration of cTnI that can be distinguished from zero. With this assay, myocardial injury is defined by a cTnI >0.5 μg/L. Major myocardial injury, that is associated with myocardial infarction, is defined by a cTnI >2.3 μg/L.

Clinical outcomes. The clinical outcomes were recurrent venous thromboembolism and death. Patients with suspected recurrent venous thromboembolism were assessed based on pre-specified and validated objective criteria so that recurrent disease was reliably confirmed or excluded [9]. Deaths were assessed based on autopsy data and other relevant clinical information. Clinical outcomes were reviewed by an independent adjudication committee that was unaware of patients' treatment allocation in the randomized trial or participation in the nested cohort study.

Statistical Analysis

Univariate and multivariate, stepwise forward, logistic regression analysis was used to identify independent predictors of venous thromboembolism and all-cause death. The odds ratio (OR), and corresponding 95% confidence interval (CI), was reported for each variable in the model. Variables included in the final (multivariate) model for the nested cohort study population was based on their level of significance in the total randomized trial population. For each variable that was considered, but not included in the final model, univariate statistics were reported. *A priori*, we considered variables that might influence an association between elevated cTnI and recurrent venous thromboembolism or all-cause death: cancer; immobility; recent (within one month) surgery or trauma; body weight; previous cardiovascular event (at least one of myocardial infarction, stroke, or peripheral vascular disease); respiratory disease; initial anticoagulant therapy (unfractionated heparin or fondaparinux).

Results

Patient Characteristics

There were 458 patients in the nested cohort study who had cTnI measured within 24 hours of clinical presentation. Their baseline clinical characteristics are presented in Table 1.

Table 1. Baseline Patient Characteristics

Clinical Characteristics and Treatment		Number (%)
age (years)	mean (range)	63.2 (19-92)
	<65 years	214 (46.7)
	65 - 75 years	120 (26.2)
	>75 years	124 (27.1)
female sex		261 (57)
mean weight (kg)	mean (range)	79.1 (38-143)
	<50 kg	12 (2.6)
	50 - 100 kg	407 (88.9)
	>100 kg	39 (8.5)
body mass index (kg/m ^{2})	<30 kg/m^2	335 (73.5)
	>30 kg/m^2	121 (26.5)
Concurrent medical disease	previous myocardial infarction	29 (6.3)
	previous stroke	19 (4.1)
	peripheral arterial disease	18 (3.9)
	hypertension †	185 (52.7)
	diabetes mellitus †	50 (14.2)
	dyslipidemia †	80 (22.8)
	current smoker †	50 (14.2)
	renal function (creatinine clearance) ‡	
	>80 mL/min	203 (45.0)
	50 - 80 mL/min	164 (36.4)
	30 - 49 mL/min	74 (16.4)
	<30 mL/min	10 (2.2)
	any cardiovascular risk factor §	307 (67.0)
	any respiratory disease	119 (26.0)
	any gastrointestinal disease	173 (37.8)
	any central nervous system disease	124 (27.1)
	any endocrine disease	154 (33.6)
	any genitourinary disease	112 (24.5)
	any musculoskeletal disease	150 (32.8)
Risk factors for venous thromboembolism	previous venous thromboembolism	101 (22.0)
	surgery or trauma	91 (20.0)
	immobility (at least 3 days)	50 (10.9)
	active cancer ¶	46 (10.0)
	cancer (previous or active)	67 (14.6)
Initial anticoagulant therapy :	- unfractionated heparin	233 (50.8)
	mean number of days of treatment (range)	6.9 (1 - 15)
	- fondaparinux	224 (49.2)
	mean number of days of treatment (range)	6.6 (1 -14)
Oral coumarin therapy start :	same day or before study drug	244 (53.3)
	1 day after start of study drug	125 (27.3)
	2 to 3 days after start of study drug	71 (15.5)
	>3 days after start of study drug	7 (1.5)
	No oral coumarin therapy	11 (2.4)

† Data available for 350 patients; ‡ calculated based on the Cockroft-Gault equation: creatinine clearance = [140 - age (yrs) H weight (kg) / serum creatinine (mg/dL) H 72] H [0.85 for females] (27); § consists of one or more of the following conditions: previous cardiovascular disease (myocardial infarction, stroke, perpipheral vascular disease), hypertension, diabetes, dyslipidemia, smoking; ¶ cancer that is metastatic or treated within 6 months

Anticoagulant Therapy

The anticoagulant therapy patients received is presented in Table 1. As initial treatment, 233 (51%) patients received intravenous unfractionated heparin, and 224 (49%) patients received fondaparinux. One patient (0.2%) who was allocated to receive fondaparinux did not receive this treatment. Oral coumarin therapy was started usually within the first 3 days after the start of unfractionated heparin or fondaparinux. Eleven patients (2.4%) who were to receive oral coumarin did not receive this treatment.

Recurrent Venous Thromboembolism and All-cause Death

The rates of recurrent venous thromboembolism and all-cause death during the 3-month follow-up period are presented in Table 2. Recurrent venous thromboembolism occurred in 14 (3.1%) patients, of which 9 episodes were non-fatal and 5 episodes were fatal. All-cause death occurred in 16 (3.5%) patients, and was due to pulmonary embolism (5 patients), cancer (7 patients), bleeding (1 patient), diabetic coma (1 patient), ischemic colitis (1 patient), or an unspecified cause (1 patient). There was no significant difference in recurrent venous thromboembolism and death in patients who received initial treatment with unfractionated heparin compared to fondaparinux (6.4% vs 4.0%; P = 0.30), thereby

Table 2. Clinical Outcomes and Elevated Troponins

Clinical Outcome	Number (%)
Recurrent venous thromboembolism (total)	14 (3.1)
non-fatal	9 (2.0)
fatal	5 (1.1)
† Bleeding (total)	*39 (8.5)*
major	10 (2.2)
non-major	29 (6.3)
Death (total)	*16 (3.5)*
pulmonary embolism	5 (1.1)
cancer	7 (1.5)
bleeding	1 (0.2)
diabetic coma	1 (0.2)
ischemic colitis	1 (0.2)
unspecified cause	1 (0.2)
Cardiac troponin I	
undetectable (<0.3 μg/L)	375 (81.9)
detectable (≥0.3 μg/L)	83 (18.1)
abnormal (>0.5 μg/L)	62 (13.5)
mean/median detectable cTnI (range)	2.2/1.2 (0.3 - 19.2)

†Bleeding that occurred during the initial treatment period with unfractionated heparin or fondaparinux.

supporting the pooling of patients who received different initial anticoagulant therapy into the nested cohort study.

Prevalence of Elevated Cardiac Troponin

The prevalence of cTnI >0.5 μg/L, indicating myocardial injury, was 13.5% (95% CI: 10.4-16.7). The prevalence of cTnI >2.3 μg/L, indicating major myocardial injury that is associated with myocardial infarction, was 3.5% (95% CI: 2.0-5.6). The distribution of elevated cTnI values is shown in the Figure. In 55 patients with a previous myocardial infarction or coronary artery disease, the prevalence of cTnI >0.5 μg/L was higher than in 403 patients without these conditions (20.0% vs. 12.7%), but this difference was not statistically significant (P = 0.14; Fisher's exact test).

Prognostic Value of Elevated cTnI

As presented in Table 3 and Table 4, an elevated cTnI (>0.5 μg/L) was associated with a significant increase in the risk of all-cause death (OR = 3.5; 95% CI: 1.0-11.9) but did not appear to confer an increased risk of recurrent venous thromboembolism (OR = 1.1; 95% CI: 0.2-4.9). Because of the small number of deaths due to specific causes, this precluded an

Table 3. Risk Factors for All-cause Death (univariable analysis)

Characteristic	Odds Ratio	
	Value	95% CI
cTnI >0.5 μg/L	4.1	1.4 - 11.8
immobility (3 consecutive days)	2.9	0.89 - 9.2
previous cardiovascular event †	3.4	1.1 - 10.2
respiratory disease	0.94	0.30 - 3.0
cancer (previous or active)	15.4	5.5 - 46.1
body weight (10-kg increments)	0.75	0.53 - 1.1
age (10-year increments)	1.8	1.1 - 2.8
recent (within one month) surgery or trauma	1.4	0.43 - 4.3
renal insufficiency	2.7	0.97 - 7.8

cTnI; cardiac troponin I; CI, confidence interval; † previous myocardial infarction, previous stroke or peripheral arterial disease.

Table 4: Risk Factors for All-cause Death (multivariable analysis)

Characteristic	Adjusted Odds Ratio †		P-value
	Value	95% CI	
cTnI >0.5 μg/L	3.5	1.0 - 11.9	0.045
cancer (previous or active)	19.4	5.3 - 70.7	<0.001
immobility (3 consecutive days)	8.4	1.6 - 43.4	0.012
previous cardiovascular event ‡	2.8	0.72 - 10.6	0.14
initial treatment with fondaparinux vs unfractionated heparin	1.1	0.34 - 3.3	0.92
Body weight (10-kg increments)	0.75	0.51 - 1.1	0.15
age (10-year increments)	1.3	0.77 - 2.1	0.35

cTnI; cardiac troponin I; CI, confidence interval; † adjusted for other variables included in the univariate analysis; ‡ previous myocardial infarction, previous stroke or peripheral arterial disease

analysis of the prognostic value of an elevated cTnI as a predictor of fatal PE or other specific causes of death.

Other Prognostic Determinants

Other significant predictors of all-cause death based on the logistic regression analysis were cancer (OR = 19.4; 95% CI: 5.3-70.7), and immobility (OR = 8.4; 95% CI: 1.6-43.4). In patients with previous myocardial infarction, stroke or peripheral arterial disease, there was a non-significant trend favoring an increased risk of all-cause death (OR = 2.8; 95% CI: 0.7-10.6).

Discussion

There are two principal findings from this study. First, an elevated cTnI occurred in about 1 in 7 patients presenting with submassive PE. Second, an elevated cTnI was associated with a 3.5-fold increased risk of all-cause death, but did not appear to confer an increased risk of recurrent venous thromboembolism. Our findings are likely to be valid and generalizable to patients with hemodynamically-stable submassive PE, who comprise the vast majority of patients presenting with PE. A well-defined patient population which satisfied standardized criteria for submassive PE was studied, and patients with massive PE were excluded. Data acquisition of cTnI measurements was complete and reliable, as blood samples were processed using a standardized method and analyzed in a central

laboratory. Furthermore, all patients received a standardized and comparable treatment for PE, underwent follow-up for 3 months, and had clinical outcomes documented based on standardized objective criteria.

Our finding that a relatively high proportion of patients with submassive PE have an elevated cTnI, although unexpected because of the smaller thrombus burden than with massive PE, may be explained by the following considerations. First, up to 40% of patients with submassive PE develop transient right ventricular dilation and strain that could cause myocardial injury [13-15]. Second, concomitant cardiorespiratory disease occurs in about 50% of patients with PE [16], and a limited cardiorespiratory reserve might make patients more susceptible to myocardial injury as a consequence of the mechanical effects (i.e., elevated pulmonary artery pressure) and biochemical effects (i.e., hypoxemia) of PE. Third, because cardiac troponins are highly sensitive markers of myocardial injury, they may be elevated after minor myocardial injury associated with submassive PE, in a similar way that cardiac troponins are elevated in patients with unstable angina [17].

Our finding that elevated cTnI confers an increased risk of all-cause death suggests that an elevated cTnI, in response to an acute illness such as PE, may be a marker of an increased burden of disease or decreased cardiorespiratory reserve. This finding is consistent with the findings in patients with end-stage renal disease and in critically ill patients without an acute coronary syndrome in whom an elevated cardiac troponin is a risk factor for death [18,19]. We could not assess whether an elevated cTnI is associated with an increased risk of fatal PE as there were too few of these events. In addition, we did not observe an association between elevated cTnI and recurrent venous thromboembolism. However, our study may be underpowered to detect such an association.

In previous studies involving patients with PE, an elevated cardiac troponin was more common, and was a stronger determinant of poor prognosis than in our study. In a study of 56 patients with massive and submassive PE, a cTnT >0.1 μg/L occurred in 32% of patients, and was associated with a 30-fold increased risk of death (OR = 29.6; 95% CI: 3.3-265) [8]. In another study of 64 patients with submassive PE, a cTnT >0.1 μg/L occurred in 50% of patients, and was associated with an increased risk of fatal PE (OR = 21; 95% CI:1.2-389) [21]. Finally, in a study of 106 patients with PE of unspecified severity, 41% had a cTnI >0.07 μg/L and a cTnI >1.5 μg/L was predictive of death or a complicated in-hospital course [20]. The discrepant results between these studies and our findings are likely due to differences in patient characteristics and the cut-off value used to define an elevated cardiac troponin. In other studies, 20-30% of patients had coronary artery disease [8,21], and 25% of patients had systemic hypotension [8], whereas in our study, only 6% of patients had

a previous myocardial infarction and 1% of patients had systemic hypotension. Furthermore, a higher cut-off level for an abnormal cTnI (>0.5 μg/L) was used in our study compared to the cut-off used in other studies (>0.1 μg/L), which would result in a lower proportion of patients with elevated cardiac troponins in our study.

One potential limitations of this study is that the nested cohort study population may not have been a representative sample from the total randomized trial population. This is unlikely for three reasons. First, the nested cohort study population consisted of consecutive, unselected patients with PE who were derived from the clinical centers that participated in the nested cohort study. Second, patients in the nested cohort study were comparable, in terms of baseline clinical characteristics, to the other patients in the randomized trial who were not involved in the nested cohort study (data not shown). Third, there were no significant differences in the nested cohort and other patients in terms of recurrent venous thromboembolism (3.1% vs. 4.7%; P= 0.13), all-cause death (3.5% vs. 5.2%; P = 0.18), or major bleeding during the initial treatment period (1.1% vs. 1.2%, P = 1.0). Furthermore, the rates of recurrent venous thromboembolism and death in the nested cohort study population were comparable to the outcome rates from a meta-analysis of 1,951 patients with submassive PE, thereby providing external validity that our study population was representative of unselected patients with submassive PE [22]. Another potential study limitation is that we measured cTnI but not cTnT. However, cTnI and cTnT myocardial subunits have comparable prognostic value in patients with an acute coronary syndrome [23,24] and PE [20], and it is unlikely that our findings would differ if cTnT also had been measured. Finally, because patients with a life expectancy of <3 months were excluded from our study, our findings would not be generalizable to such patients, some of whom may have advanced malignancy or other major comorbidity that would affect prognosis.

There are two clinical implications of our study. First, in hemodyamically-stable patients presenting with undifferentiated chest pain or dyspnea and elevated cardiac troponins, PE should be considered in the differential diagnosis. Prior knowledge that elevated cardiac troponins occur in a sizeable proportion of patients with submassive PE might result in fewer patients being misdiagnosed with an acute coronary syndrome when, in fact, they have PE [25,26]. Second, in patients with confirmed submassive PE, the presence of elevated cardiac troponins do not appear to be predictive of an increased risk of recurrent venous thromboembolism and, therefore, may not warrant the need to pursue in such patients more aggressive antithrombotic therapy with thrombolytic or other treatment modalities.

In summary, in patients who present with submassive PE, an elevated cTnI occurs in about 1 in 7 patients and is associated with a 3.5-fold increased risk of all-cause death.

Reference List

1. Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med 1997;337:1648-53.
2. Hetland O, Dickstein K. Cardiac troponin I and T in patients with suspected acute coronary syndrome: a comparative study in a routine setting. Clin Chem 1998;44:1430-6.
3. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina). Circulation 2000;102:1193-1209.
4. Hamm CW, Giannitsis E, Katus HA. Cardiac troponin elevations in patients without acute coronary syndrome. Circulation 2002;106:871-2.
5. Freda BJ, Tang WHW, van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. J Am Coll Cardiol 2002;40:2065-71.
6. Tapson VF, Witty LA. Massive pulmonary embolism: diagnostic and therapeutic strategies. Clin Chest Med 1995;16:329-40.
7. Vlahakes GJ, Turley K, Hoffman JIE. The pathophysiology of failure in acute right ventricular hypertension: Hemodynamic and biochemical correlations. Circulation 1981;63:87-95.
8. Giannitsis E, Muller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000;102:211-7.
9. The Columbus Investigators. Low molecular weight heparin is an effective and safe treatment for deep vein thrombosis and pulmonary embolism. N Engl J Med 1997;337:657-62.
10. Pacouret G, Schellenberg F, Hamel E, et al. Troponine I dans l'embolie pulmonaire aigue massive: resultats d'une serie prospective. Presse Med 1998;27:1627.
11. Douketis JD, Crowther MA, Stanton EB, Ginsberg JS. Elevated cardiac troponin levels in patients with submassive pulmonary embolism. Arch Intern Med 2002;162:79-81.
12. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the intial treatment of pulmonary embolism. N Engl J Med 2003;349:1695-1702.
13. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, for the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347:1143-50.
14. Goldhaber SZ, Visani L, De Rosa M, for ICOPER. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386-9.
15. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfelt L. Echocardiography Doppler in pulmonary embolism: Right ventricular dysfunction as a predictor of mortality rate. Am Heart J 1997;134:479-87.
16. 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;160:3431-6.
17. Stubbs P, Colinson P, Moseley D, Greenwood T, Noble M. Prospective study of the role of cardiac troponin T in patients admitted with unstable angina. BMJ 1996;313:262-4.
18. Ammann P, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oeschslin E, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. J Am Coll Cardiol 2003;41:2004-9.
19. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for

subsequent death in end-stage renal disease. Circulation 2002;106:2941-5.
20. Konstantinides S, Geibel A, Olschewewski M, Kasper W, Hruska N, Jackle A, Binder L. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002;106:1263-8.
21. Pruszczyk P, Bochowicz A, Torbicki A, Szule M, Kurzyna M, Fijalkowska A, et al. Cardiac troponin T monitoring identifies high-risk group of normotensive patients with acute pulmonary embolism. Chest 2003;123:1947-52.
22. Quinlan DJ, McQuinlan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism. Ann Intern Med 2004;140:175-83.
23. Olatidoye A, Wu AHB, Feng YJ, Waters D. Prognostic role of troponin T versus troponin I in unstable angina pectoris for cardiac events with meta-analysis comparing published studies. Am J Cardiol 1998;81:917-27.
24. Wu AH, Feng YJ, Moore R, et al. Characterization of cardiac troponin subunit release into serum after myocardial infarction and comparison of assays for troponin T and I: American Association for Clinical Chemistry Subcommittee on cTnI Standardization. Clin Chem 1998;44:1198-1208.
25. Gibson TN, Hanchard B. False positive troponin I in a case of metastatic small cell bronchogenic carcinoma complicated by pulmonary thromboembolism. West Indian Med J 2001;50:171-2.
26. Wong CB, Tang IT, Tiu A. Pulmonary embolism mimicking acute myocardial infarction. Tex Med 1999;95:67-8.
27. Cockroft DW, Gault MN. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.

Summary

In this thesis two different aspects of the management of pulmonary embolism are discussed. In the first part different diagnostic strategies to safely and efficiently exclude or confirm pulmonary embolism in patients in whom this disease was suspected are described. The second part focuses on the prognosis of those patients in whom pulmonary embolism was confirmed. Several prognostic indicators for (fatal) recurrent venous thromboembolism were studied.

Diagnosis

Chapter 2 gives an overview of the diagnostic methods available to rule out or confirm pulmonary embolism. In **chapter 3** the safety of a diagnostic algorithm, combining clinical probability, D-dimer testing and spiral computed tomography (s-CT) in patients with clinically suspected pulmonary embolism was assessed. Patients were categorized in unlikely or likely for pulmonary embolism using the validated clinical decision rule (CDR) of Wells et al. The disease was considered excluded if the clinical decision rule (CDR) score was unlikely and the D-dimer test normal. All other patients underwent s-CT. Anticoagulant treatment was withheld in patients without pulmonary embolism and they were followed to assess the three-month incidence of venous thromboembolism. Of the 3306 patients included, 1057 (32%) had the combination of an unlikely CDR and a normal D-dimer test. The incidence of venous thromboembolism in this group was 0.5% (95%CI: 0.2-1.1%). A s-CT negative for pulmonary embolism was observed in 1505 patients, in whom the three-month venous thromboembolic incidence rate was 1.3% (95% CI: 0.7-2.0%). The algorithm was completed and allowed a management decision in almost 98% of patients. Hence, it was concluded that the evaluated diagnostic strategy was efficient, safe and widely applicable. However, whether this diagnostic approach can also be applied to several subgroups with suspected pulmonary embolism, such as patients with malignancy, previous venous thromboembolism, COPD, heart failure or older age is a matter of debate. This was assessed in **chapter 4**. In this analysis not only the safety of the algorithm was studied, but also the diagnostic yield of the combination of an unlikely CDR and a normal D-dimer test and the s-CT were calculated for the different subgroups. This study demonstrated that these tests appear to have a similar safety in excluding pulmonary embolism irrespective of the presence of malignancy, previous VTE, COPD, heart failure or older age. However, the proportion of patients with normal results for the CDR and D-dimer varied and was lowest in those with malignancy and 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 patient from pulmonary

embolism was highest in the cancer subgroup and the elderly.

Chapter 5 evaluated the frequency of an alternative diagnoses in consecutive patients in whom pulmonary embolism was ruled out by s-CT. Furthermore, it was evaluated whether systematic reading of the s-CT would show an important change of clinically relevant diagnoses compared to the diagnoses given by the attending physician in the acute setting. Of the 76 patients without pulmonary embolism s-CT provided an alternative clinical diagnosis that may have therapeutic consequences in approximately 36% of the patients. The most frequently observed diagnosis was pneumonia, which was seen in one third of the patients with an alternative diagnosis. A comparison of the clinical diagnoses given by the attending physician in the emergency department and those given after systematic reading showed a difference in diagnoses in 21 of the 46 patients with an alternative diagnosis. In a modest proportion (about a quarter) these differences might have a possible therapeutic consequence.

Although a CDR combined with a D-dimer test is commonly used to rule out suspected pulmonary embolism, still 70% of patients need to undergo further imaging tests because of its low specificity. C-reactive protein (CRP) has been shown to be also related to the presence or absence of pulmonary embolism. In **Chapter 6** 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 was evaluated. In 790 patients 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%). Therefore, the use of CRP in addition to CDR and D-dimer appears safe, however the efficiency is marginal.

Chapter 7 aimed to assess the accuracy of the D-dimer test in patients with suspected pulmonary embolism and concurrent malignant disease. The sensitivity and negative predictive value in patients with and without cancer were high, however the specificity was lower in those with cancer. In **chapter 8** the combination of CDR and D-dimer was evaluated for patients in different age categories. Although the safety of these tests remained good in outpatients older than 75 years of age, the proportion of patients in which this strategy excludes pulmonary embolism was markedly lower compared to younger patients. For inpatients of older age the safety was not confirmed.

Prognosis

Once the diagnosis of pulmonary embolism has been established, anticoagulant therapy is initiated to prevent (fatal) recurrent venous thromboembolism. For hemodynamically

instable patients there is consensus to administer a short course of thrombolytic therapy to prevent an adverse outcome, while hemodynamic stable patients in general are treated with heparin and vitamin K antagonists. The incidence of (fatal) recurrent venous thromboembolism in this latter group during treatment is still around 4%. To further decrease this percentage, those patients with a high risk of pulmonary embolism related outcome events might benefit from thrombolysis as well. Echocardiographically assessed right ventricular dysfunction has been advocated as a tool to select those high-risk patients. **Chapter 9** reviews the literature to assess the prognostic value of echocardiographic right ventricular dysfunction. The seven included studies suggested an at least two fold increased risk of pulmonary embolism related mortality. However, the only two studies that allowed for an estimation of pulmonary embolism associated mortality in hemodynamically stable patients showed positive predictive values for this adverse outcome of only 5%.

Other, easier to perform tests in the risk assessment of patients with pulmonary embolism are the cardiac biomarkers troponin I and T and brain natriuretic peptide (BNP). The studies reviewed in **chapter 10** showed prevalences of elevated cardiac biomarkers of 16 to 84%. Positive predictive values for in-hospital mortality varied from 6 to 44%, whereas negative predictive values for an uneventful outcome were above 93%. Although a correlation between elevated biomarkers and in-hospital mortality in pulmonary embolism patients was present in most of the studies, the positive predictive value appeared to be insufficiently to extend the indication for thrombolytic therapy to all patients with elevated biomarkers.

In **chapter 11** BNP concentrations were measured in 110 consecutive hemodynamically stable patients with pulmonary embolism. This study showed that the higher the BNP value, the higher the risk of pulmonary embolism related death, with a positive predictive value of 16% if the BNP concentration was above the 67th percentile, i.e. 21.7 pmol/L. In **chapter 12** the relation between BNP and adverse outcome, i.e. fatal or non-fatal recurrent venous thromboembolism, was investigated in a nested case-control study. Cases had significantly higher mean baseline BNP levels. The odds ratio for every logarithmic unit increase in BNP concentration was 2.4 (95% CI: 1.5-3.7). Hence, a 10-fold increase in the BNP concentration more than doubles the odds of developing an adverse event. However, although BNP level at presentation was significantly associated with early (fatal) recurrent venous thromboembolism in hemodynamically stable patients with acute pulmonary embolism, this relationship is clinically insufficient to guide the initiation of thrombolytic therapy. In **Chapter 13** the incidence and prognostic significance of elevated cardiac

troponin I in 458 patients with hemodynamically stable pulmonary embolism were evaluated. An elevated troponin I concentration > 0.5 μg/L occurred in approximately 1 in 7 patients and was associated with an increased risk of all-cause death (odds ratio 3.5; 95% CI: 1.0-11.9). The risk for recurrent venous thromboembolism was not increased in those with elevated troponin concentrations.

Samenvatting

Dit proefschrift beschrijft verschillende aspecten van longembolieën. In het eerste deel worden diagnostische strategieën beschreven om longembolieën veilig en efficiënt uit te sluiten of om deze te bevestigen. Het tweede deel van dit proefschrift beschrijft de prognose van patiënten waarbij de diagnose is bevestigd. Verschillende prognostische indicatoren om (fatale) recidief veneuze trombo-embolieën te voorspellen zijn onderzocht.

Diagnostiek

Hoofdstuk 2 is een overzicht van de diagnostische methoden die beschikbaar zijn om longembolieën uit te sluiten of aan te tonen. In **hoofdstuk 3** is de veiligheid van een diagnostisch algoritme, bestaande uit de combinatie van klinische waarschijnlijkheid, D-dimeer test en spiraal CT, onderzocht in patiënten met een klinische verdenking op longembolieën. Patiënten met een verdenking werden op basis van een klinische beslisregel (KBR) ingedeeld in een categorie waarbij longembolieën onwaarschijnlijk waren dan wel in een categorie waarbij deze waarschijnlijk waren. Longembolieën werden uitgesloten als de KBR onwaarschijnlijk was en de D-dimeertest normaal. Alle andere patiënten ondergingen een spiraal CT. De patiënten bij wie longembolieën uitgesloten waren kregen geen anticoagulante behandeling. Zij werden drie maanden gevolgd om de incidentie van veneuze trombo-embolische complicaties te bepalen. Van de 3306 geïncludeerde patiënten hadden er 1057 (32%) een KBR score die longembolieën onwaarschijnlijk maakte in combinatie met een normale D-dimeertest. De incidentie van veneuze trombo-embolische complicaties in deze groep was 0.5% (95% betrouwbaarheidsinterval [BI]: 0.2-1.1%). In 1505 patiënten toonde de CT scan geen longembolieën aan. Hiervan werd bij 1.3% (95% BI: 0.7-2.0%) gedurende de 3 maanden follow-up alsnog een veneuze trombo-embolie gediagnosticeerd. Het algoritme is gevolgd in 98% van de patiënten. Deze strategie lijkt dus veilig, efficiënt en wijd toepasbaar. Of deze strategie ook veilig en efficiënt is in verschillende subgroepen van patiënten met een verdenking op longembolieën, zoals patiënten met een maligniteit, een veneuze trombo-embolie in de voorgeschiedenis, COPD, hartfalen of oudere patiënten is onderzocht in **hoofdstuk 4**. Deze studie laat zien dat de combinatie van KBR en D-dimeertest of spiraal CT ook veilig is in deze specifieke groepen patiënten. De proportie van patiënten met een normale KBR en D-dimeer uitslag is echter verschillend en is het laagst in patiënten met een maligniteit en oudere patiënten (ongeveer 10%). In de andere bestudeerde subgroepen is dit percentage ongeveer 20%. Het aantal testen wat gedaan moet worden om bij 1 patiënt longembolieën uit te sluiten is dus het hoogste in de kankerpatiënten en de ouderen. In **hoofdstuk 5** is de frequentie van het optreden van alternatieve diagnoses op

de CT scan geëvalueerd in patiënten waar de diagnose longembolieën was uitgesloten middels CT scan. Er is bovendien gekeken of systematische beoordeling van de CT scan een belangrijk verschil in klinische relevante diagnoses liet zien ten opzichte van de diagnoses die door de dienstdoende arts tijdens het acute moment waren gegeven. De CT toonde een alternatieve klinische diagnose, welke mogelijk therapeutische consequenties heeft, in ongeveer 36% van de 76 patiënten zonder longembolieën. In 21 van de 46 patiënten met een alternatieve diagnose was er een verschil tussen de diagnose op de spoedeisende hulp en de diagnose na systematische beoordeling achteraf. In een bescheiden deel van deze patiënten(ongeveer een kwart) zouden deze verschillen therapeutische consequenties kunnen hebben.

Hoewel de KBR in combinatie met de D-dimeertest veilig is om longembolieën uit te sluiten moet nog steeds 70% van de patiënten met een verdenking aanvullende beeldvormende diagnostiek ondergaan vanwege de lage specificiteit. C-reactive proteïn (CRP) blijkt gerelateerd te zijn aan de aan- of afwezigheid van longembolieën. In **hoofdstuk 6** wordt dan ook geëvalueerd of een sensitieve CRP test gebruikt kan worden in de diagnostiek van longembolieën, ofwel als enige test of in combinatie met KBR en D-dimeer, om het percentage patiënten dat beeldvorming nodig heeft veilig te verkleinen. Een diagnostisch algoritme dat gebruikt maakte van de combinatie van alledrie de testen verhoogde het percentage van patiënten waarbij de diagnose uitgesloten kon worden van 32% naar 40% in de 790 geïncludeerde patiënten. Het percentage veneuze trombo-embolieën gedurende de 3 maanden follow-up in deze groep was 1.3% (95% BI: 0.3-3.2%). De veiligheid van het toevoegen van deze CRP-test aan de KBR en D-dimeer was dus goed, echter de efficiëntie was marginaal.

Of de D-dimeertest als enige test gebruikt kan worden in patiënten met een verdenking op longembolieën en dan met name in die patiënten die ook een maligniteit hebben is onderzocht in **hoofdstuk 7**. De sensitiviteit en de negatief voorspellende waarde van de D-dimeertest waren hoog in patiënten met en zonder maligniteit, echter de specificiteit van de test was lager in de patiënten met een maligniteit. De veiligheid en effectiviteit van de combinatie van KBR en D-dimeer in patiënten van verschillende leeftijdscategorieën met een verdenking op longembolieën is geëvalueerd in **hoofdstuk 8**, waarbij de veiligheid van deze testen om longembolieën uit te sluiten ook in de poliklinische patiënten ouder dan 75 jaar goed was. Voor opgenomen patiënten met een hogere leeftijd was de veiligheid niet voldoende. De proportie oudere poliklinische patiënten waar dankzij een onwaarschijnlijke klinische kans en een normale D-dimeer uitslag aanvullende beeldvorming kon worden onthouden was aanzienlijk lager in vergelijking met jongere

poliklinische patiënten.

Prognose

Als eenmaal de diagnose longembolieën is gesteld dan wordt anticoagulante behandeling gestart om (fatale) recidieven te voorkomen. Het geven van trombolytische therapie om complicaties van de ziekte te voorkomen heeft op dit moment alleen een plaats in de behandeling van die patiënten die op het moment van de diagnose hemodynamisch instabiel zijn. Bij hemodynamisch stabiele patiënten weegt de mogelijke effectiviteit niet op tegen het bloedingsrisico. Deze patiënten worden behandeld met vitamine K antagonisten. De incidentie van (fatale) recidief veneuze trombo-embolieën gedurende therapie in deze laatste groep is nog altijd ongeveer 4%. Om dit percentage verder te verlagen is het van belang in deze heterogene groep van hemodynamisch stabiele patiënten diegenen met een hoog risico op aan longembolieën gerelateerde uitkomsten te identificeren, bij wie trombolyse misschien toch zinvol kan zijn. Echocardiografisch vastgestelde rechter ventrikel dysfunctie zou een methode kunnen zijn om deze hoog risico patiënten te selecteren. In **hoofdstuk 9** is de literatuur aangaande de prognostische waarde van echografisch vastgestelde rechter ventrikel dysfunctie samengevat. De zeven geïncludeerde studies suggereerden een tenminste tweevoudig verhoogd risico op overlijden als gevolg van de longembolieën. Slechts twee studies maakten een schatting mogelijk voor hemodynamisch stabiele patiënten. De positief voorspellende waarde van rechter ventrikel dysfunctie voor aan longembolie gerelateerde mortaliteit in deze populatie was laag (5%). Andere potentiële indicatoren om patiënten te selecteren met een hoog risico op complicaties zijn de cardiale biomarkers troponine I en T en brain natriuretic peptide(BNP). Troponine I en T komen vrij bij ischemie van de hartspier, terwijl BNP vrijkomt bij verhoogde druk in de ventrikels. De studies welke zijn samengevat in **hoofdstuk 10** toonden prevalenties van verhoogde cardiale biomarkers in 16% tot 84% van de geïncludeerde patiënten met longembolieën. De positief voorspellende waarden voor overlijden gedurende de ziekenhuisopname varieerden van 6% tot 44%, terwijl de negatief voorspellende waarden voor een follow-up zonder aan longembolie gerelateerde complicaties boven de 93% waren. Hoewel er dus een correlatie tussen verhoogde biomarkers en mortaliteit gedurende de opname van longembolie patiënten bestond in de meeste van de studies, lijkt de positief voorspellende waarde toch niet voldoende om de indicatie voor trombolytische therapie uit te breiden naar alle patiënten met verhoogde biomarkers. In **hoofdstuk 11** en **12** is de relatie tussen BNP en complicaties van de longembolieën onderzocht in twee verschillende hemodynamisch stabiele populaties met

longembolieën. **Hoofdstuk 11** beschrijft 110 patiënten met acute longembolieën . In deze studiepopulatie bleek dat patiënten met hogere BNP concentraties een hoger risico op aan longembolieën gerelateerde mortaliteit gedurende drie maanden follow-up hadden, met een positief voorspellende waarde van 16% als de BNP concentratie boven de 67e percentiel was (i.e. 21.7pmol/L). **Hoofdstuk 12** is een case-control studie waarbij de relatie tussen BNP en (fatale) recidief veneuze trombo-embolieën is onderzocht. De gemiddelde BNP concentratie op de dag van diagnostiek was significant hoger voor de cases dan voor de controle patiënten. De odds ratio voor elke logaritmische eenheid toename van de BNP concentratie was 2.4 (95% BI: 1.5-3.7). Een tienvoudige toename van de BNP concentratie geeft dus een meer dan tweevoudig verhoogd risico op het ontwikkelen van een (fatale) recidief veneuze trombo-embolie. Hoewel deze relatie statistisch significant is, is dit klinisch onvoldoende om op basis van een verhoogde BNP concentratie bij een hemodynamisch stabiele longemboliepatiënt trombolytische therapie te starten. De prognostische waarde van verhoogde troponine I concentraties is onderzocht in 458 patiënten met hemodynamisch stabiele longembolieën in **hoofdstuk 13**. Een verhoogde troponine I concentratie was aanwezig bij 1 op de 7 patiënten en was geassocieerd met een verhoogd risico op overlijden, terwijl het risico op het krijgen van recidief veneuze trombo-embolieën niet toegenomen was in de patiënten met een verhoogde troponine concentratie.

Co-authors

Academic Medical Center, Amsterdam

Department of Vascular Medicine

Harry R. Büller, Victor E.A. Gerdes, Marcello DiNisio, Elske Quak, Marije ten Wolde

Department of Clinical Epidemiology and Biostatistics

Patrick Bossuyt, Carlo J.J. van Dongen, Johannes B. Reitsma, Jeroen C. van Rijn

Department of Pulmonology

Paul Bresser, Arthur A. Smit

Department of Radiology

Otto M. van Delden

Department of Cardiology

Barbara J.M. Mulder, Jasper W.M. Mulder, Igor I. Tulevski

Academic Hospital Maastricht

Arne van Belle, Martin H.Prins

Erasmus Medical Center, Rotterdam

Department of Internal Medicine, Section of Vascular and Metabolic Diseases

Frans Boomsma, Marieke J.H.A. Kruip, Frank W.G. Leebeek

Leiden University Medical Center, Leiden

Department of Vascular Medicine

Menno V.Huisman, Mathilde Nijkeuter, Lidwine Tick

Meander Medisch Centrum, Amersfoort

Department of Internal Medicine

Stijn Halkes, Mark H.H. Kramer

Rijnstate Hospital, Arnhem

Department of Pulmonology

Karin Kaasjager, Johanna M. Kwakkel-van Erp

Department of Geriatric Medicine

Patricia J.W.B. van Mierlo

Slotervaart Hospital, Amsterdam
Department of Internal Medicine
Melvin R. MacGillavry

University Medical Center, Nijmegen
Department of Internal Medicine
Pieter W.Kamphuisen

Ziekenhuis Hilversum
Department of Radiology
Peter M.Huisman

McMaster University, Hamilton, Ontario, Canada
Department of Medicine
James D. Douketis, Peter Grobara, Marilyn Johnston

Royal Hallamshire Hospital, Sheffield, United Kingdom
Edwin J.R. van Beek

NV Organon, Oss
Oscar Leeuwenkamp

Dankwoord

Mijn dankwoord begint bij Dees Brandjes, omdat dit proefschrift drie jaar geleden ook bij hem begonnen is. Dees, in de lift van B9 naar de eerste hulp vertelde je me dat je me 'beroemd' ging maken en voor we beneden waren had jij al een afspraak met de grote Harry Büller voor me gemaakt. Een maand later was ik aan het promoveren op de Vasculaire Geneeskunde in het AMC en daarvoor veel dank. Ik kijk uit naar de 'geregelde gedachtenwisseling', maar ik kijk er vooral naar uit om weer in de, onder jouw leiding, zo motiverende sfeer in het Slotervaart te komen werken.

Harry, toen ik een gesprek met je had over het al of niet gaan promoveren, sloeg mijn gevoel van twijfel acuut om in enthousiasme en zin om te beginnen. En met dat stimulerende gevoel ben ik vervolgens de afgelopen jaren altijd jouw kamer uitgelopen, nou ja bijna altijd. Ik heb veel artikelen samen met je mogen schrijven en de schrijfsessies aan jouw bureau, met klassieke muziek op de achtergrond en vulpen in de aanslag, heb ik zeer gewaardeerd en waren echt hoogtepunten. Ik heb bewondering voor je kennis, je inzicht en je overzicht van de wetenschap en de manier waarop je dat aan ons probeert over te brengen. Ik hoop dat ik bij de afdeling betrokken kan blijven om zo nog veel van jou en ook de andere stafleden te leren.

Victor, jou co-promotorschap is achteraf eigenlijk al begonnen toen ik in het Slotervaart ziekenhuis kwam werken. Als oudste en in mijn ogen zeker ook wijste assistent was je altijd bereid advies te geven, te overleggen of te helpen. En ook de afgelopen tijd stond je deur altijd open. Je gefundeerde wetenschappelijke mening, je opbouwende kritiek en je relativerende opmerkingen zijn zeer zeker belangrijk voor mij geweest.

Ook de andere stafleden die ervoor zorgen dat onze afdeling zo'n bijzondere sfeer heeft, waarin je je eigen pad kunt kiezen en waar je de vrijheid krijgt zelfstandig te werken, wil ik bedanken. John Kastelein, zeer respectabel hoofd van de Vasculaire Geneeskunde. Rianne, veel over hemofilie van je geleerd. Saskia, altijd duidelijk en onderbouwd advies op elk moment. Ik respecteer je zeer, ook op de piste en zeker op het hockeyveld;-). Erik, jij denkt snel, je praat snel, je loopt snel en je weet zo veel. Bovendien ben ik gek op je 'flauwe'grappen. Besprekingen zonder jou zijn toch anders. Joost, tijdens de besprekingen vraag ik me soms af of je behalve de absolute stollingssysteemkenner niet ook een verborgen clinicus bent. Mieke, altijd een vriendelijk woord en erg leuke multi-culti etentjes.

(S)Marnix, vanaf dag 1 was je mijn favoriete collega, nu veel meer dan dat. Je enthousiasme, je positiviteit, je motivatie, je gedrevenheid, je levensinstelling en je persoonlijk advies, maar vooral je vriendschap zijn TOP. Bedankt! Bovendien heb je ook nog eens een supervrouw. Margot ik ben je zeer dankbaar voor het lay-outen.

De stollingsdiensten tijdens mijn promotie waren zeker leuk en hebben gezorgd voor de continuïteit van mijn klinische leercurve, al was het af en toe ook wel 'lekker' afzien. Met de collega-stollingsartsen is het vanaf het begin super geweest. Snieckie, jouw pionierswerk om promotie onderzoek als werkervaring te laten tellen heeft effect gehad, Jeroen, zeer harde werker. Roel, bij jou de kamer binnenlopen was altijd gezellig en bovendien erg 'informatief'. Marije, co-co-promotor, toen ik op die rijdende trein stapte waar jij bijna van ging afstappen wist ik nog niet dat jij op elk station klaar zou staan om mij te motiveren, mijn opzetjes te bekritiseren en mij te helpen mijn bestemming te bereiken. Heel veel dank daarvoor. Clara, altijd positief en altijd aardig. Ivan, ontzettend attent. Tijmen, dat jij op die legendarische 'nieuwmarktborrels' toch altijd weer diezelfde draaitafel bij Nam Kee weet te regelen, fantastisch. Max, jij bent de erg leuke uitzondering op mijn vooroordeel. Anja, eerst vriendin, nu ook collega. De weekenden met jou en de andere topmeiden, Joyce, Charlotte, Maaike, Simone en Phyllis, zijn altijd zo ontspannen en supergezellig. Saskia, altijd grappig als 's nachts de telefoon gaat. Michiel, jouw collegialiteit en je bereidheid tot hulp bij van alles heb ik gewaardeerd. Nadine, opvolgster, dat jij een mooi proefschrift gaat schrijven daar twijfel ik niet aan. Ik hoop dat we veel samen kunnen blijven werken. En natuurlijk Iris. Lieve Ier, behalve een fijne collega ben je vooral een goede vriendin geworden in de afgelopen paar jaar. Natuurlijk sta ik ook voor jou klaar tijdens alle laatste of eerste loodjes.
De andere collega's, met wie ik heb samengewerkt, wil ik eveneens bedanken. Sabine, altijd gezellig samen met jou, en Bert-Jan. Marcello, 'El professore', en de cardiomannen Arno en Matthijs. Sikkelceller Ward, aanstekelijk vrolijk en beste afgrondskiër van de afdeling. En de (ook al mag ik het niet zeggen) lipidencollega's. Melchior, initiator van menig borrel, Sanne, fantastisch regisseur, Kees, Radjesh, Greetje, superoptimist, Angelique, E.m.i.l.y., Maud, Anouk, Lily, Fatima, Marijn, Karim, Menno. De 'mannenkamer'. Als de deur dicht gaat is wel duidelijk dat het 'werk'overleg weer begonnen is, en Jessica. Lieve Je$$, het was echt fijn om samen met jou die laatste loodjes af te ronden, daardoor waren ze een stuk minder zwaar.

Els, Agnes, Marianne, Margreet, Debby en natuurlijk Marianna, ik kon altijd even bij je binnenlopen en zelfs tot in Sydney was je er om alles voor ons altijd zo goed mogelijk te regelen, bedankt!

De vasculisten wil ik bedanken, omdat zij het werk op het vaatcentrum een stuk aangenamer maken, maar ook Riet, Dominique, Anita, Dian, Karin, Johan en Marja, de drijvende krachten van het vaatcentrum bedank ik voor de prettige samenwerking.

Super trialnurse Belia, zonder jou had ik zeker nog een jaartje extra nodig gehad, bedankt voor je enorme hulp en ook voor al die 'bijzondere' mailtjes. Trees, Bologna zal ik niet snel vergeten, net als je humor en al die kwartiertjes op jouw kamertje. En ook Liesbeth(je) en de andere medewerkers van het trial bureau zijn onmisbaar in de promotietrajecten voor velen van ons.

Erik-Jan en je stollingslab collega's, bedankt voor het zo trouw doorbellen van al die D-dimeren, waardoor de inclusie van de Christopher-studie zo voorspoedig kon verlopen.

Enkele hooggeschatte mannen van de KEB wil ik bedanken. Patrick Bossuyt, het is zeer prettig met jou samenwerken en bovendien leerzaam en productief. Hans Reitsma, bedankt voor al je statistische hulp met het BNP stuk. Ik weet nu dat ik de volgende keer al met de eerste versie van het studieprotocol naar je toe kom. Jeroen, succes met jouw afronding. Doctor, dokter Carlo, behalve voor statistisch advies kan ik nu ook al met icc-tjes bij je terecht, knap.

Beste Paul en Otto en ook Arthur, als ik op een menukaart 'soep van de dag' zie staan moet ik altijd lachen. Behalve ontzettend leerzaam voor mij, waarvoor veel dank, waren al die dinsdagmiddag uurtjes CT scans bekijken erg leuk.

Alle Christopher onderzoekers wil ik bedanken. Marieke, Mathilde, Stijn, Lidwine en Hanneke, bedankt voor jullie bijdrage en succes met jullie 4 proefschriften.

Geachte commissieleden, Professor dr. M.M.Levi, beste Marcel, ik vind het een eer dat je in mijn promotiecommissie zit. Professor dr. M.H. Prins, beste Martin, samen de Christopher database bijwerken in Maastricht was inspirerend. Professor dr. R.J.G. Peters, beste Ron, een fantastische dag de 7e! Professor dr. G.J. den Heeten en Dr. D.P.M. Brandjes. Allen

hartelijk dank voor het beoordelen van de inhoud van mijn proefschrift.

Jeroen, totaal jezelf kunnen zijn bij elkaar, zonder voorwaarden, la pura vida. El, je bent er altijd en al heel lang, echt top. Mirel, onze vele lach- en kickmomenten zijn niet uit te leggen, maar blijven een bron van blij gevoel. Bar, met jou samen is alles ontspannen en super, zelfs totaal uitgedroogd en oververhit op zoek naar kamelenstallen. Bas, bedankt en nu jouw boek. Joyce, als je weet dat het goed zit dan zit het gewoon goed en beter kan niet. Jokie, salsaqueen, we gaan er een toptijd van maken.

Dames M, superteam, superseizoen, superkampioen. Graci!

En dan mijn paranimfen, Rogier en Ruud. Rotje, ik haalde vroeger al, als het nodig was, altijd even trots mijn grote, sterke broer(tje) erbij; tegenwoordig ben je er uit jezelf! Ik vind het heel bijzonder en ben echt blij dat jij naast me staat. Ruud, vanaf 52 tot en met 190 cm gesteund en gehugd worden door zo'n lieve, uitermate intelligente, vrolijke, behoorlijk gestoorde, maar toch zeer woest aantrekkelijke satéprikker zonder vetrachels was echt fantastisch en is, zeker ook nu weer, superfijn.

Lies en Juul, mijn liefste, leukste, knapste nichten. Ik was het al vaak, maar ik weet zeker dat ik nog veel vaker heel trots zal zijn dat jullie mijn nichtjes zijn. Melle, lekker theekopje dat je bent, volgens mij wordt jij net zo gek als je vader en dat is een compliment. Angelique, toppunt van lief. Michelle, altijd geïnteresseerd en superattent.

Lieve pap en mam, hoe kan ik mijn dank aan jullie nou beschrijven. Ik kan de onvoorwaardelijke liefde, de steun voor alles wat ik doe, de vrijheid die ik kreeg en krijg of alles wat jullie me hebben laten zien van de wereld, waardoor ik zoveel genoten en geleerd heb, noemen. Of de ruimte om af te reageren, de altijd positieve woorden, de motivatie en het doorzettingsvermogen wat jullie me geven. Maar eigenlijk is het toch een beetje onbeschrijflijk en hoop ik vooral dat ik allang heb laten merken hoe ontzettend blij ik met jullie ben, want dat ben ik!