Diagnosis of venous thrombosis and the post-thrombotic syndrome

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Aan Renke, Meike, Julia en mijn ouders

Contents

CHAPTER 1

Introduction

Introduction

Venous thrombosis is a common disorder with an incidence in the general population of 1 to 3 in 1000 individuals per year[1].

Deep venous thrombosis is caused by pathological thrombus formation in the leg. When part of the thrombus is dislodged and migrates through the venous system to the pulmonary arteries, a pulmonary embolism arises. Hence deep venous thrombosis and pulmonary embolism are often regarded as different expressions of a single clinical entity called venous thrombosis.

In 1846 Virchow was the first to recognize that blood clots in the pulmonary artery originate as venous thrombi[2]. He proposed three pathophysiologic concepts that contribute to thrombosis, namely vessel wall injury, blood stasis, and changes in the composition of blood (hypercoagulability). Virchow´s famous triad has withstood the test of time and still contributes to our understanding of the pathophysiology of venous thrombosis[3].

Venous thrombosis, if not treated, is associated with high morbidity and mortality[4]. Treatment with anticoagulants can prevent mortality. However, anticoagulant treatment carries a substantial risk of major hemorrhage. The risk of bleeding is 2.7 major bleeds per 100 treatment-years[5]. Therefore it is important to confirm or exclude the diagnosis in patients with clinically suspected venous thrombosis.

Diagnosis of Venous Thrombosis

Imaging tests are necessary to diagnose venous thrombosis. The test of choice for clinically suspected deep venous thrombosis is venous ultrasonography. For pulmonary embolism, computed tomography is replacing ventilation perfusion scanning. Despite the accuracy of imaging tests, the post-test probability of disease is highly dependent on pretest probability[6].

The clinical appearance of venous thrombosis is heterogeneous and for a long time the clinical parameters have been considered to be useless. The introduction in the nineties of a standardized clinical probability test enabled physicians to stratify patients with clinically suspected venous thrombosis into clinical probability categories with concomitant low and high risk of venous

thrombosis[7,8]. This clinical probability test accurately categorizes patients' risk prior to diagnostic imaging.

Another strategy to determine the pretest probability in patients with clinically suspected venous thrombosis is to incorporate D-dimer test in the diagnostic algorithm. D-dimer is a degradation product of a cross-linked fibrin blood clot. The levels of D-dimer increase in the presence of coagulation activation and subsequent fibrinolysis. D-dimer tests have a high sensitivity in excluding thrombosis[9]. It has been suggested that a normal D-dimer level can be used to exclude thrombosis, where high D-dimer levels necessitate further investigation with diagnostic imaging.

The pretest probability determination can be optimized by combining clinical probability assessment and D-dimer test. The integration of clinical probability and D-dimer in diagnostic algorithms for venous thrombosis led to a reduced need for imaging techniques[10-15].

In patient with clinically suspected deep vein thrombosis, serial repeated testing with ultrasonography is required to detect the few patients with progression of calf vein thrombosis to the proximal veins[16,17]. However, routine serial testing is inefficient, inconvenient and not cost-effective[18,19]. To reduce the need for repeat ultrasonography, we developed a new diagnostic strategy introducing D-dimer test after ultrasonography in patients with an intermediate or high clinical probability test.

Pulmonary angiography is regarded as the gold standard test for the diagnosis of pulmonary embolism. This procedure is invasive, expensive and requires a skilled radiologist and a cooperative patient[20]. Ventilation perfusion scanning has been the imaging procedure of choice. The major disadvantage of this procedure is that further testing is needed in 40% to 60% of patients due to non-diagnostic test results. As a consequence computed tomography replaced ventilation perfusion scanning. The position of computed tomography was unclear and complex and impractical algorithms were used in the diagnosis of pulmonary embolism[21-24]. We developed a novel simplified diagnostic algorithm using a dichotomized clinical decision rule, D-dimer testing and computed tomography.

The Post-Thrombotic Syndrome

The most common complication of venous thrombosis is the post-thrombotic syndrome (PTS) and PTS develops in up to one half of patients after symptomatic deep vein thrombosis. PTS becomes established within 1 to 2 years after deep vein thrombosis[25].

The clinical manifestations of PTS are probably due to high walking venous pressure. Venous hypertension occurs as a consequence of venous valvular incompetence with diminished calf muscle pump function and persistent obstruction. This results in alterations of the skin microcirculation and morphological skin changes[26]. Typical features of PTS include symptoms such as heaviness and pain of the leg and signs such as oedema, hyperpigmentation and new venous ectasia. In severe cases venous ulcers may develop[27].

As PTS reduces quality of life[28], and is costly to society[29], it is important to identify patients at risk for PTS at an early stage. However, there is no 'gold standard' test that establishes the diagnosis of PTS. Venous hypertension will be present before clinical symptoms are manifest. Non-invasive venous examinations, such as duplex scanning and strain gauge plethysmography, can be useful to predict the development of PTS. With duplex scanning it is possible to measure the extend of the initial thrombus, residual thrombosis and valvular reflux, while strain gauge plethysmography quantifies venous outflow resistance and calf muscle pump function.

In contrast to the many identified risk factors for deep venous thrombosis[30], the only identified risk factors for the development of PTS are recurrent, ipsilateral deep venous thrombosis and an increased body mass index. Other factors such as age, sex, idiopathic thrombosis, localization of thrombosis, duration of anticoagulant therapy, factor V Leiden or prothrombin 20210A mutation residual vein thrombosis, valvular reflux, venous outflow resistance and calf muscle pump function show inconsistent results in previous studies[31-36].

Elastic compression stockings are not only effective in preventing deep venous thrombosis but also play an important role in the prevention of PTS. These stockings assist the calf muscle pump function and reduce venous hypertension and reflux, thereby reducing edema and improving tissue

microcirculation. Randomized controlled trials have shown that daily use of elastic compression stockings after deep venous thrombosis reduces the risk of PTS by approximately 50%[33,37].

Although PTS is a common condition, it received little attention within the field of venous thromboembolism research. The start of the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study provided us with the opportunity to assess the cumulative incidence of PTS and to study risk factors in the development of PTS. At the same time we designed a follow-up study to elucidate the functional hemodynamic changes that lead to PTS and to identify patients at risk for PTS at an early stage.

Outline of the Thesis

The aim of the first part of this thesis is to investigate new diagnostic strategies for patients with suspected venous thrombosis. For this purpose two multicenter studies addressing different aspects of the diagnostic work up have been performed.

Chapter 2 describes the safety of ruling out deep vein thrombosis in patients with clinically suspected thrombosis, using a management strategy, which combines clinical probability test, compression ultrasonography, and D-dimer measurements. It also reports the reduced need for repeat ultrasonogaphy. This management strategy is notable for introducing the D-dimer test after the ultrasonography, and only selectively in patient with intermediate or high probability on the clinical prediction rule. **Chapter 3** presents the findings of a large clinical follow-up study in patients with suspected pulmonary embolism. 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 level or a normal computed tomography is evaluated. Whether the cut-off levels of the clinical decision rule as well as the D-dimer test should be varied to increase the clinical utility in excluding pulmonary embolism is discussed in **Chapter 4**. The clinical consequences of strongly elevated D-dimer levels combined with a clinical probability score in the management strategy in patients with suspected pulmonary embolism are addressed in **Chapter 5**.

The second part concerns the incidence, risk factors and early predictors of the PTS. **Chapter 6** reports the cumulative incidence of PTS after a first deep vein thrombosis and the contribution of risk factors in the development of PTS. The analyses are performed in the Multiple Environmental and

Genetic Assessment (MEGA) study of risk factors for venous thrombosis, a large population-based study. Patients aged 18 to 70, with a first episode of deep venous thrombosis of the leg, are included from six participating anticoagulation clinics in the Netherlands, between March 1999 and June 2002. **Chapter 7** describes the predictive value of non-invasive venous examination for the development of PTS, assessed in a 2-year follow-up study.

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CHAPTER 2

Practical diagnostic management of patients with clinically suspected deep-vein thrombosis by clinical probability test, compression ultrasonography, and D-dimer test

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Purpose To evaluate a new non-invasive diagnostic strategy for ruling out deep vein thrombosis consisting of either a combination of low clinical probability and normal ultrasonography or a combination of moderate-to-high clinical probability, normal ultrasonography, and normal D-dimer test.

Subjects and Methods We studied 811 patients with clinically suspected deep vein thrombosis using a diagnostic management strategy that combined clinical probability, ultrasonography, and measurement of D-dimers. The primary endpoint was venous thromboembolism occurring during a 3-month follow-up.

Results Of the 280 patients (35%) with a low clinical probability, 30 (11%) had an abnormal initial ultrasonography and were treated. Of the other 250 untreated patients with low clinical probability and a normal ultrasonography, 5 (2%; 95% confidence interval [CI]: 1% to 5%) developed a nonfatal venous thromboembolism during follow-up. Of the 531 patients (65%) with a moderate-to-high clinical probability, 300 (56%) had an abnormal ultrasonography. Of the remaining 231 patients with a normal ultrasonography, 148 had a normal D-dimer test; none of these patients developed deep vein thrombosis during follow-up (0%; 95% CI: 0% to 3%). Of the 83 patients with an abnormal D-dimer test, 77 underwent repeat ultrasonography about 1 week later; none of the 64 patients with a second normal ultrasound developed symptomatic deep vein thrombosis during follow-up (0%; 95% CI: 0% to 6%).

Conclusion This management strategy, which combines clinical probability, ultrasonography, and D-dimer measurements, is practical and safe in ruling out deep vein thrombosis in patients with clinically suspected thrombosis and reduces the need for repeat ultrasonography.

Introduction

Because the clinical diagnosis of deep vein thrombosis is nonspecific, objective diagnostic tests are needed to confirm or refute the diagnosis. Noninvasive compression ultrasonography, which is widely used in the diagnostic work-up of these patients (1,2), has a high sensitivity and specificity for proximal vein thrombosis (3). However, owing to high intra- and interobserver variability, ultrasonography is less reliable for calf vein thrombosis, 20% to 30% of which progress to the proximal veins (3,4). It has therefore been considered necessary to follow patients who have the first normal ultrasonography to identify the relatively few patients in whom the test becomes abnormal (5,6). For example, in one study of 1702 patients with clinically suspected deep vein thrombosis, only 12 (0.9%) had an abnormal repeat ultrasonography 1 week after a normal test (6).

Two options have been proposed to avoid unnecessary repeat ultrasonography: the use of a D-dimer test and basing decisions on clinical probability. D-dimers are degradation products of cross-linked fibrin generated by plasmin, and their presence has a high sensitivity, moderate specificity, and high negative predictive value for deep vein thrombosis (7-14). Bernardi et al. (8) used the enzyme-linked immunosorbent assay (ELISA) D-dimer test in combination with ultrasonography. This combination resulted in an 87% reduction in repeat ultrasonography, with an incidence of venous thromboembolism during 3-month follow-up of only 0.4% in patients with normal ultrasonography and a normal ELISA D-dimer test. In another study, a normal ELISA D-dimer test had a negative predictive value of 99.3% at 3 months (9). The diagnostic algorithm for suspected deep vein thrombosis can also be simplified by use of a standardized clinical probability test. For example, Wells et al. developed a clinical model that enables physicians to stratify patients with clinically suspected deep vein thrombosis into categories with concomitant low (3%), intermediate (17%), and high (75%) risk of deep vein thrombosis (15,16).

We studied a combination of a clinical probability test, ultrasonography, and a D-dimer test in patients who were referred to nonacademic teaching hospitals with clinically suspected deep vein thrombosis. We evaluated the safety of withholding anticoagulant treatment in patients with a low clinical probability test and a normal ultrasonography, as well as in patients with a moderate-to-high clinical probability, a normal ultrasonography, and a normal D-dimer test. In patients with a moderate-to-high

clinical probability and an abnormal D-dimer test, ultrasonography was repeated 8 days later. Our primary endpoint was the incidence of venous thromboembolism during a 3-month follow-up.

Subjects and Methods

We performed a prospective cohort study in 921 consecutive outpatients with suspected deep vein thrombosis of the leg who were referred by their family physicians to one of the participating centers. Our study was carried out at four nonacademic teaching hospitals in The Netherlands: Eemland Ziekenhuis (presently known as Meander Medical Center) in Amersfoort, Ziekenhuis Hilversum, St. Elisabeth Ziekenhuis in Tilburg, and Amphia Ziekenhuis in Breda. After approval by the medical ethical committee, patients seen from November 1997 to August 2000 were included. All patients with suspected deep vein thrombosis were eligible for the study. Patients with any of the following criteria were excluded: treatment with anticoagulants for more than 48 hours before diagnosis, suspected pulmonary embolism, history of documented venous thromboembolism in the previous 6 months, age younger than 18 years, or allergy to contrast media. Eligible patients who gave informed consent were enrolled.

Clinical Probability Test

All patients were assessed clinically by the attending physician at the emergency department before undergoing ultrasonography and D-dimer testing. We used the Wells' criteria to estimate the pretest probability for deep vein thrombosis (Table 1) (15,16).

Table 1. The Wells' Clinical Probability Test

Clinical feature	**Score***
Active cancer	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremity	1
Immobilisation for more than 3 days or major surgery within 4 weeks	1
Localised tenderness along the distribution of the venous system	1
Thigh and calf swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting oedema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of deep vein thrombosis	-2

* A score of zero or less indicates a low clinical probability; a score of one point or more indicates a moderate-to-high clinical probability.

We combined the intermediate- and high-probability group into a “moderate-to-high” clinical probability category. The nine items included in the clinical model fell into three groups: signs of deep vein thrombosis, risk factors for deep vein thrombosis, and potential alternative diagnosis. Each item scored one point; when an alternative diagnosis was given, two points were subtracted. Patients were categorized as low clinical probability for deep vein thrombosis with a score of zero or less. Patients had a moderate-to-high probability when the score was one point or more.

Diagnostic Management Strategy

Patients with a low clinical probability underwent a single ultrasonography (see below). In our algorithm, a normal ultrasonography excluded the diagnosis of deep vein thrombosis, whereas an abnormal ultrasonography confirmed the diagnosis of deep vein thrombosis. These latter patients were treated with anticoagulants according to standard protocol, consisting of 5 to 10 days of therapeutic low-molecular-weight heparin followed by oral anticoagulants for 3 to 6 months.

Patients with a moderate-to-high clinical probability also underwent ultrasonography. A normal result was followed by D-dimer testing. According to our algorithm, a normal D-dimer test excluded the diagnosis of deep vein thrombosis. Those who had an abnormal D-dimer test underwent a repeat ultrasonography on day 8; a normal repeat study excluded the diagnosis of deep vein thrombosis. An abnormal initial or repeat ultrasonography confirmed the diagnosis, and patients were treated according to a standard protocol. Anticoagulants were withheld in all patients in whom the diagnosis of deep vein thrombosis was excluded; these patients were followed for 3 months to monitor the development of any symptomatic venous thromboembolic complications (Figure).

Ultrasonography

Ultrasonography, using real-time B mode with compression only, was performed using a standard 5- to 12-MHz linear array transducer. Veins were scanned in the transverse plane only. We examined the common femoral vein in the groin, and the popliteal vein at the knee joint extending down to the trifurcation of the calf veins (3). Results were judged as abnormal and called proximal vein thrombosis if a noncompressible segment was identified. The test was considered normal if all segments were fully compressible and no residual lumen was seen. No attempt to identify isolated calf vein thrombosis was made (3,6).

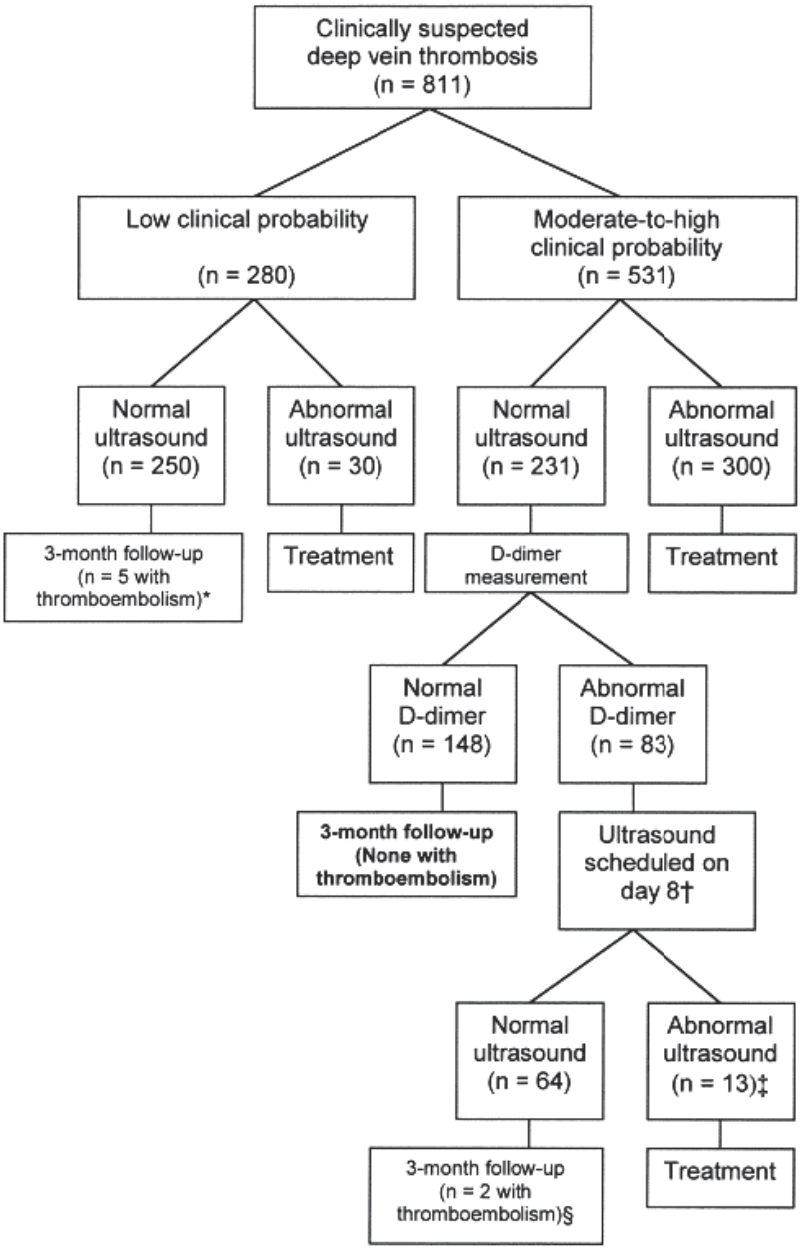

Figure. Study flow chart for patients with suspected deep-vein thrombosis. The 5 patients (*) with thromboembolism despite a normal ultrasound are described in Table 3. Repeat ultrasound was not performed in 6 patients (†). Two patients (‡) returned earlier with increased leg complaints, and 1 patient returned with pulmonary complaints. One patient who had refused the second ultrasonography on day 8 returned on day 14 with increased leg complaints. Two patients (§) had asymptomatic deep vein thrombosis diagnosed during follow-up.

D-dimer Test

We used the SimpliRED red cell agglutination assay (Agen Biomedical LTD, Brisbane, Australia) (10-14). All assays were performed using venous blood samples collected in laboratory citrate tubes according to the manufacturer's instructions by experienced laboratory technicians who were unaware of the results of the clinical probability test and ultrasonography. This assay is designed for use with freshly collected capillary or venous whole blood (10). The whole blood sample is mixed with a conjugate of a monoclonal antibody to D-dimer (3B6/22) linked to a monoclonal antibody to red blood cells (RAT-IC3/86). The detection limit is a whole blood D-dimer concentration of 0.2 mg/l corresponding to 0.4 mg/l Fibrinogen Equivalent Units (FEU). If any agglutination was present after 2 minutes, the test was considered to be positive.

Follow-up and Primary Endpoint

All patients had a 3-month follow-up and were asked to return to the study center at 3 months or immediately if they had signs or symptoms of venous thromboembolism or complications. Patients who did not return for follow-up assessment (n=24) were interviewed by telephone. Confirmatory testing with ultrasonography, phlebography, (spiral) computed tomographic scanning, ventilation perfusion (V-Q) lung scanning, or pulmonary angiography was performed in patients with suspected venous thromboembolic complications.

Statistical Analysis

We calculated the required sample size assuming an expected prevalence of 33% for deep vein thrombosis. We hypothesized that, among patients found by our management strategy not to have deep vein thrombosis, the rate of venous thromboembolism during a 3-month follow-up would be less than 2%. We calculated that 800 patients would be necessary to provide 95% confidence intervals (CI), which exclude a frequency of 5% of symptomatic thromboembolic events.

The outcome was the total rate of symptomatic venous thromboembolic complications during a follow-up of 3 months. We calculated the 95% confidence intervals with the binominal distribution.

Results

We evaluated 921 symptomatic outpatients for eligibility and excluded 75 patients for the following reasons: 19 had been treated with anticoagulants for more than 48 hours before diagnosis; 10 had

suspected pulmonary embolism; 1 had a history of documented venous thromboembolism in the previous 6 months; and 45 did not participate for other reasons, such as geographic inaccessibility, dementia, very old age, or mental incompetence. Of the remaining 846 eligible patients, 35 (4%) refused to participate. Thus, 811 patients were enrolled, of whom 522 (64%) were women. The mean (± SD) age was 62 ± 17 years (range, 18 to 99 years). The clinical probability test scored an alternative diagnosis as likely or greater than that of deep vein thrombosis in 361 patients (45%) (Table 2).

Table 2. Alternative Diagnoses among the 811 Patients

Alternative diagnosis	Number (%)
Erysipelas, cellulitis	89 (24)
Muscle tear, hematoma, trauma	65 (18)
Baker cyst	31 (9)
Superficial thrombophlebitis	30 (8)
Post-thrombotic syndrome	22 (6)
Lymphedema, lymphangitis	10 (3)
Edema due to heart failure	9 (2)
External compression due to malignancy	1 (1)
Other (gout, varices, arthritis, arterial thrombosis)	53 (15)
Not specified	51 (14)
Total*	361

* Some patients had more than one alternative diagnosis.

Patients with a Low Clinical Probability

Of the 811 enrolled patients, 280 (35%) had a low clinical probability of thromboembolism, of whom 30 (11%) had an abnormal ultrasonography (Figure).

During the 3-month follow-up of the remaining 250 untreated patients, 4 patients developed a deep vein thrombosis and 1 had a nonfatal pulmonary embolism, for a venous thromboembolic complication rate of 2% (95% CI: 1% to 5%). These 5 patients had increasing complaints within 2 weeks of the initial normal ultrasonography and returned to the hospital according to the physicians' instructions (Table 3).

Table 3. Patients with a Low Clinical Probability Test and an Initial Normal Ultrasonography in Whom Venous Thromboembolic Complications Were Diagnosed by Ultrasonography or V-Q Scanning during the 3-Month Follow-up

Patient	Diagnosis
31-year-old woman; third-term pregnancy, increased leg swelling on day 8	Ultrasonography shows femoral vein thrombosis
72-year-old man; treated for erysipelas,, increased leg swelling on day 15	Ultrasonography shows external iliac vein thrombosis
51-year-old woman; trauma, increased leg pain and swelling on day 5	Ultrasonography shows popliteal vein thrombosis
42-year-old woman; increased leg pain and pleuritic chest pain on day 10	Ultrasonography shows popliteal vein thrombosis; V-Q is not high probability for pulmonary embolism
44-year-old woman; increased leg pain and dyspnea on day 4	Ultrasonography is normal; V-Q is high probability for pulmonary embolism

Moderate-to-High Clinical Probability Test

Five hundred and thirty-one patients (65%) had a moderate-to-high clinical probability of thromboembolism, of whom 300 (56%) had ultrasonographic evidence of deep vein thrombosis (Figure). The remaining 231 patients had D-dimer measurements, of whom 148 (64%) had a normal D-dimer test. None of these 148 patients were treated, and none had a venous thromboembolism during the 3-month follow-up (0%; 95% CI: 0% to 3%).

In 83 (36%) of the 231 patients, the D-dimer test was abnormal. These patients were not treated with anticoagulants pending the results of a second ultrasonography that was scheduled on day 8. Nine of these patients had a deep vein thrombosis diagnosed with repeat ultrasonography. Three of these patients had returned to the hospital on days 2, 4, and 7 with increased complaints. Two complained of leg pain and swelling, which a second ultrasonography revealed to be a deep vein thrombosis. The third patient had symptoms of pulmonary embolism, and pulmonary angiography confirmed the diagnosis. In 7 patients, a repeat ultrasonography test was not performed because of patient refusal or logistic reasons. One patient, who had refused the second ultrasonography, returned to the hospital on day 14 with increased leg pain and swelling; an ultrasonography confirmed a deep vein thrombosis. The 6 remaining patients were followed for 3 months but did not develop venous thromboembolic complications.

None of the 64 patients with two normal serial ultrasonography results developed symptomatic deep vein thrombosis during follow-up (0%; 95% CI: 0% to 6%). However, 2 of these 64 patients developed asymptomatic deep vein thrombosis during follow-up. Both patients had cancer and had asymptomatic thrombosis diagnosed with routine computed tomographic scan during evaluation of their tumor.

Death during Follow-up

No deaths due to venous thromboembolic complications were reported during the 3-month follow-up. Of the 6 patients who died during that period, 4 had been diagnosed with, and treated for, deep vein thrombosis: 1 died of lung carcinoma, 1 of pancreas carcinoma, 1 of myocardial infarction, and 1 of unknown case. Of the 2 patients in whom deep vein thrombosis was not diagnosed, 1 died of lung carcinoma and the other patient died of unknown causes without suspected venous thromboembolism.

Discussion

This study shows that the combination of a low clinical probability test, as assessed by a standardized clinical score at the emergency department, combined with a normal ultrasonography can be used safely to exclude deep vein thrombosis in outpatients referred for evaluation of suspected deep vein thrombosis. Of 250 patients who met these criteria, only 5 had a thromboembolism during the 3-month follow-up. In patients with a moderate-to-high clinical probability for deep vein thrombosis, the combination of a normal ultrasonography and normal D-dimer test also excluded deep vein thrombosis, with no episodes of venous thromboembolic complications during follow-up, in 148 patients with these criteria. These rates of venous thromboembolic complication are consistent with those seen in other studies (6).

Ultrasonography fails to detect isolated calf vein thrombosis in some patients, and serial testing is considered necessary to detect clinically important venous thrombi that may extend proximally (4,17). In our study, combining clinical probability assessment, ultrasonography, and D-dimer measurements reduced the need for repeat ultrasonography by 83% (from 250 + 231 = 481 patients to 83 patients). Bernardi et al. (8) showed a similar 87% reduction in repeat ultrasonography using ELISA D-dimer as

an adjunct to ultrasonography. Fewer repeat ultrasonography examinations are convenient for patients and also cost-effective (18).

We used a qualitative assay for D-dimers. However, in a previous study, the combination of a low clinical probability test and a negative qualitative D-dimer test rules out deep vein thrombosis in symptomatic outpatients, with a venous thromboembolic complication rate of <1% (19). Although rapid ELISA D-dimer tests have greater sensitivity, we chose the qualitative assay because it was the most extensively studied test when our study was designed (11,12). This assay must be performed by experienced personnel, with whom it has a reported sensitivity of 97% (95% CI: 85% to 99%) (20). Alternatively, quantitative D-dimer tests, which have sensitivities ranging from 95% to 100%, can be used in our management strategy (13).

Patients with a positive D-dimer test but a normal repeat ultrasonography on day 8 were at low risk for venous thromboembolic complications during the 3-month follow-up, as was also seen in a previous study (8). We found a higher prevalence (41%) of deep vein thrombosis than did other studies (6,14-16), perhaps because all patients had been referred by a family physician. We believe that the safety of the algorithm that we used is strengthened by this higher prevalence of deep vein thrombosis. Our study was carried out in the emergency departments of nonacademic teaching hospitals and involved several physicians. This approach appears to be safe, provided a checklist is used for every patient to ensure that the management strategy is followed properly. Moreover, the attending physician should always instruct patients to return to the hospital if their symptoms worsen.

Many noninvasive combination strategies can be used to diagnose deep vein thrombosis. This management study shows that the combination of a low clinical probability test and a normal ultrasonography excludes the diagnosis of deep vein thrombosis in symptomatic outpatients. In patients with a moderate-to-high clinical probability who have normal ultrasonography and a normal D-dimer test, anticoagulant therapy can be withheld safely. This diagnostic strategy may simplify the management of the majority of patients with suspected deep vein thrombosis. It enables making treatment decisions on the day of referral without a substantial increase in the risk of venous thromboembolism-related morbidity and mortality, while saving health care costs.

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CHAPTER 3

Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography

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

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

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

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

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

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

Conclusions

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

Introduction

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

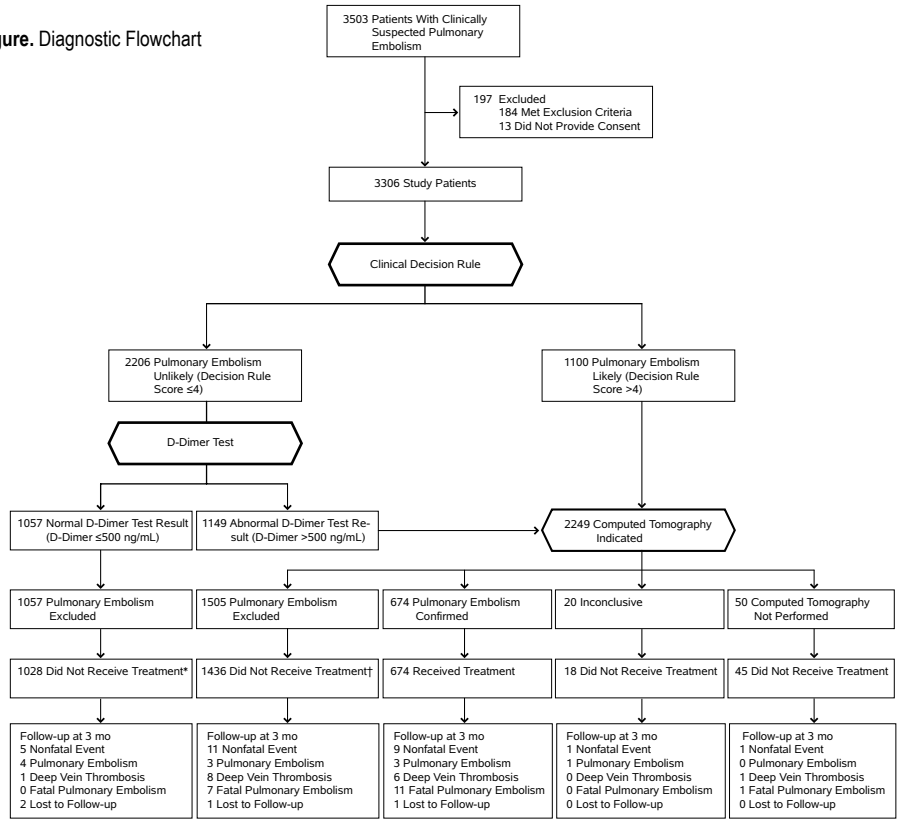
Another advancement is computed tomography (CT), which has emerged as a prominent imaging technique for the exclusion or confirmation of pulmonary embolism, as well as the detection of alternative diagnoses.[6-10] However, a critical missing piece of information has been whether it is safe to withhold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

Methods

Study Design

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

Figure. Diagnostic Flowchart



*Excludes 29 patients with anticoagulant therapy for reasons other than venous thromboembolism

†Excludes 69 patients with anticoagulant therapy for reasons other than venous thromboembolism

Patients

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

directly to the emergency department for evaluation. Patients were recruited between November 2002 and September 2004.

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

Clinical Decision Rule and D-Dimer Assay

Patients with clinically suspected pulmonary embolism were evaluated by an attending physician using a validated clinical decision rule (Table 1).[3]

Table 1. Clinical Decision Rule*

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

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

Pulmonary embolism was classified as "unlikely" with a clinical decision rule score of 4 or less points, and "likely" with a score of more than 4 points. This cutoff was chosen because it has been shown to give an acceptable VTE diagnostic failure rate of 1.7% to 2.2% in combination with a normal D-dimer

test result.[3] An estimated 300 attending physicians in the participating hospitals used the clinical decision rule with the study participants.

In patients with a clinical decision rule indicating pulmonary embolism unlikely, a D-dimer concentration was measured, using either the VIDAS D-dimer assay (Biomerieux, Marcy L'Etoile, France) or the Tinaquant assay (Roche Diagnostica, Mannheim, Germany). A D-dimer concentration of 500 ng/mL or less was defined as normal. In patients with pulmonary embolism unlikely and a normal D-dimer test result, the diagnosis of pulmonary embolism was considered excluded and anticoagulant treatment was withheld. Those patients who had a combination of clinical decision rule indicating pulmonary embolism unlikely with an abnormal D-dimer test result, or who had a clinical decision rule indicating pulmonary embolism likely, underwent CT.

Radiological Evaluation

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

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

not be performed or who had an inconclusive CT scan was left to the discretion of the attending physician.

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

Outcome Measures

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

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

Statistical Analysis

The 2 primary analyses were incidence of symptomatic VTE during follow-up, confirmed by objective testing, in (1) the group of patients in whom anticoagulant treatment was withheld based on a

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

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

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

Results

Study Patients

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

Table 2. Baseline Demographic and Clinical Characteristics of Study Population (N = 3306)* study patients

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

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

Results of Diagnostic Algorithm

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

Of the 2249 patients with either abnormal D-dimer concentrations (n = 1149) or a clinical decision rule indicating pulmonary embolism likely (n = 1100), 2199 underwent CT. In the other 50 patients a CT was indicated but not performed because of lack of venous access, extreme obesity, DVT confirmed by CUS prior to CT, or a deteriorating clinical condition prior to CT. Multidetector-row CT was

performed in 1939 patients and single-detector row CT in 260 patients. Computed tomography excluded pulmonary embolism in 1505 patients (45.5% of the study population). In these patients, 702 (21.2% of the study population) had additional diagnostic information visualized on CT: pneumonia (n = 212), pleural effusion (n = 163), malignancy (n = 50), and other diagnoses (n = 277). Pulmonary embolism was confirmed in 674 patients (20.4% of the study population). Computed tomography was inconclusive in 20 patients (0.9%). Hence, the diagnostic algorithm could be completed according to the protocol in 3256 patients (98.5%) and allowed a management decision in 3236 patients (97.9%).

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

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

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

Variable	No.	Total VTEs, No. (%) [95% CI]	Fatal Pulmonary Embolism, No. (%) [95% CI]
Pulmonary embolism unlikely and normal D-dimer test result	1028	5 (0.5) [0.2 to 1.1]	0 (0) [0.0 to 0.3]
Pulmonary embolism 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]
Pulmonary embolism diagnosed by CT	674	20 (3) [1.8-4.6]	11 (1.6) [0.8-2.9]

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

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

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

Patients With CT Excluding Pulmonary Embolism

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

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

Twenty patients returned with symptoms of pulmonary embolism during follow-up. Computed tomography was again used as the diagnostic method in 13 of these 20 patients and was normal in

all. No VTE was demonstrated at later follow-up. The overall mortality rate in patients in whom CT excluded pulmonary embolism was 8.6% (129 patients).

Table 4. Deaths Attributed to Pulmonary Embolism

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

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

Patients With CT That Was Inconclusive or Not Performed

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

Patients With Pulmonary Embolism Confirmed by CT

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

Comment

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

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

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

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

Despite concerns that the sensitivity of CT for pulmonary embolism is lower than that of pulmonary angiography,[18-19] the observed risk of subsequent symptomatic VTE in those patients in whom pulmonary embolism was excluded by CT was comparable to the risk reported after a normal pulmonary angiogram (3-month incidence, 1.3% [95% CI, 0.7%-2.0%] vs 1.7% [95% CI, 1.0%-2.7%],[16] respectively). In addition, in our study fatal pulmonary embolism occurred in 0.5% (95% CI, 0.2%-1.0%) of patients in whom CT had excluded pulmonary embolism, compared with 0.3% (95% CI, 0.02%-0.7%) after normal pulmonary angiography.[16] Computed tomography has the potential advantage of providing additional diagnostic information for the presenting symptoms in patients without pulmonary embolism.

Several potential limitations in our study require comment. First, the absence of pulmonary embolism was not verified by pulmonary angiography. However, the clinical outcome after a 3-month follow-up is widely accepted as an appropriate alternative to establish the safety of a diagnostic strategy, given a near-complete follow-up.[20]

Second, while our cohort study has the strength of minimal loss to follow-up (3 patients, 0.1%) and independent blinded adjudication of all outcomes, a randomized controlled study design would have allowed a direct comparison to other validated strategies.

Third, CT was again used to exclude pulmonary embolism in 13 of 20 patients who returned during follow-up with symptoms after CT had excluded pulmonary embolism at baseline. Although these could represent false-negative results, these patients were not treated and further follow-up was uneventful, making this unlikely.

Fourth, the use of multidetector-row CT has the potential for overdiagnosis by imaging very small peripheral subsegmental emboli. Because patients did not undergo confirmatory pulmonary angiography, our study design did not permit assessing the false-positive rate of CT scans. Only 10% of our patients underwent single-detector row CT, so we could not make a meaningful comparison of the impact of each test. However, the overall prevalence of pulmonary embolism in our study (20%) is comparable to the prevalence in a previous multicenter study performed with single-detector row CT (24%).[9] This does not support a concern that multidetector-row CT technology will lead to a high number of false-positive results.

Finally, a definitive cause of death could not be established for all patients with normal test results who died during follow-up. However, pulmonary embolism was assigned as the cause of death if it could not be confidently excluded, a conservative assumption that strengthens our conclusions about low risk for this strategy.

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

In conclusion, a diagnostic management strategy using a simple clinical decision rule, D-dimer testing, and CT is as effective as other more complex diagnostic strategies in the evaluation and

management of patients with clinically suspected pulmonary embolism. Its use is associated with low risk for subsequent fatal and nonfatal VTE.

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CHAPTER 4

Excluding pulmonary embolism without imaging tests; can our diagnostic algorithm be optimized?

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Rationale Excluding pulmonary embolism by a cut-off level of the Wells clinical decision rule of four points to designate patients as "pulmonary embolism unlikely" combined with a D-dimer concentration of 500 ng/ml or less has been demonstrated to be safe.

Objective To investigate whether varying the cut-off level of the clinical decision rule as well as the D-dimer test could lead to an increase in clinical utility without jeopardizing safety.

Methods Data were obtained from a diagnostic outcome study of patients suspected of pulmonary embolism. The number of patients with PE at baseline or during follow-up, clinical utility and 3-months thrombo-embolic failure rate were calculated for different cut-off points of the clinical decision rule and D-dimer test.

Results By increasing the cut-off level of the clinical decision rule from 4 to 5 points, pulmonary embolism could be ruled out in an additional 4% of the study population (from 29.3 to 33.3%) at an expense of an increased 3-months venous thrombo-embolic failure rate of 1.5% (95%CI: 0.6-3.0%). By increasing the D-dimer cut-off level from 500 to 600 ng/ml, PE could be ruled out in an additional 3% of the study population but the 3-months thrombo-embolic failure rate increased to 2.2% (95%CI: 1.1-4.0).

Conclusions The cut-off level of the clinical decision rule as well as the cut-off level of the D-dimer test should be kept at the original 4 points and 500 ng/ml respectively, in order to prevent exposure of patients to a 3-months thrombo-embolic failure rate exceeding that of normal pulmonary angiography.

Introduction

Pulmonary embolism (PE) is a potentially fatal disease and one of the leading causes of cardiovascular mortality. Due to the non-specificity of clinical signs and symptoms, only 20-30% of patients with clinically suspected PE are diagnosed with the disease. Excluding PE has been simplified in recent years by the introduction of non-invasive tests as standardized clinical decision rules (CDR) and quantitative D-dimer assays. Several management studies have demonstrated that the combination of a low to moderate clinical probability of PE and a normal D-dimer test result safely rules out PE with a 3-months thrombo-embolic failure rate of less than 1% ([1-4]). Importantly, with this approach, it has been established that additional imaging tests including computed tomography (CT) or ventilation-perfusion lung scans can be withheld in approximately 15 to 50% of patients. Increasing the clinical utility, i.e. the proportion of patients in whom the diagnosis of PE can be safely excluded without additional imaging tests, would be desirable, provided that the safety of excluding PE with this approach is not jeopardized. The original CDR according to Wells categorized patients with clinically suspected PE into three groups, i.e. patients with a low (< 2 points), intermediate (2-6 points) and high clinical probability (>6 points) occurring in 59%, 33% and 8% of the study population respectively ([5]). In comparison to patients with a low probability and normal D-dimer test results, occurring in 29% of the study population, in a post-hoc analysis it was shown that PE could be confidently ruled out in an additional 20% of patients by using a dichotomized cut-off level of 4 points or less. The safety of using this cut-off level in combination with a normal quantitative D-dimer test has recently been demonstrated in a large prospective cohort study in patients with clinically suspected PE. The 3-months thrombo-embolic failure rate in this study was 0.5% (95%CI: 0.2-1.1%) ([6]). We retrospectively analyzed the data of this study to evaluate 1) the safety and clinical utility of increasing the cut-off level of the CDR to designate patients as "PE unlikely" while the D-dimer cut-off level remained at 500 ng/ml; and 2) the safety and clinical utility of increasing the cut-off level of the D-dimer test to levels above 500 ng/ml while the CDR cut-off level was kept at 4 points.

Methods

Patients

Data were obtained from a prospective cohort follow-up study performed between November 2002 and December 2004 in the Netherlands ([6]). In this study, the safety of excluding pulmonary embolism by a diagnostic algorithm consisting of a CDR, a quantitative D-dimer test and helical CT was

evaluated. In- and outpatients with a clinical suspicion of PE were eligible for the study. Exclusion criteria were age under 18 years, treatment with therapeutic doses of unfractionated or low-molecular weight heparin for more than 24 hours prior to inclusion, a life expectancy of less than three months, pregnancy, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance less than 30 ml/min), logistic reasons, geographic inaccessibility precluding follow up or hemodynamic instability.

Diagnostic Work-up

PE was considered unlikely if the Wells CDR was ≤ 4 points. PE was considered likely in case of a CDR > 4 points ([1;5]). Patients with a CDR indicating PE unlikely underwent D-dimer testing and when normal, the diagnosis of PE was considered excluded. In these patients anti-coagulant treatment was withheld. Patients with a CDR indicating "PE unlikely" and an abnormal D-dimer test and patients with a CDR indicating "PE likely" underwent helical CT to diagnose or exclude PE.

All patients were followed for a period of three months to document the occurrence of symptomatic venous thromboembolic events. In five of the twelve hospitals participating in the Christopher study, D-dimer tests were performed in all patients, irrespective of their clinical probability, for logistic reasons. However, these results were only communicated to the treating physician in case of a CDR indicating "PE unlikely". Only patient data in these five hospitals were used in this analysis.

The D-dimer concentration was measured in three hospitals using the Vidas D-Dimer assay (Biomerieux, Marcy L'Etoile, France). The Tinaquant assay (Roche Diagnostica, Mannheim, Germany) was used in the two other hospitals. A cut-off level below or equal to 500 ng/ml was defined as normal for both tests ([6]).

The Institutional Review Boards (IRB's) of all participating hospitals approved the study protocol and written or oral informed consent was obtained from all participants, depending on the requirements of the local IRB's.

Statistical Analysis

Increments of 100 ng/ml for the D-dimer test result and 1 score-point for the CDR were used as the varying elements in this analysis. The reference test for calculation of the test characteristics sensitivity and specificity was the diagnosis of PE at baseline by helical CT or the occurrence of an objectively diagnosed venous thrombo-embolic event during the three months of follow-up. For each

increment of CDR and D-dimer cut-off point, the number of patients with PE at baseline or during follow-up and the associated sensitivity, specificity, negative and positive predictive values were calculated. Exact 95% confidence intervals (CI) were calculated around the observed incidences using JavaStat software (http://hometown.aol.com/johnp71/confint.html). Ruling out PE by a combination of a CDR score and a negative D-dimer test was considered safe if the negative predictive value was at least 98% and if the upper confidence limit of the 3-months thrombo-embolic failure rate did not exceed 2.7%, being the upper confidence limit of the 3-months thrombo-embolic rate of a normal pulmonary angiography ([7]).

Results

Of 1605 eligible patients recruited in the 5 hospitals, 90 were excluded because of predefined exclusion criteria or declined informed consent. Of the included patients, data regarding the CDR score were missing in 3 patients and 46 patients were treated with anticoagulants for reasons other than venous thrombo-embolism (VTE), resulting in a total of 1466 patients (91%) available for this analysis (Table 1).

Table 1. Baseline characteristics of the study population (n=1466)

Characteristics	*n (%)*
Age in years	54 (19)
Female sex	822 (54)
Estrogen use*	168 (20)
Immobilisation > 3 days or surgery	303 (20)
History of VTE	209 (14)
COPD	156 (10)
Heart failure	138 (9)
Malignancy	238 (16)
Outpatients	1155 (76)
PE at baseline	321 (22)

AI data are represented as mean (Standard Deviation)
*in females only

The mean age of the patients was 54 years, 54% of patients were female and 76% were outpatients. The prevalence of PE was 22% (321 patients diagnosed with PE at baseline and nine patients with PE during three months follow up).

The prevalence of PE increased with increasing score on the CDR, ranging from 5% in patients with a score of 1 point or less, to 59% in patients with a score of more than 7 points (Figure 1).

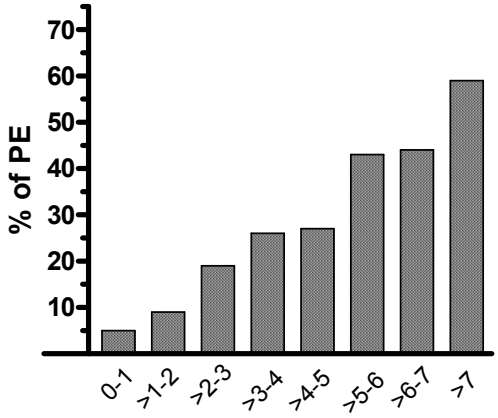

Figure 1 Prevalence of PE according to CDR score

Similarly, the prevalence of PE increased with increasing concentration of D-dimer, ranging from 1% in patients with D-dimer concentrations below 300 ng/ml to more than 60% with D-dimer concentrations above 5000 ng/ml (Figure 2).

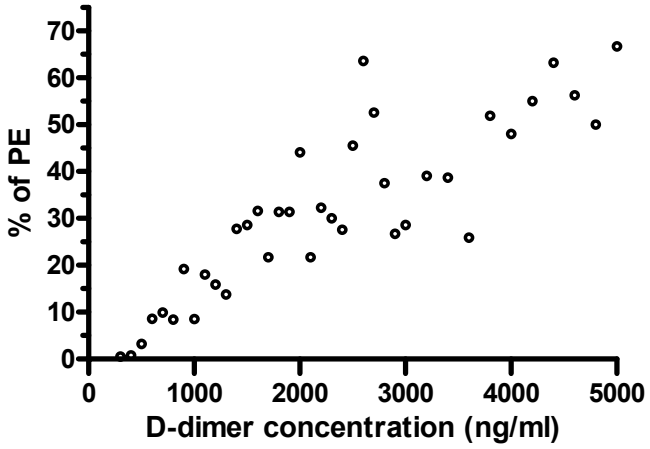

Figure 2 Prevalence of PE according to D-dimer level

Varying the Cut-off Level of the Clinical Decision Rule

The sensitivity of a normal D-dimer and a CDR cut-off level of four points or less was 98.8% (95%CI: 96.9-99.7), the specificity 37.5% (95%CI: 34.7-40.4) and the negative predictive value was 99.1% (95%CI: 97.6-99.8).

Increasing the CDR cut-off level from 4 to 5 points or less would have resulted in a total of 1213 patients (82.7%) designated as "PE unlikely". D-dimer tests would have been normal in 488 patients (33.3%) (Table 2).

Table 2. Influence of varying CDR cut-off value*

CDR score	DD tests performed N (%)	D-dimer normal N (%)	3-months VTE failure rate n	% (95%CI)
≤ 4	960 (65.5)	430 (29.3)	4	0.9 (0.3-2.4)
≤ 5	1213 (82.7)	488 (33.3)	7	1.5 (0.6-3.0)
≤ 6	1384 (94.4)	502 (34.2)	10	2.0 (1.0-3.7)

*D-dimer cut-off remained 500 ng/ml;
CDR: Clinical Decision Rule; DD: D-dimer; VTE: Venous Thromboembolic Events

The sensitivity was 97.9% (95%CI: 95.7-99.1), the specificity 42.3% (95%CI: 39.5-45.3) and the negative predictive value 98.6% (95%CI: 97.1-99.4) (Table 3).

Table 3. Effect of varying CDR cut-off on test characteristics*

CDR score	Sens (95%CI)	Spec (95%CI)	NPV (95%CI)
≤ 4	98.8 (96.9-99.7)	37.5 (34.7-40.4)	99.1 (97.6-99.8)
≤ 5	97.9 (95.7-99.1)	42.3 (39.5-45.3)	98.6 (97.1-99.4)
≤ 6	97.0 (94.5-98.5)	43.3 (40.4-46.3)	98.0 (96.4-99.0)

*D-dimer cut-off level remained 500 ng/ml;
CDR: Clinical Decision Rule, NPV: Negative Predictive Value; Sens: Sensitivity; Spec: Specificity

The number of patients in whom the diagnosis of PE would have been ruled out without performing a CT scan increased from 430 patients (29.3% of total study population) at a cut-off level of 4 points or less to 488 patients (33.3% of total study population) at a cut-off level of 5 points or less, (difference 58 patients, 4.0 % increase in total study population), This would be associated with an increase from

4 to 7 venous thrombo-embolic events, resulting in an increase in 3-months VTE failure rate to 1.5% (95%CI: 0.6-3.0%).

Further increasing the cut-off level of the CDR to 6 points or less would have resulted in 14 more patients (from 488 to 502, 0.9 % of the total study population) in whom the diagnosis of PE was ruled out without performing a CT scan. This would lead to 3 more thrombo-embolic events (from 7 to 10) with a 3-months thrombo-embolic rate of 2.0% (95%CI: 1.0-3.7).

Varying the Cut-off Level of the D-dimer Test

Table 4 demonstrates the effect of varying the cut-off level of the D-dimer test when the CDR cut-off level remained at 4 points or less to designate patients as "PE unlikely". Increasing the D-dimer test cut-off level from 500 to 600 would have resulted in a total of 474 patients (32.3%) designated as having no PE.

Table 4. Influence of varying D-dimer cut-off value*

D-dimer cut-off	DD tests performed n (%)	D-dimer normal n (%)	3-months VTE failure rate N	% (95%CI)
≤ 500	960 (65.5)	430 (29.3)	4	0.9 (0.3-2.4)
≤ 600	960 (65.5)	474 (32.3)	11	2.2 (1.1-4.0)
≤ 700	960 (65.5)	507 (34.6)	16	3.0 (1.8-4.9)

* Clinical Decision Rule cut-off remained ≤ 4 points;
DD: D-dimer; VTE: Venous Thromboembolic Events

The sensitivity was 96.7% (95%CI: 94.1-98.3), the specificity 40.8 (95%CI: 37.9-43.7) and the negative predictive value 97.7% (95%CI: 95.9-98.8). The number of patients in whom the diagnosis of PE would have been ruled out without performing a CT-scan increased from 430 at a cut-off level of 500 ng/ml to 474 patients at a cut-off level of 600 ng/ml (44 patients, 3% of the study population), at an expense of 7 additional venous thrombo-embolic events. This would result in a 3-months thrombo-embolic failure rate of 2.2% (95%CI:1.1-4.0)).

Table 5. Effect of varying D-dimer cut-off on test characteristics*

D-dimer cut-off	Sens (95%CI)	Spec (95%CI)	NPV (95%CI)
≤ 500	98.8 (96.9-99.7)	37.5 (34.7-40.4)	99.1 (97.6-99.8)
≤ 600	96.7 (94.1-98.3)	40.8 (37.9-43.7)	97.7 (95.9-98.8)
≤ 700	95.2 (92.3-97.2)	43.2 (40.3-46.2)	96.8 (94.9-98.2)

*CDR cut-off level remained ≤ 4 points,
NPV: Negative Predictive Value; Sens: Sensitivity; Spec: Specificity

By increasing the cut-off level of the D-dimer concentration to 700 ng/ml, the diagnosis of PE could have been ruled out in 507 patients (34.6% of the study population) at an expense of 12 additional thrombo-embolic events compared. This resulted in a 3-months thrombo-embolic failure rate of 3.0% (95%CI: 1.8-4.9%). Sensitivity dropped to 95.2% (95%CI:92.3-97.2) and negative predictive value to 96.8% (95%CI:94.9-98.2).

Discussion

This is the first study that investigated the effect of stepwise variation of both the cut-off level of the CDR as well as the D-dimer test.

There are two important conclusions to be drawn from our analysis. First, our results show that increasing the cut-off level of the CDR, while keeping the D-dimer test cut-of at 500 ng/ml, is not safe. The upper 95 % confidence interval, of the hypothetical 3-months thrombo-embolic failure rate of 1.5 %, was 3%. This exceeded a generally accepted upper safety limit of 2.7% even when the CDR cut-off level was only raised from 4 to 5 points. Second, increasing the cut-off level of the D-dimer test had an even more profound effect on safety. By increasing the cut-off level from 500 to 600 ng/ml, the negative predictive value of a clinical decision rule indicating PE unlikely, combined with a normal D-dimer test, dropped below 98% while the hypothetical 3-months thrombo-embolic failure rate would have an upper 95 % confidence limit of 4.0% which clearly exceeded our predefined upper safety limit.

Importantly, the gain of clinical utility, i.e. the proportion of patients in whom PE could be ruled out without the need for additional imaging tests, as a result of changing the cut-off values was relatively

modest. By raising the cut-off level of the CDR from 4 to 5 points, PE could be ruled out in an extra 4.0% of the study population. Similarly, by raising the D-dimer cut-off level from 500 to 600 ng/ml in an extra 3.0% of the study population PE could be ruled out without imaging tests.

Two earlier studies have investigated the effect of varying the cut-off level of the D-dimer test in categories of pre-test probability without changing the cut-off levels to designate patients as low, intermediate or high clinical probability ([8;9]). In the first study, increasing the D-dimer test cut-off level from 500 to 600 ng/ml in patients with a low pre-test probability led to a marginal gain in diagnostic yield since PE could be ruled out in an additional 2.7% of the total study population. According to our predefined safety limit, the safety was only marginally diminished since the 3-months thrombo-embolic failure rate only increased from 0% (95%CI:0-0.8%) to 0.3% (95%CI: 0.01-1.4). This might be explained due to the low prevalence of PE (7%) in this subgroup with a low pre-test probability. Indeed, raising the D-dimer cut-off level from 500 to 600 ng/ml in patients with an intermediate probability (prevalence of PE 35%) in the same study led to an unacceptably high 3-months thrombo-embolic rate of 5.8% (95%CI: 1.9-13.1) ([9]).

The second study concluded that the use of three pre-test probability-specific D-dimer cut-off points excluded VTE in a larger proportion of patients (49.2%) than using a single cut-off point (36.4%) without sacrificing NPV (98%) ([8]). However, the 3-months thrombo-embolic failure rate in patients with a low pre-test probability increased from 0% (upper 95% confidence limit 1.5%) to 1.5% (upper 95% confidence limit 4.2%) and the sensitivity decreased dramatically from 100 to 75%. Of note, in this study the highest D-dimer cut-off level was selected on the basis of a negative predictive value of at least 98%. The use of the NPV as a sole criterion of safety may be misleading since it is critically dependent on the prevalence of disease in the population tested. Finally, in the second study a mixed population of patients with clinically suspected PE and DVT was included.

There are some limitations to be discussed. We used data of only 5 of the 12 hospitals participating in the Christopher study. We do not think this has led to selection bias, since the prevalence of PE as well as the baseline characteristics of the study patients was similar to the overall population of our original cohort ([6]). Second, two different D-dimer assays were used. Since there was no statistically

significant difference in failure rate between the two tests in the original study, we felt confident to combine data from both assays.

Strengths of our study are that we had a relatively large cohort of patients with suspected PE in which the diagnosis was ruled out or diagnosed by a simple algorithm and all outcome events were adjudicated by an independent committee.

In conclusion, our results demonstrate that the cut-off level of the CDR to designate patients as "PE unlikely" and the cut-off level of the D-dimer test to designate a test result as "normal" should be kept at the regular CDR cut-off level of 4 points and D-dimer concentration of 500 ng/ml, in order to prevent exposure of patients, with initial normal diagnostic tests, to a 3-months thrombo-embolic failure rate exceeding that after a normal pulmonary angiography. The challenge for future studies is to provide algorithms, which can safely reduce the percentage of patients undergoing imaging tests for PE.

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CHAPTER 5

High D-dimer levels increase the likelihood of pulmonary embolism

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Objective to determine the utility of high quantitative D-dimer levels in the diagnosis of pulmonary embolism.

Methods D-dimer testing was performed in consecutive patients with suspected pulmonary embolism. We included patients with suspected pulmonary embolism with a high-risk for venous thrombo-embolism, i.e., hospitalized patients, patients older than 80 years, with malignancy or previous surgery. Presence of pulmonary embolism was based on a diagnostic management strategy using a clinical decision rule (CDR), D-dimer testing and computed tomography.

Results a total of 1515 patients were included with an overall pulmonary embolism prevalence of 21%. The pulmonary embolism prevalence was strongly associated with the height of the D-dimer level, and increased fourfold with D-dimer levels greater than 4000 ng mL^{-1} compared to levels between 500 and 1000 ng mL^{-1}. Patients with D-dimer levels higher than 2000 ng mL^{-1} and an unlikely CDR had a pulmonary embolism prevalence of 36%. This prevalence is comparable to the pulmonary embolism likely CDR group. When D-dimer levels were above 4000 ng mL^{-1}, the observed pulmonary embolism prevalence was very high, independent of CDR score.

Conclusions strongly elevated D-dimer levels substantially increase the likelihood of pulmonary embolism. Whether this should translate into more intensive diagnostic and therapeutic measures in patients with high D-dimer levels irrespective of CDR remains to be studied.

Introduction

D-dimer measurement is widely used in the diagnostic work-up of patients with suspected venous thromboembolism (VTE) [1]. D-dimers are formed by the degradation of cross-linked fibrin [2] and are the best currently available laboratory marker of coagulation activation [3]. Several large management studies have used an algorithm combining normal D-dimer tests with low clinical probability to rule out pulmonary embolism [4-7]. Using well-evaluated quantitative D-dimer tests, levels below 500 ng mL^{-1} are regarded as a sensitive cut-off level in excluding VTE [8]. The sensitivity ranges from 91 to 97% in various studies and the specificity varies between 40 and 70% [9]. It is possible to increase the specificity of D-dimer tests by increasing D-dimer cut-off levels. Specificity of D-dimer levels exceeding 4000 ng mL^{-1} (Asserachrom Ddi ELISA) was 93% in a study evaluating outpatients with suspected pulmonary embolism [10]. Another study showed a seven-fold increased risk of pulmonary embolism when D-dimer levels exceed 2000 ng mL^{-1} (STA-Liatest D-Di®; Diagnostica Stago, Asnieres, France) compared with D-dimer levels between 500 and 1000 ng mL^{-1} [11]. However, it should be noted that these two studies were restricted to populations with a lowrisk for VTE. It has been suggested that in patients with high risk for VTE, i.e., hospitalized patients, patients older than 80 years and patients with malignancy or previous surgery the use of D-dimer is inefficient because of a high rate of false-positive tests, leading to pulmonary embolism exclusion in less than 5% of patients [12,13]. Combining a quantitative high D-dimer level with a high clinical probability score can improve the positive predictive value of pulmonary embolism and it has been suggested that the combination of these tests might be sufficient for establishing the diagnosis of VTE [14,15]. In the present study our aim was to assess the clinical consequences of high quantitative D-dimer levels combined with clinical probability score in the management strategy in patients with suspected pulmonary embolism.

Patients and 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 computed tomography [7]. Patients were included between November 2002 and September 2004. The Institutional Review Boards of all participating hospitals approved the study protocol, and written or oral informed consent was obtained from all participants.

Patients

Consecutive patients with clinically suspected pulmonary embolism and quantitative D-dimer results from five teaching hospitals were included in this analysis. Baseline demographic clinical characteristics were fully comparable to the original management study. Exclusion criteria were: treatment with therapeutic doses of unfractionated or low-molecular weight heparin for more than 24 h, life expectancy <3 months, pregnancy, geographical inaccessibility precluding follow-up, age younger than 18 years, allergy to intravenous contrast agents, renal insufficiency (creatinine clearance <30 ml min^{-1}), logistic reasons or hemodynamic instability.

Diagnostic Algorithm

Patients with clinically suspected pulmonary embolism were evaluated by an attending doctor using a validated CDR [4]. Pulmonary embolism was considered unlikely if the CDR score was $\leq$ 4 points, and considered likely if the CDR score > 4 points. In the five teaching hospitals included in this analysis, D-dimer tests were performed in all patients irrespective of the CDR score. The D-dimer results were only communicated to the attending doctor in case of a CDR indicating pulmonary embolism unlikely. Three hospitals used the Vidas D-dimer assay (Biomerieux, Marcy L'Etoile, France) and two used the Tinaquant assay (Roche Diagnostica, Mannheim, Germany). A D-dimer concentration of 500 Fibrinogen Equivalent Units ng mL^{-1} or less was defined as normal. In patients with an unlikely CDR and a normal D-dimer concentration, the diagnosis of pulmonary embolism was considered excluded and anticoagulation treatment was withheld. All other patients underwent spiral computed tomography. All patients were followed up for a period of 3 months.

Outcome

The primary outcome of the study was the incidence of symptomatic VTE events during 3 months of follow-up, defined as fatal pulmonary embolism, nonfatal pulmonary embolism, or deep vein thrombosis (DVT). An independent adjudication committee, whose members were unaware of the results of the diagnostic algorithm, evaluated all suspected VTE and deaths. A diagnosis of pulmonary embolism or DVT was based on a priori defined and generally accepted criteria [16]. Deaths were classified as caused by pulmonary embolism in case of confirmation by autopsy, in case of an objective test positive for pulmonary embolism prior to death, or if pulmonary embolism could not be confidently excluded as the cause of death.

Follow-up consisted of a scheduled outpatient visit or telephone interview at 3 months. In addition, patients were instructed to contact the study centre or their general practitioner immediately in the case of complaints suggestive of DVT or pulmonary embolism. On each visit, information was obtained on complaints suggestive of VTE and use of anticoagulants. In case of clinically suspected DVT or pulmonary embolism, appropriate objective tests (compression ultrasound for suspected DVT, ventilation-perfusion scintigraphy or computed tomography for suspected pulmonary embolism) 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.

Statistical Analysis

D-dimer increments of 500-4000 ng mL^{-1} and unlikely or likely CDR score were used as the varying units of analysis. Sensitivities reflect the proportion of patients with disease who had a positive D-dimer, while specificities reflect the proportion of patients without disease who had a negative D-dimer result, depending on the cut-off level. The reference test for calculation of the test characteristics sensitivity and specificity was the diagnosis of pulmonary embolism at baseline by spiral computed tomography or the occurrence of an objectively diagnosed venous thrombo-embolic event during the 3 months of follow-up.

Results

Of 1704 eligible patients, 90 were excluded because of predefined exclusion criteria or declined informed consent. Data regarding D-dimer results were missing in 99 patients, resulting in a total of 1515 patients (94%) available for analysis. The mean age was 54 years, 16% of patients had a malignancy, 6% underwent surgery in the previous three weeks and 76% were outpatients (Table 1). The overall prevalence of pulmonary embolism was 21% (324 of 1515 patients).

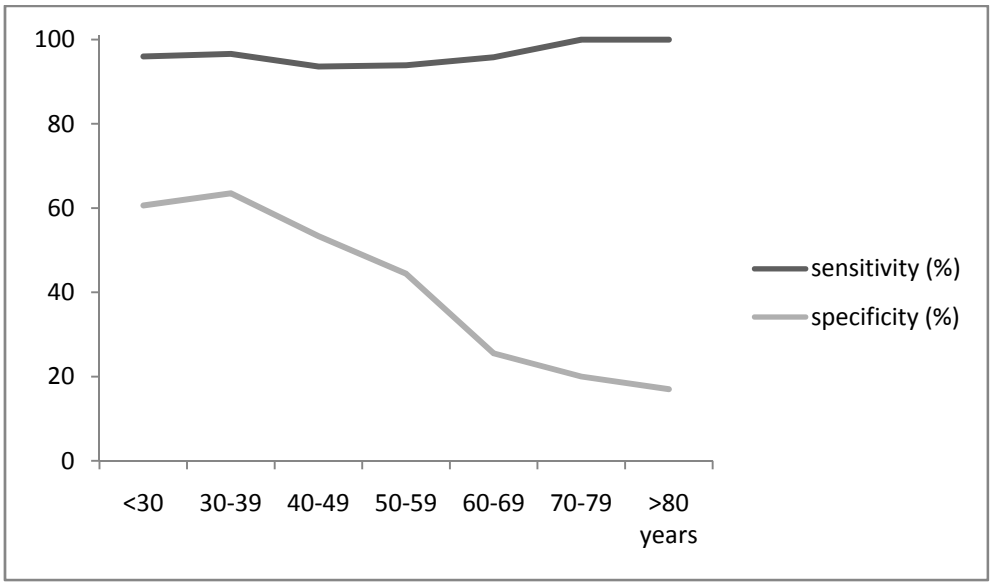
Table 1. Baseline demographic and clinical characteristics of the study population (*n* = 1515)

Characteristic	Value
Age, mean (SD), years	54 (19)
Female	824 (54.4)
Previous venous thromboembolism	209 (13.8)
Malignancy	239 (15.8)
Recent surgery	95 (6.3)
Outpatients	1158 (76.4)
Pulmonary embolism prevalence	324 (21.4)

Data are presented as *n* (%).

In 314 of 324 patients with pulmonary embolism the D-dimer concentration was above the cut-off value (500 ng mL^{-1}), resulting in a sensitivity of the D-dimer test of 96.9% (95% CI: 94.3-98.4). This sensitivity was not influenced by age and varied from 93.6% to 100% (Figure 1).

Figure 1. Performance of D-dimer in the diagnosis of pulmonary embolism according to age



In 519 of the 1191 patients without pulmonary embolism plasma levels were normal (<500 ng mL^{-1}) resulting in a specificity of the D-dimer test of 43.6% (95% CI: 40.8-46.4).

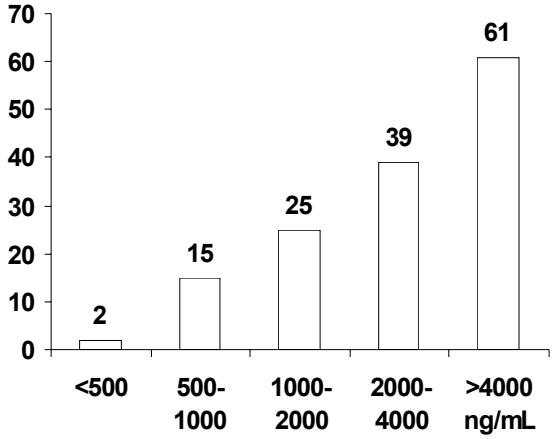
The specificity of the D-dimer concentration was influenced by age. The maximum value was 63.5 % in the 30- to 39- year group and the lowest value was 17% in the group above 80 years of age (Figure 1).

Overall, in 986 out of 1515 patients, D-dimer levels were abnormal (more than 500 ng mL^{-1}) and 314 of these 986 patients had pulmonary embolism (prevalence 32%). In the 125 of 545 patients with a CDR indicating PE unlikely, but a D-dimer more than 500 ng mL^{-1} pulmonary embolism was present (prevalence 23%) whilst 189 of 441 patients with a CDR, indicating PE likely, and a D-dimer more than 500 ng mL^{-1} had pulmonary embolism (prevalence 43%) (p-value < 0.001).

High D-dimer Levels and Prevalence of Pulmonary Embolism

Pulmonary embolism prevalence increased with higher D-dimer levels. The increase was nearly twofold for D-dimer levels between 1000 and 2000 ng mL^{-1}, nearly threefold for levels between 2000 and 4000 ng mL^{-1} and fourfold for levels greater than 4000 ng mL^{-1} compared to D-dimer levels between 500 and 1000 ng mL^{-1} (Figure 2).

Figure 2. Observed pulmonary embolism prevalence accrding to the quantitative level of D-dimers



In the unlikely CDR group with D-dimer levels between 500 and 1000 ng mL^{-1}, the observed pulmonary embolism prevalence was close to the prevalence observed in the overall unlikely CDR group (12 versus 13%) with a moderate increase in the likely CDR group (12 vs. 19%) (Table 2).

Table 2. Observed pulmonary embolism (PE) prevalence for each interval of D-dimer (DD) levels (ng mL^{-1}) and for each level of clinical PE probability

Study population *n* = 1515	CDR ≤ 4 (*n* = 994) (66)	CDR > 4 (*n* = 521) (34)
PE prevalence, %	129/994 (13)	195/521 (37)
DD <500 (*n* = 529)	4/449 (0.9)	6/80 (8)
DD 500-1000 (*n* = 276)	21/175 (12)	19/101 (19)
DD 1000-2000 (*n* = 297)	40/191 (21)	35/106 (33)
DD 2000-4000 (*n* = 236)	32/118 (27)	60/118 (51)
DD >4000 (*n* = 177)	32/61 (53)	75/116 (65)

Values within parenthesis are expressed as *n* (%) unless otherwise stated.

D-dimer levels between 1000 and 4000 ng mL^{-1} showed almost a two-fold increased pulmonary embolism prevalence in the unlikely CDR group compared with the overall unlikely CDR group (23% vs. 13%), in the likely CDR group a higher pulmonary embolism prevalence was seen than in the overall CDR likely group (42% vs. 37%). When D-dimer levels were above 4000 ng mL^{-1} the observed pulmonary embolism prevalence was systematically higher than expected, independent of CDR score (53% and 65%). Even with these high D-dimer levels, the CDR score influenced the pulmonary embolism prevalence although the influence of CDR score was limited in patients with the highest D-dimer levels. Among patients with D-dimer levels higher than 2000 ng mL^{-1}, 179 had an unlikely CDR with a pulmonary embolism prevalence of 36%. This is comparable to the CDR likely group with a pulmonary embolism prevalence of 37%. These results were substantiated by logistic regression, showing a fourfold increased risk of pulmonary embolism with a likely CDR score or when D-dimer levels were between 2000 and 4000 ng mL^{-1}. CDR and D-dimer levels were independently and significantly associated with pulmonary embolism prevalence (Table 3). The Vidas and Tinaquant

D-dimer assays showed fully comparable results for the observed pulmonary embolism prevalence for each cut-off level and with logistic regression analysis (data not shown).

Table 3. Logistic regression for the risk of pulmonary embolism

Study population	Odds ratio	95% CI
CDR		
unlikely	1	
likely	4.0	(3.1-5.2)
D-dimer		
500-1000	1	
1000-2000	2.0	(1.3-3.1)
2000-4000	3.8	(2.5-5.8)
>4000	9.0	(5.7-14.2)

CDR, clinical decision rule, CI, confidence interval.

Discussion

It has been repeatedly demonstrated that, due to its low specificity, D-dimer levels above 500 ng mL^{-1} have a low capability of establishing the diagnosis of pulmonary embolism. In our study, the prevalence of pulmonary embolism increased significantly with increasing D-dimer levels. Pulmonary embolism prevalence was 15% in the 500-1000 ng mL^{-1} group and 61% in the group with D-dimer levels above 4000 ng mL^{-1}. In addition, we and others have previously shown an association between the level of D-dimer and the severity of pulmonary embolism which is reflected by the extent of embolic obstruction in the pulmonary arteries [17, 18]. The results of the present study therefore contain several potential clinical consequences of high quantitative D-dimer levels.

First, the integration of high to very high D-dimer levels may refine the diagnostic process in pulmonary embolism and improve medical management. Based on our results, clinicians may consider initiating anticoagulant treatment in patients with either a combination of D-dimer levels higher than 2000 ng mL^{-1} and likely CDR, or D-dimer levels higher than 4000 ng mL^{-1} independent of the CDR score, given the 50 % prevalence of pulmonary embolism in this group in our study. This consideration may be especially relevant when imaging diagnostic facilities are not available 24 h

around the clock. In addition, the positive D-dimer value could be taken into account to decide the urgency of further imaging testing. In absence of evidence however, we would like to stress the safety and efficiency of this potential management approach should be prospectively evaluated.

Secondly, as D-dimer specificity decreases with advancing age and elevated D-dimer levels are present in hospitalized patients with malignancy or recent surgery, several authors have stated that evaluating the use of D-dimer in the diagnostic management of pulmonary embolism should only be performed in predefined low-risk populations [11]. However, in our study we observed a ninefold increased risk of pulmonary embolism with D-dimer levels higher than 4000 ng mL^{-1} compared with D-dimer levels between 500 and 1000 ng mL^{-1}, independent of CDR score. We conclude that D-dimer testing is useful in an unselected population with risk factors for VTE such as older age, inpatients, malignancy or recent surgery.

Thirdly, assessment of CDR is an important step in the diagnostic management of pulmonary embolism. A likely CDR showed a fourfold increased risk of pulmonary embolism independent of D-dimer results. The influence of CDR on pulmonary embolism prevalence was still present even when D-dimer levels exceeded 4000 ng mL^{-1}.

We conclude that strongly elevated D-dimer levels increase the likelihood of pulmonary embolism. Whether the integration of high to very high D-dimer levels in the diagnostic management of pulmonary embolism should translate into more intensive diagnostic and therapeutic measures in patients with high D-dimer levels, irrespective of CDR, remains to be studied.

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CHAPTER 6

Risk factors for the post-thrombotic syndrome in patients with a first deep venous thrombosis

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Background The post-thrombotic syndrome (PTS) is a chronic complication of deep venous thrombosis and is characterised by signs and symptoms of venous hypertension. The objectives of this study were to determine the risk of PTS after deep venous thrombosis and to assess risk factors for PTS.

Methods Patients were recruited from the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis. Consecutive patients who suffered a first deep venous thrombosis of the leg before the age of 70 were included in a follow-up study. All patients completed a questionnaire and DNA was obtained through blood samples or buccal swabs. PTS was ascertained in a structured interview using a clinical classification score.

Results The one-year cumulative incidence of PTS was 25%, and 7% for severe PTS. Elastic compression stockings were prescribed in 1412 (85%) patients. The majority used their stockings every day. Women were at increased risk compared to men (risk ratio (RR) 1.5, 95%CI 1.3-1.8). Similarly, obese patients had a 1.5 fold increased risk of PTS compared to patients with normal weight (RR 1.5, 95%CI 1.2-1.9), with a one-year cumulative incidence of 34% compared to 22%. Patients who already had varicose veins had an increased risk (RR 1.5, 95%CI 1.2-1.8) of PTS. Deep venous thrombosis in femoral and iliac vein was associated with a 1.3-fold increased risk of PTS compared to popliteal vein thrombosis (RR 1.3, 95%CI 1.1-1.6). Patients over 60 years were less likely to develop PTS than patients below the age of 30 (RR 0.6, 95%CI 0.4-0.9). Malignancy, surgery, minor injury, plaster cast, pregnancy or hormone use did not influence the risk of PTS, neither did the factor V Leiden or prothrombin 20210A mutation.

Conclusions PTS is a frequent complication of deep venous thrombosis, despite the widespread use of elastic compression stockings. Women, obese patients, patients with proximal deep venous thrombosis and those with varicose veins have an increased risk of PTS, whereas the elderly appeared to have a decreased risk.

Introduction

The post-thrombotic syndrome (PTS) is a chronic complication of deep venous thrombosis. Venous hypertension caused by venous valvular incompetence and persistent obstruction are likely to be the pathogenic mechanism underlying PTS.[1-4] PTS is characterized by symptoms such as a feeling of heaviness and pain and by signs such as oedema, hyperpigmentation and new venous ectasia. Severe PTS can lead to leg ulcers. Several studies assessed the incidence of PTS which varied from 15 to 50% between studies.[3-10] This wide range is due to differences in the definition of PTS, patient selection and study design. There is no gold standard test for the diagnosis of PTS and the diagnosis is primarily based on clinical features. Elastic compression stockings assist the calf muscle pump and reduce venous hypertension and reflux, thereby reducing edema and improving tissue microcirculation.[1] Randomized controlled trials have shown that daily use of elastic compression stockings after deep venous thrombosis reduces the risk of PTS by approximately 50%.[6,8,11]

In contrast to the many identified risk factors for deep venous thrombosis,[12] the only identified risk factors for PTS so far are recurrent, ipsilateral deep venous thrombosis and an increased body mass index (BMI).[7,8,13-18] Age, sex and duration of anticoagulant therapy did not appear to be associated with the risk of developing PTS, but results are conflicting, and most studies are characterized by small numbers of patients.[8,14-18]

Hypercoagulable states have been reported to be associated with venous leg ulcers.[19-21] However, factor V Leiden or prothrombin 20210A mutation were not associated with an increased risk of developing PTS.[8,14,18,21] One study even showed a reduced risk of PTS with the presence of factor V Leiden or prothrombin 20210 mutation.[17] Other venous thrombotic risk factors such as surgery and hormone use have not yet been investigated as potential risk factors for PTS.

The objectives of the present large study were to assess the cumulative incidence of PTS after a first deep venous thrombosis and to assess the contribution of risk factors in the development of PTS.

Methods

Study Design

This study was performed in the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis, a large population-based case-control study. Between March 1999 and June 2002, consecutive patients aged 18 to 70 years with a first episode of deep venous thrombosis of the leg were included from six participating anticoagulation clinics in the Netherlands. Discharge letters and radiology reports of the venous thrombotic event were obtained. Compression ultrasonography and Doppler ultrasound were by far the most commonly used diagnostic procedures (98%). Deep venous thrombosis was objectively confirmed in 97%.[22]

Patients who were unable to fill in a questionnaire (see below) because of language or severe psychiatric problems were excluded. Among the 2730 eligible patients, 132 died before they could participate, 31 patients were in the end stage of a disease and 651 patients could not be located or refused to participate. In April 2000 three questions regarding PTS were added to the interview (see below) and 157 patients, who were interviewed before this date, and 13 patients with missing items regarding PTS in the interview, were excluded. Of 78 patients no information on the left or right side of deep venous thrombosis was available which led to 1668 patients included in the present analysis.

All patients filled in a detailed questionnaire on acquired risk factors for venous thrombosis such as malignancy, surgery, minor injury, plaster cast, bedridden, pregnancy and use of female hormones. The questionnaire was sent within a few weeks after the event and covered the period of 1 year prior to the date of the thrombotic event. When the patient was unable to fill in the questionnaire, questions were asked by phone, using a standardized mini-questionnaire. Patients were divided in a group with idiopathic deep venous thrombosis and provoked venous thrombosis associated with one or more of the following risk factors; malignancy, surgery, plaster cast, minor injury, bedridden at home or in the hospital, pregnancy and the use of female hormones. Body mass index (BMI) was calculated from self-reported weight and height (weight/height^2). BMI was categorized according to the criteria of the World Health Organization (1998), defining BMI in adults under 18.5 kg/m^2 as underweight, a BMI between 18.5 and 25 kg/m^2 as normal, a BMI of 25 to 30 kg/m^2 as overweight and a BMI equal to or greater than 30 kg/m^2 as obesity.

Three months after the patients had discontinued their oral anticoagulant therapy, they were invited to the anticoagulation clinic. An independent research assistant, who was not involved in their treatment, interviewed the patients and took a blood sample. In those patients who continued to take oral anticoagulant therapy for more than 1 year after the event, blood samples were drawn during therapy. If patients were unable to come to the anticoagulation clinic, an interview was conducted by telephone and buccal swabs were sent by mail to replace the blood sample (229 out of 1668 patients (13.7%)).

During the in-person or telephone interview details on frequency and duration of the use of elastic compression stockings were asked. PTS was assessed by asking for five symptoms and four signs (table 1). These items were based on the Villalta scale and modified in order to be used in the interview.[7] Each item scored one point if present. The nine items were summed into a post-thrombotic score. PTS was considered absent with a post-thrombotic score between zero and 3 points. PTS was considered moderate in patients with a score between 4 and 6 points and severe with a score equal to or greater than seven or the presence of a venous ulcer. Only the symptoms and signs of the leg in which the deep venous thrombosis occurred, were used to assess the presence and severity of PTS. The study protocol was approved by the Ethics Committee of the Leiden University Medical Center, Leiden, The Netherlands. Written informed consent was obtained from all participants.[22]

Table 1. Post-thrombotic symptoms and signs in 1668 patients

Symptoms	N (%)	Signs	N (%)
Spontaneous pain in calf	433 (26)	Newly formed varicose veins	218 (13)
Spontaneous pain on walking	243 (15)	Swelling of foot or calf	576 (35)
Spontaneous pain on standing	293 (18)	Skin changes, pigmentation, discoloration	418 (25)
Pain worsening during the day	393 (24)	Skin changes with venous ulcer	48 (3)
Heaviness of leg	620 (37)		

Laboratory Measurements

Blood was collected from the antecubital vein into vacuum tubes containing 0.106 mol/l trisodium citrate. High molecular weight DNA was isolated from leukocytes using a standard salting-out procedure and stored at -20ºC until amplification. When a blood sample was unavailable, three large cotton (buccal) swabs in a total of 6 ml SDS-proteinase K solution were obtained. DNA was extracted from these buccal swabs and frozen at −20 °C until further analysis.[22] The factor V Leiden mutation (G1691A) and the prothrombin (G20210A) mutation were simultaneously detected by duplex polymerase chain reaction.[24,25]

Statistical Analysis

The follow-up started at diagnosis of deep venous thrombosis in the leg and ended at the time of the interview. Cumulative incidence was estimated by Kaplan-Meier life table technique. The reported risk ratios are based on the method of Zhang.[23] In short, crude odds ratios were used to estimate the relative risk of PTS. Logistic regression was used to adjust for age and sex only, and for age and sex combined with BMI, duration of symptoms, varicose veins, localization of deep venous thrombosis, malignancy and elastic compression stockings. 95% Confidence intervals (CI) were calculated by using the standard error obtained from the logistic regression model. As PTS is common (over 10% incidence), these odds ratio overestimates the true relative risk. Therefore, the odds ratio and 95% CI were converted to the risk ratio by taking into account the prevalence of the risk factor in non-exposed individuals.[23]

As patients had various durations of follow-up and anticoagulation use, all analyses were stratified by follow-up and anticoagulation use period. Mantel-Haenszel common odds ratio was used to estimate the relative risk of PTS, taking these various durations into account. As these stratified odds ratios did not differ from the crude analyses, the risk ratios presented are adjusted for age and sex and other risk factors as indicated above.

All computations were performed with the use of SPSS software, version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics of the 1668 patients are summarized in table 2. There were 880 (53%) women, mean age at diagnosis of deep venous thrombosis was 48 years and patients had a mean BMI of 27 kg/m^2. Median duration of symptoms before diagnosis of deep venous thrombosis was 4 days (5th - 95th percentile 0-69).

Table 2. Characteristics of 1668 patients with a first deep venous thrombosis of the leg

Characteristic	
Women No (%)	880 (53%)
Age (years), mean (SD*)	48 (13)
5th -95th percentile	26-67
BMI† (kg/m2), mean (SD)‡	27 (5)
5th -95th percentile	21-36
Duration of symptoms before diagnosis (days), median‡	4
5th -95th percentile	0-69
Varicose veins at diagnosis§	470 (28%)
Side of DVT||	
left	972 (58%)
right	683 (41%)
bilateral	13 (1%)
Localization of DVT¶	
calf vein	203 (17%)
popliteal vein	498 (41%)
femoral and iliac vein	502 (42%)
Malignancy‡	137 (8%)
Recent surgery‡	357 (21%)
Minor Injury‡	405 (24%)
Plaster cast	105 (6%)
Pregnancy among women < 50 years‡	73 (13%)
Oral anticonceptive use among women < 50 years	417 (74%)
Hormonal replacement therapy among women ≥ 50 years‡	39 (13%)
Idiopathic DVT‡	389 (24%)
Factor V Leiden mutation‡	315 (19%)
Prothrombin 20210A mutation‡	92 (6%)

* SD = standard deviation
‡ unknown in ≤ 74 patients
|| DVT = deep venous thrombosis
† BMI = body mass index
§ unknown in 213 patients
¶ unknown in 465 patients

Thrombosis was unilateral on the left side in 972 (58%) patients, on the right side in 683 (41%), and bilateral in 13 (1%) patients. Deep venous thrombosis was idiopathic in 24% of all patients. Median duration of anticoagulation use was 6 months (5^{th} -95^{th} percentile 2-14). Median duration of follow-up was 10 months (5^{th} -95^{th} percentile 6-18).

Cumulative Incidence and Severity of the Post-thrombotic Syndrome

The one-year cumulative incidence of PTS was 25%, with a cumulative incidence of 7% for severe PTS. Table 1 shows the frequency of the nine post-thrombotic symptoms and signs. The most frequent symptom reported by 620 (37%) patients was a feeling of heaviness of the leg. Swelling of the foot or calf was present in 576 (35%) of the patients. An ulcer was present in 48 out of 1668 (3%) patients. Only 466 out of 1668 patients (28%) had a post-thrombotic score of zero points.

Risk Factors for Post-thrombotic Syndrome

The one-year cumulative incidence of PTS in women was 31% compared to 17% in men. Women had a 1.5-fold higher risk of developing PTS than men (RR 1.5, 95%CI 1.3-1.8), also after adjustment for other risk factors ($RR_{adjusted}$ 1.5, 95%CI 1.1-1.9) (table 3).

The one-year cumulative incidence in patients over 60 years was 16%, which was much lower than the 26% cumulative incidence in patients below the age of 30 (RR 0.6, 95%CI 0.4-0.9). In obese patients the one-year cumulative incidence was 34%, compared to 22% in normal weight patients, leading to a 1.5-fold increased risk of PTS (RR 1.5, 95%CI 1.2-1.9). Height of patients did not affect the risk of PTS. Patients with more than two weeks of symptoms before the deep venous thrombosis had a 1.4 fold increased risk compared to patient with symptoms less than two weeks (RR 1.4, 95%CI 1.2-1.7). After adjustment for other risk factors for PTS this effect was no longer present ($RR_{adjusted}$ 1.2, 95%CI 0.9-1.6). Varicose veins were present in 470 out of 1455 (28%) patients prior to the deep venous thrombosis, in whom the one-year cumulative incidence of PTS was 30%. These patients had a 1.5-fold increased risk of PTS compared to patients without varicose veins (RR 1.5, 95%CI 1.2-1.8).

Table 3. Risk factors associated with post-thrombotic syndrome

Risk factor		N	N PTS	1 yr cum inc*	Risk Ratio†	Risk Ratio $_{adjusted}$‡
Sex						
	women	880	235	31%	1.5 (1.3-1.8)	1.5 (1.1-1.9)
	men	788	129	17%	1	1
Age (years)						
	18-29	200	51	25%	1	1
	30-39	311	75	26%	1.0 (0.7-1.4)	0.8 (0.5-1.2)
	40-49	391	111	30%	1.2 (0.9-1.6)	1.1 (0.8-1.6)
	50-59	456	87	24%	0.9 (0.6-1.2)	0.7 (0.4-1.1)
	60-69	310	40	16%	0.6 (0.4-0.9)	0.4 (0.2-0.7)
BMI§						
	underweight	15	4	36%	1.3 (0.5-2.7)	1.4 (0.4-3.6)
	normal	549	109	22%	1	1
	overweight	702	132	22%	1.1 (0.8-1.3)	1.2 (0.9-1.6)
	obese	343	102	34%	1.5 (1.2-1.9)	1.9 (1.4-2.4)
Duration symptoms before diagnosis‖						
	≥2 weeks	368	105	29%	1.4 (1.2-1.7)	1.2 (0.9-1.6)
	<2 weeks	1240	245	24%	1	1
Varicose veins at diagnosis¶						
	yes					
	no	470	130	30%	1.5 (1.2-1.8)	1.5 (1.2-1.9)
		985	180	20%	1	1
Localization of DVT**††						
	calf vein	203	37	25%	0.9 (0.6-1.3)	0.9 (0.6-1.3)
	popliteal vein	498	100	23%	1	1
	femoral and iliac vein	502	128	26%	1.3 (1.1-1.6)	1.4 (1.1-1.8)
Malignancy‖						
	yes	137	19	15%	0.7 (0.4-1.0)	0.8 (0.4-1.4)
	no	1530	344	25%	1	1

* 1 yr cum inc = one-year cumulative incidence
† adjusted for age and sex if applicable
‡ adjusted for age, sex, and other risk factors for PTS if applicable (BMI, duration of symptoms, varicose veins, localization, malignancy, elastic compression stocking)
§ BMI = body mass index
‖ unknown in ≤ 74 patients
¶ unknown in 213 patients
** DVT = deep venous thrombosis
†† unknown in 465 patients

Newly formed varicose veins is one of the items of the post-thrombotic score. When this specific item was excluded from the post-thrombotic score the risk ratio for varicose veins was only slightly lower (RR 1.4, 95%CI 1.1-1.7). Proximal localization of thrombosis in the femoral and iliac vein was associated with a 1.3-fold increased risk of PTS compared to popliteal vein thrombosis (RR 1.3, 95%CI 1.1-1.6). Calf vein thrombosis conferred a similar risk for PTS as popliteal vein thrombosis. Patients with malignancy were less likely to develop PTS than patients without a malignancy (RR 0.7,

95%CI 0.4-1.0), which was less pronounced after adjustment for other risk factors ($RR_{adjusted}$ 0.8, 95%CI 0.4-1.4).

Surgery, minor injury or plaster cast were not associated with the development of PTS, nor were pregnancy or the use of female hormones. Patients with an idiopathic deep venous thrombosis conferred a similar risk for PTS compared to patients with a provoked deep venous thrombosis (RR 0.9, 95%CI 0.7-1.2). The presence of factor V Leiden or the prothrombin 20210A mutation was not associated with the development of PTS (table 4).

Table 4. Risk factors not associated with post-thrombotic syndrome

Risk factor	N	N PTS	1 yr cum inc*	Risk Ratio†
Surgery‡				
yes	357	82	22%	1.1 (0.9-1.3)
no	1308	281	25%	1
Minor injury‡				
yes	405	87	25%	1.0 (0.8-1.2)
no	1251	274	25%	1
Plaster cast				
yes	105	24	28%	1.1 (0.7-1.5)
no	1563	340	24%	1
Pregnant among women <50 years‡				
yes				
no	73	23	35%	1.1 (0.8-1.6)
	489	141	32%	1
Oral anticonceptive use among women <50				
yes				
no	417	120	30%	1.0 (0.7-1.3)
	146	44	37%	1
HRT among women ≥ 50 years‡				
yes				
no	39	9	39%	1.0 (0.5-1.8)
	265	58	27%	1
Idiopathic DVT‡§				
yes	389	64	18%	0.9 (0.7-1.2)
no	1205	284	27%	1
Factor V Leiden mutation‡				
yes				
no	315	74	30%	1.1 (0.9-1.4)
	1311	284	24%	1
Prothrombin 20210A mutation‡				
yes				
no	92	25	24%	1.2 (0.9-1.7)
	1535	333	25%	1

* 1 yr cum inc = one-year cumulative incidence
‡ unknown in ≤ 74 patients
† adjusted for age and sex
§ DVT = deep venous thrombosis

Elastic Compression Stockings

Elastic compression stockings were prescribed in 1412 (85%) patients. The majority (77%) of these patients reported to wear their stockings every day, 300 (21%) patients did not wear them daily and only 30 (2%) never used their elastic compression stockings. In patients who used their elastic compression stockings daily the one-year cumulative incidence of PTS was 29% as compared to 33% in patients who did not use their elastic compression stockings daily.

Most patients (81%) started to wear elastic compression stockings within two months after the deep venous thrombosis. The one-year cumulative incidence of PTS in patients who started elastic compression stocking use within two months was 26% compared to 28% in patients who started use two months after the diagnosis.

Discussion

Twenty-five percent of all patients with a first deep venous thrombosis in the leg developed PTS within a year, even though a large majority of the patients reported to wear elastic stockings. Women, obese patients, patients with proximal deep venous thrombosis and those with varicose veins had an increased risk of PTS, whereas elderly patients appeared to have a decreased risk. Factor V Leiden and prothrombin 20210A mutation were not associated with the risk of PTS.

The 25% one-year cumulative incidence of PTS in our study is comparable with the 20 to 27% incidence of PTS after one to two years reported in patients who used elastic compression stockings.[3,6-10]

This is the first large follow-up study that assesses acquired and genetic risk factors for the development of PTS in 1668 patients with a first deep venous thrombosis. Women were at higher risk of PTS than men, with a cumulative incidence of 31% versus 17%. The influence of sex on the development of PTS showed contradictionary results in previous studies. Only one follow-up study in 244 patients showed an increased risk for women,[16] whereas another study showed an increased risk for men.[18] However, most studies did not find an association.[8,15,17] These contradictory results may be explained by small study populations[15,17] and the inclusion of patients with recurrent thrombosis.[8,16-18]

Recurrent deep venous thrombosis is a risk factor for PTS and might have concealed the impact of sex.

Our finding that obesity was associated with PTS has been reported before.[14-18] Excess body weight might increase venous pressure and promote reflux in already compromised veins. Moreover, a high BMI might be related to a lack of physical exercise and therefore a poor function of the muscle pump. Obesity is highly prevalent in the general population, with a prevalence of 21% in our study population, and showed an increased risk of PTS, with a cumulative incidence of 34% after one year. It is of interest that a high BMI is a risk factor for PTS, as obesity is a potentially modifiable risk factor and thus weight reduction may play a role in the prevention of PTS.

This study identified the presence of varicose veins before the development of deep venous thrombosis as a risk factor for PTS. Patients with varicose veins might have a diminished calf muscle pump function due to preexisting reflux, leading to higher walking venous pressure and the development of chronic venous insufficiency.[1] Our study found that proximal deep venous thrombosis is a risk factor for PTS.[18,26] This association between localization of the initial thrombus and PTS was not observed in all previous studies.[7,18] It is an important finding that calf vein thrombosis conferred a similar risk for PTS as popliteal vein thrombosis. This finding stresses the importance of treatment for symptomatic calf vein thrombosis.

The reduced PTS risk in older patients is an interesting finding and in contradiction to the increased risk in elderly patients reported in some,[8,16,18] but not all other studies.[15,17] We included patients below 70 years, where older patients were included in other studies, which makes it difficult to compare the results.[8,15-17] The reduced PTS risk may reflect differences in thrombus propagation in elderly patients. Recanalization of the thrombus is a relatively fast process, and most vein segments are recanalized within three months. In older patients thrombus evolution is an unstable process with continuing propagation for two years[27] and therefore older people might develop PTS later than younger people.

In our study neither factor V Leiden nor prothrombin 20210A mutation were associated with the onset of PTS, which is in contrast to what has been suggested by other investigators.[19-21] This is an

important observation as the role of inherited thrombophilia with regard to the risk of PTS is not well established.[8,14,17-21] It was recently shown that factor V Leiden and prothrombin 20210A mutation do not, increase the risk of a recurrent thrombotic event.[28] These results suggest that inherited thrombophilic work-up is not likely to confer clinical benefit to the patient regarding the prediction of the development of PTS.

This study describes the widespread use of elastic compression stockings. Wearing elastic compression stockings is a hassle in daily life for patients. It can be difficult to put them on and take them off, and they can be discomforting. The appearance of elastic compression stockings is also considered a reason for non-regular use. Despite these disadvantages the majority of these patients reported to be compliant and use their stockings every day. This is in accordance with a survey that shows that patients with deep venous thrombosis are willing to comply with elastic compression stocking therapy.[29] There may have been an overreported use of elastic compression stockings because of socially desirable response behaviour. This may explain the minimal difference in risk of PTS between patients who used elastic compression stockings daily and patients who did not.

The 25% one-year cumulative incidence of PTS is based on symptoms and signs reported by patients. There is no gold standard test for the diagnosis of PTS. This diagnosis can be based on clinical signs and symptoms or on objective assessment of venous valvular insufficiency and venous hypertension. We used a standardized clinical scale, with signs and symptoms to define presence and severity PTS, which was derived from the Villalta scale. Sustained venous hypertension, the underlying pathogenic mechanism of PTS, can be reliably measured by invasive ambulatory venous pressure tests. This technique requires special equipment, is invasive, time-consuming and cumbersome. It has been shown that PTS diagnosed with the Villalta scale is associated with an increased mean invasive venous ambulatory pressure of over 40 mmHg,[30] suggesting that the use of this scale seems justified. However, until uniform diagnostic criteria for PTS diagnosis are defined, this will remain a limitation of all clinical studies.

We assessed the presence and severity of PTS at a median of ten months after diagnosis of deep venous thrombosis. It usually takes 3 to 6 months after an acute deep venous thrombosis for the initial pain and swelling to resolve and the diagnosis of PTS should be deferred until later.[9,10,27] In

most cases PTS will become apparent within 1 year after the acute deep venous thrombosis, with little increase in incidence thereafter.[9] Thus, the 25% one-year cumulative incidence we found may have been an underestimation.

We conclude that PTS remains a frequent complication in patients with deep venous thrombosis despite the frequent use of elastic compression stockings. Female sex, older age, obesity and varicose veins were all associated with the development of PTS, whereas genetic risk factors were not.

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CHAPTER 7

Predictors of the post-thrombotic syndrome with non-invasive venous examinations in patients six weeks after a first episode of deep venous thrombosis

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Background Post-thrombotic syndrome is a chronic complication of deep venous thrombosis affecting a large number of patients. Because of its potential debilitating effects, identification of patients at high risk for the development of this syndrome is relevant and only a few predictors are known.

Objectives To assess the incidence and potential predictors of the post-thrombotic syndrome.

Methods We prospectively followed 111 consecutive patients for two years after a first episode of objectively documented deep venous thrombosis of the leg. With non-invasive tests, residual thrombosis, valvular reflux, calf muscle pump function, and venous outflow resistance were assessed at 6 weeks, 3 and 6 months, and at 1 and 2 years. The CEAP-classification served to record the occurrence and severity of the post-thrombotic syndrome. Regression analysis with area under the receiver operating characteristic (ROC) curve was performed to identify potential predictors.

Results The cumulative incidence of the post-thrombotic syndrome was 49% after one year, and the incidence and severity did not further increase afterwards. Men were at an increased risk compared to women (risk ratio (RR) 1.4, 95% confidence interval (CI) 0.9-2.2), as were patients over 50 years compared to younger patients (RR 1.4, 95%CI 0.9-2.1). Patients with thrombosis localized in the proximal veins at diagnosis had an increased risk of the post-thrombotic syndrome compared to patients with distal thrombosis (RR 2.3, 95%CI 1.0-5.6). The post-thrombotic syndrome developed in 32 out of 52 patients (62%) with residual thrombosis in the proximal veins six weeks after diagnosis, compared to 17 out of 45 patients (38%) without residual proximal thrombosis, leading to a 1.6-fold increased risk (95%CI 1.0-2.5). The presence of valvular reflux in the superficial veins was also a predictor at six weeks with a 1.6-fold increased risk compared to patients without superficial reflux (95%CI 1.1-2.3). A multivariate analysis of these predictors yielded a ROC area-under-the-curve of 0.72 (95%CI: 0.62-0.82).

Conclusion Post-thrombotic syndrome develops in half of all patients within one year, with no further increase up to two years of follow-up. Male sex, age over 50 years, proximal localization of the thrombus at entry, residual proximal thrombosis and superficial valvular reflux at six weeks are predictors of the post-thrombotic syndrome in patients with a first episode of deep venous thrombosis. Duplex scanning six weeks after diagnosis appears to be clinically useful to identify patients at risk of the post-thrombotic syndrome.

Introduction

Acute deep venous thrombosis may lead to chronic venous complications in 20 to 50% of patients (1). Factors that play a role in the pathophysiology of this so-called post-thrombotic syndrome are 1) damage to venous valves, which causes valvular reflux with diminished calf muscle pump function nd 2) persistent venous obstruction due to incomplete thrombus clearance. This leads to high walking venous pressure resulting in alterations of the skin microcirculation and morphological skin changes(2). These changes can be classified with the clinical score of the Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) classification (3,4).

As the post-thrombotic syndrome reduces quality of life (5), and is costly to society (6), it would be desirable to identify patients at risk for post-thrombotic syndrome at an early stage. Strategies for the prevention and management of the post-thrombotic syndrome should be applied in these high-risk patients. Recurrent ipsilateral deep venous thrombosis is a risk factor and should be prevented with adequate anticoagulation therapy (7,8). Continuous use of elastic compression therapy after deep venous thrombosis reduces the risk of the post-thrombotic syndrome by approximately 50% (8,9). Non-invasive venous examinations, such as duplex scanning and strain gauge plethysmography may be useful to predict the development of post-thrombotic syndrome. With duplex scanning it is possible to measure the extent of the initial thrombus, residual thrombosis and valvular reflux, while strain gauge plethysmography quantifies venous outflow resistance and calf muscle pump function (10-13). These non-invasive examinations are however not routinely applied in clinical practice. Factors that have been associated with the development of the post-thrombotic syndrome are male sex, advanced age, increased body mass index, idiopathic deep venous thrombosis, proximal localization of deep venous thrombosis, extent of residual vein thrombosis, presence of valvular reflux, reduced calf muscle pump function, and increased venous outflow resistance (14-22). However, results of previous studies are conflicting with regard to the predictive value of these factors.

The objectives of the present study were to assess the incidence of post-thrombotic syndrome during two years of follow-up with standardized compression treatment after a first episode of deep venous thrombosis, and to determine the predictive value of non-invasive venous examination for the development of the post-thrombotic syndrome.

Methods

Study Design

Between May 2002 and September 2005, consecutive patients aged 18 to 70 with a first episode of deep venous thrombosis of the leg seen at the Meander Medical Center, Amersfoort, the Netherlands, were included in this follow-up study. All patients participated in the multicenter Multiple Environmental and Genetic Assessment (MEGA) of risk factors for venous thrombosis study (23). Patients with a life expectancy of less than one year and those with an inability to undergo ambulant compression therapy were excluded. Among the 134 eligible patients, 23 patients refused to participate, which led to 111 participating patients.

All patients were treated according to a standardized protocol with low molecular weight heparin and vitamin K antagonists for six months. Short-stretch elastic bandages were applied immediately after diagnosis. As soon as edema was reduced elastic therapeutic stockings were prescribed with compression class III (ankle pressure 35-45 mm Hg). The length of the bandages and the elastic therapeutic stockings were dependent on the localization of the thrombus. In case of proximal deep venous thrombosis thigh-length bandages and stockings were applied during three months, and followed by knee-length elastic compression stockings. In patients with distal deep venous thrombosis knee-length bandages and stockings were applied only. Elastic compression stockings were adapted for each patient by an experienced professional bandagist. Patients were instructed and motivated to wear the elastic compression stockings for at least two years. At each visit details on the frequency and duration of the use of elastic compression stockings were recorded.

Patients filled in a detailed questionnaire on demographic variables and acquired risk factors for venous thrombosis. The questionnaire covered the period of one year prior to the thrombotic event. Deep venous thrombosis was defined as idiopathic in the absence of malignancy, surgery, plaster cast, minor injury, bed rest at home or in the hospital, pregnancy and the use of female hormones. Body mass index was calculated from self-reported weight and height (kg/m^2).

All patients underwent physical examinations of the leg and non-invasive venous tests at regular intervals. The non-invasive venous tests consisted of duplex scanning and strain gauge plethysmography. These tests were performed at the time of diagnosis of deep venous thrombosis,

after six weeks, three and six months and after one and two years or when recurrent venous thrombosis occurred. Symptomatic recurrent deep venous thrombosis was objectively confirmed with duplex scanning.

A dermatologist who was unaware of the findings of non-invasive venous tests, performed the physical examinations of the leg and classified the skin changes in patients according to the clinical score of the Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) classification (3,4). In this classification patients with class 0 represent no visible or palpable signs of the post-thrombotic syndrome; class 1 telangiectasies or reticular veins; class 2 varicose veins; class 3 oedema without skin changes; class 4 skin changes ascribed to venous disease (pigmentation, venous eczema, lipodermatosclerosis, white atrophy, corona phlebectatica); class 5 skin changes with healed venous ulcer and class 6 skin changes with active venous ulcer. The post-thrombotic syndrome was considered to be present if the score was 3 or more. The presence and severity of the post-thrombotic syndrome was assessed in the leg in which the deep venous thrombosis occurred.

Duplex scanning was performed by one of three experienced vascular technologists with a Philips iU22 scanner with a 5 to 12 MHz linear array probe. Seventeen vein segments were examined with the patient in a 45° sitting position (10). The common femoral vein, superficial femoral vein, long and short saphenous vein, popliteal vein, posterior and anterior tibial veins, peroneal and gastrocnemial veins were examined. In the calf a distinction was made between the superficial and the deeper vein. Compressibility was assessed in the transverse plane. A vein was considered non-compressible when it was not completely compressed under gentle pressure of the duplex probe. A thrombosis score was based on the extent of occlusion by the thrombus (3). A vein segment scored one point when it was occluded completely or in part. A fully patent vein segment showed complete compressibility and flow, and scored zero points. Thrombosis score values for each patient were calculated by adding the thrombosis score values of each of the 17 vein segments. The thrombosis score was separately scored for the five proximal deep vein segments (common femoral, superficial femoral [proximal, middle, and distal], and popliteal veins), the eight distal deep vein segments (two posterior tibial, two anterior tibial, two peroneal, and two gastrocnemial), and the four superficial vein segments (long saphenous vein [proximal, middle, and distal] and short saphenous).

In the longitudinal plane, the presence of venous flow and valvular reflux was measured by duplex examination. Pathological valvular reflux was defined as a reversed flow duration of more than 1 sec in the proximal veins and more than 0.5 sec in the distal veins. Reflux score values were calculated by adding the number of vein segments with pathological valvular reflux (10).

Calf muscle pump function and venous outflow resistance were measured by a Filtrass angio strain gauge plethysmograph (compumedics ltd.) (11-13). Patients were examined in the supine position with the knees slightly bent at an angle of 90° and pneumatic cuffs around the thighs, and strain-gauges around the calves. The cuffs were inflated with a cuff pressure of 50 mmHg which resulted in an increase of venous volume and pressure. Maximum volume was achieved when the venous pressure equaled the effective congestion pressure. Then, with the cuffs still inflated, the patient was instructed to perform 10 dorsal extensions. The calf muscle pump action resulted in a volume decrease in the limb. In the period of rest after the exercise, with the cuffs still inflated, venous volume and pressure returned to their maximum value and the expelled volume was measured. By use of individual pressure-volume gradients, the expelled volume was converted to a pressure decrease. Pressure decrease (P1-P2) was expressed as a percentage of the initial pressure (P1) before the exercise and was a measure of the calf muscle pump function [PF = (P1-P2/P1) x 100%] (11).

Venous outflow resistance was assessed by measuring the maximum venous outflow at five different cuff pressures (60 to 20 mmHg). The maximum volume change ($\Delta V/V$) for each occlusion pressure was measured, and plotted against the effective cuff pressure. The slope of the line through the points gave an angle ß. In analogy with Ohm's law venous outflow resistance was calculated as 1/tangent ß and expressed in resistance units (RU): (mmHg x min)/%.

The study protocol was approved by the institutional review board and written informed consent was obtained from all participants.

Predictors

Based on previous studies, we a priori selected candidate predictors of post-thrombotic syndrome (14-22). These included sex, age, body mass index, varicose veins at diagnosis, idiopathic deep

venous thrombosis, localization of deep venous thrombosis, the extent of residual vein thrombosis quantified with the thrombosis score, and the presence of valvular reflux quantified with the reflux score, and calf muscle pump function and venous outflow resistance.

Statistical Analysis

The cumulative incidence of post-thrombotic syndrome was calculated as the number of patients with post-thrombotic syndrome divided by the overall number of patients. The relative risk of each predictor was calculated by risk ratios, with corresponding 95% confidence interval (95%CI). The risk ratios indicate the risk of post-thrombotic syndrome in the presence of a candidate predictor relative to the absence of that predictor. The chi-square test was used to assess differences between proportions. Subsequently, we included all candidate predictors with a P-value ≤0.10 in a multivariate logistic regression model. The ability of the model to discriminate between patients with and without post-thrombotic syndrome was estimated by the area-under-the-receiver operating characteristic (ROC) curve. All computations were performed with the use of SPSS software, version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics of the 111 patients with a first episode of symptomatic deep venous thrombosis are summarized in Table 1. There were 52 women (47%), the mean age of all patients at time of diagnosis was 48 years (5^{th} -95^{th} percentile 27-68) and the overall mean age was 5 years higher in men than in women. Varicose veins, as assessed by the dermatologist, were present at entry in 15 patients (13%). Thrombosis was unilateral on the left side in 55 patients (50%), and none of the patients had bilateral deep venous thrombosis. Distal thrombosis was present in 18 patients (16%), and deep venous thrombosis was idiopathic in 34 patients (31%) (Table 1).

A total of 94 patients (85%) completed the two years of follow-up, 11 patients did not complete the follow-up because they were unable to come to the hospital for all examinations, and six patients died of various causes. Recurrent symptomatic deep vein thrombosis was diagnosed in six patients. Two recurrences occurred in the ipsilateral leg and four in the contralateral leg. Median duration to recurrence was 7 months (5^{th}-95^{th} percentile 4-13). Three patients used vitamin K antagonists during their recurrence.

Table 1. Characteristics of 111 patients with a first episode of deep venous thrombosis of the leg

Characteristic	
Women, No (%)	52 (47%)
Age (years), mean (SD)	48 (12)
5th -95th percentile	27-68
BMI (kg/m2), mean (SD)	27 (4)
5th -95th percentile	21-36
Varicose veins at diagnosis	15 (13%)
Side of DVT	
left	55 (50%)
right	56 (50%)
Localization of DVT	
proximal	73 (66%)
proximal and superficial	13 (12%)
superficial	7 (6%)
distal	18 (16%)
Malignancy	6 (5%)
Surgery	25 (23%)
Plaster cast	9 (8%)
Minor injury	34 (31%)
Bed rest at home or in hospital	29 (26%)
Pregnancy	2 (2%)
Hormone use among women	24 (46%)
Idiopathic DVT	34 (31%)

BMI = body mass index, SD = standard deviation, DVT = deep venous thrombosis

Mean duration of initial bandages was 19 days (5th-95th percentile 8-36). Thigh-length compression therapy was used in 80 out of 111 patients (72%) for the first three months followed by knee-length stockings, the remaining 31 patients used knee-length compression therapy from diagnosis onwards. Elastic therapeutic stockings with compression class III were used in 107 out of 111 patients (96%), 4 patients (4%) used class II stockings. Despite the advise to use elastic compression stockings for two years, 22 patients used them for a shorter period. In seven of these patients this was due to intercurrent disease or death and 15 patients were non compliant because of other reasons. Good compliance (≥ 6 days per week) was reported by 74 patients (67%).

Anticoagulation was given during six months in 83 patients (75%), six patients (5%) were treated for a shorter period, with a mean duration of 95 days (5th-95th percentile 45-128). In 13 out of 22 patients

who were treated for more than six months, vitamin K antagonists treatment was continued for more than one year.

Incidence and Severity of the Post-thrombotic Syndrome

The cumulative incidence of PTS (CEAP ≥3) was 46% at 6 weeks after the deep venous thrombosis, 49% after one year and did not increase afterwards (Table 2). The incidence of CEAP classification 4 progressed from 26% at entry to 33% at 6 weeks and then also stabilized, at 39% after one and two years. The initial increase in CEAP classification 4 skin changes was mainly due to newly formed corona phlebectatica. None of the patients was diagnosed with CEAP classification 5 or 6. Post-thrombotic syndrome was established in the first year after deep venous thrombosis, without progression of the incidence or severity in the second year.

Table 2. CEAP score during follow-up in 111 patients with a first episode of deep venous thrombosis in the leg.

CEAP score	*Clinical signs*	*diagnosis*	*six weeks*	*three months*	*six months*	*one year*	*two* years*
0	No visible or palpable signs	25	44	42	42	39	42
1-2	Telangiectases, reticular veins, malleolar flare or varicose veins	6	10	12	10	12	14
3	Oedema, without skin changes	43	13	8	7	10	5
4	Skin changes ascribed to venous disease	26	33	38	41	39	39
5-6	Skin changes with (healed) ulceration	0	0	0	0	0	0
≥ 3	Post-thrombotic syndrome		46	46	48	49	44

All values are percentages of all patients, i.e. 25 means 25% of all patients had a CEAP score of zero at diagnosis
* in 13 patients CEAP was incomplete during two-years of follow-up

Residual Thrombosis and Valvular Reflux

In all veins thrombus resolution was a continuing process. The resolution of thrombus was more rapid and complete in patients with thrombosis in distal vein segments than in those with proximal thrombosis. At diagnosis 78% of the five proximal vein segments was occluded completely or in part, after six weeks this was reduced to 54%, and after two years 33% showed residual thrombosis (Table

3). The superficial and distal vein segments showed less residual thrombosis after two years, respectively 7% and 3%. Men had more proximal residual thrombosis at six weeks than women; 35 out of 55 men (64%), compared to 20 out of 47 women (43%). The thrombosis score declined from a mean of 3.8 non-compressible segments at diagnosis to 2.0 after six weeks and 0.8 after 2 years. Valvular reflux was present at an average of 0.6 segments at diagnosis and this increased slightly to 0.9 segments after 6 weeks and 1.1 after two years.

Table 3. Residual thrombosis and valvular reflux over time in patients with a first episode of deep venous thrombosis.

Vein segments	residual thrombosis			valvular reflux		
	diagnosis n=111	six weeks n=102	two years n=97	diagnosis n=72	six weeks n=102	two years n=97
Proximal, n (%)* (5 vein segments)	87 (78)	55 (54)	32 (33)	6 (8)	21 (21)	36 (37)
Superficial, n (%) (4 vein segments)	20 (18)	17 (17)	2 (7)	9 (13)	22 (22)	15 (16)
Distal, n (%) (8 vein segments)	69 (62)	29 (28)	3 (3)	5 (7)	0 (0)	7 (7)
Thrombosis score Reflux score, Mean** (range)	3.8 (0-11)	2.0 (0-9)	0.8 (0-5)	0.6 (0-5)	0.9 (0-7)	1.1 (0-7)

* n (%) is number and percentage of patients with residual thrombosis or valvular reflux at that specific point in time. For example 87 (87) means that 87 out of 111 patients (78%) had thrombosis in a proximal vein.
** Mean score of 17 vein segments

Functional Venous Hemodynamic Tests

At diagnosis, 22% of patients had a calf muscle pump function under 40%, six weeks later this was only 13%, and the number declined to 6% after one and two years (Table 4). Only 20% of patients had a calf muscle pump function greater than 60% at diagnosis, this number increased to 38% after six weeks and then stabilized at 40% after one and two years. Mean calf muscle pump function improved from 48% at diagnosis to 54% after 6 weeks and was stable at 56% at one and two years.

Mean venous outflow resistance declined during treatment from 3.0 RU at diagnosis to 2.5 RU after three months and remained stable during one year follow-up and showed an increase to 2.9 RU after two years of follow-up.

Table 4. Calf Muscle Pump and Venous Outflow Resistance measured by Strain Gauge Plethysmography during two-years of follow-up

	diagnosis	*six weeks*	*three months*	*six months*	*one year*	*two years*[*]
CMP < 40%, n (%)[**]	22 (22)	13 (13)	13 (13)	11 (11)	6 (6)	6 (6)
CMP 40-60%, n (%)	59 (58)	50 (49)	41 (41)	43 (42)	51 (54)	51 (54)
CMP ≥ 60%, n (%)	20 (20)	38 (38)	47 (46)	48 (47)	37 (40)	37 (40)
CMP in %, mean (range)	48 (10-76)	54 (14-79)	55 (10-80)	56 (20-76)	56 (23-80)	56 (24-94)
VOR in RU, mean (range)	3.0 (0.6-17.2)	2.9 (0.3-25.0)	2.5 (0.7-19.3)	2.5 (0.6-9.2)	2.5 (0.4-13.2)	2.9 (0.7-16.1)

CMP=calf muscle pump function, VOR=venous outflow resistance, RU=resistance unit, SD=standard deviation
[*] in 17 patients strain gauge plethysmography was not complete during two-years of follow-up
[**]n (%) number and percentage of patients with calf muscle pump function below 40%

Predictors of the Post-thrombotic Syndrome

Men had a 1.4-fold higher risk of developing the post-thrombotic syndrome than women (risk ratio (RR) 1.4, 95% confidence interval (CI) 0.9-2.2) (Table 5).

Patients over 50 years had a 1.4-fold increased risk of the post-thrombotic syndrome compared to patients below this age (RR 1.4, 95%CI 0.9-2.1). The risk of the post-thrombotic syndrome was 2.3-fold higher in patients with thrombosis localized in the proximal veins compared to distal thrombosis (RR 2.3, 95%CI 1.0-5.6). Post-thrombotic syndrome developed in 39 out of 64 patients (61%) with residual thrombosis, i.e. thrombosis score ≥1, six weeks after diagnosis, compared to 10 out of 33 patients (30%) without residual thrombosis, leading to a two-fold increased risk (RR 2.0, 95%CI 1.6-3.5). Patients with residual thrombosis in the proximal veins, i.e. proximal thrombosis score ≥1, also had an increased risk compared to patients without proximal residual thrombosis (RR 1.6, 95%CI 1.0-2.5).

Table 5. Risk of post-thrombotic syndrome one year after deep venous thrombosis in 99 patients.

	With PTS N=49 N (%)	Without PTS N=50 N (%)	Rate ratio (95%CI)	P-value*
Sex				
men	30 (58)	22 (42)	1.4 (0.9-2.2)	<0.1
women	19 (40)	28 (60)		
Age				
≥50 years	24 (59)	17 (41)	1.4 (0.9-2.1)	0.1
<50 years	25 (43)	33 (57)		
BMI				
≥25 kg/m^2	33 (51)	32 (49)	1.1 (0.7-1.7)	0.7
<25 kg/m^2	16 (47)	18 (53)		
Varicose veins at diagnosis				
yes	8 (62)	5 (38)	1.3 (0.8-2.1)	0.4
no	41 (48)	45 (52)		
Idiopathic DVT				
yes	14 (45)	17 (55)	0.9 (0.5-1.4)	0.6
no	35 (51)	33 (49)		
DVT localization				
proximal	45 (55)	37 (45)	2.3 (1.0-5.6)	<0.05
distal	4 (23)	13 (77)		
TS at 6 weeks**				
≥1	39 (61)	25 (39)	2.0 (1.6-3.5)	<0.01
<1	10 (30)	23 (70)		
$TS_{proximal}$ at 6 weeks**				
≥1	32 (62)	20 (38)	1.6 (1.1-2.5)	<0.05
<1	17 (38)	28 (62)		
Reflux score at 6 weeks**				
≥1	19 (66)	10 (34)	1.5 (1.0-2.2)	<0.05
<1	30 (44)	38 (56)		
Superficial reflux at 6 weeks**				
yes	13 (72)	5 (28)	1.6 (1.1-2.3)	<0.05
no	36 (46)	43 (54)		
Popliteal reflux at 6 weeks**				
yes	8 (67)	4 (33)	1.4 (0.9-2.2)	0.2
no	41 (48)	44 (52)		
CMP at 6 weeks**				
<60 %	33 (57)	25 (43)	1.3 (0.8-2.0)	0.2
≥60 %	16 (44)	20 (56)		
VOR at 6 weeks**				
≥1.5 RU	38 (53)	34 (47)	1.1 (0.7-1.7)	0.8
<1.5 RU	11 (50)	11 (50)		

PTS=post-thrombotic syndrome, BMI=body mass index, DVT=deep venous thrombosis, TS=thrombosis score, CMP=calf muscle pump function, VOR=venous outflow resistance, RU=resistance unit

* P-value of chi-square test

** Unknown in ≤5 patients

The presence of valvular reflux in one or more vein segments six weeks after diagnosis, i.e. reflux score ≥1, compared to no reflux showed a 1.5-fold increased risk of the post-thrombotic syndrome (RR 1.5, 95%CI 1.0-2.2). Post-thrombotic syndrome developed in 13 out of 18 patients (72%) with

superficial valvular reflux six weeks after diagnosis, compared to 36 out of 79 patients (46%) without superficial reflux. The presence of superficial valvular reflux was a predictor of the post-thrombotic syndrome with a 1.6-fold increased risk compared to patients without superficial reflux (RR 1.6, 95%CI 1.1-2.3). The combination of residual thrombosis in the proximal veins and the presence of superficial valvular reflux was seen in eight patients of whom seven developed the post-thrombotic syndrome (88%) at one year.

Body mass index, varicose veins at diagnosis or idiopathic deep venous thrombosis were not associated with the development of the post-thrombotic syndrome, nor were calf muscle pump function or venous outflow resistance.

Thus, sex, age, localization of deep venous thrombosis, (proximal) thrombosis score at 6 weeks, reflux score, and the presence of superficial valvular reflux at 6 weeks, were associated (all P-value ≤ 0.1) with the development of the post-thrombotic syndrome (Table 5). Proximal thrombosis score and superficial valvular reflux were included in a multivariate model together with sex, age and localization. This model yielded a ROC area-under-the-curve of 0.72 (95%CI: 0.62-0.82). Subsequent addition of venous outflow resistance and calf muscle pump function to this model resulted in a minor improvement with a ROC area-under-the-curve of 0.75 (95%CI: 0.66-0.85). Replacement of proximal thrombosis score with overall thrombosis score and superficial valvular reflux with overall reflux score led to a ROC area-under-the-curve of 0.77 (95%CI: 0.68-0.87). Subsequent addition of idiopathic thrombosis showed the highest ROC area-under-the-curve of 0.79 (95%CI: 0.70-0.88). Addition of body mass index or varicose veins at diagnosis did not show further improvement of the ROC area-under-the-curve.

Discussion

This study revealed that the post-thrombotic syndrome occurs in half of all patients within one year after a first episode of symptomatic deep venous thrombosis of the leg when elastic compression stockings are applied. Non-invasive venous examination six weeks after diagnosis showed that residual thrombosis of the proximal veins and valvular reflux in the superficial veins were predictors of the post-thrombotic syndrome. Other predictors included proximal localization of thrombosis at diagnosis, age over 50 years and male sex.

Residual thrombosis and valvular reflux were measured with duplex examination in 17 vein segments of the leg, which is an elaborate examination even in the hands of experienced vascular technicians. Both proximal thrombosis score, which quantifies the occlusion of five proximal vein segments, and the superficial reflux score, which quantifies valvular reflux in the four superficial vein segments, were predictors of post-thrombotic syndrome. Previous studies showed that (proximal) thrombosis score and (superficial) reflux score, measured three to six months after diagnosis, are predictors of post-thrombotic syndrome (15,16,18,20). Here we show the predictive value of a simplified duplex examination as early as six weeks after deep vein thrombosis.

Proximal localization of thrombosis at diagnosis showed an increased risk of the post-thrombotic syndrome. Results of previous studies have been inconsistent with regard to the relationship between localization of the initial thrombus and the subsequent development of the post-thrombotic syndrome (7,21,24). An explanation for the increased risk of the post-thrombotic syndrome may be that patients with proximal thrombosis have more residual thrombosis, and residual thrombosis increases the risk for the post-thrombotic syndrome. Another possible explanation is that the collateral circulation in the proximal veins is less extensive compared to the distal veins of the calf, as each artery in the calf is accompanied by two veins.

We found that older age and male sex conferred an increased risk of developing the post-thrombotic syndrome. The increased risk in elderly patients has been reported in some (8,21), but not all studies (19,22). Male sex was a risk factor in one other study (21). The higher risk of the post-thrombotic syndrome in men might be related to the older age of men in this study and the higher rate of proximal residual thrombosis. The reason why men might have a delayed thrombus regression is currently unknown but can explain the higher risk of recurrent thrombosis in men (17, 25-27). Overall, the predictive value of age and sex were not consistent in previous studies.

In contrast to other studies body mass index was not associated with the development of the post-thrombotic syndrome in our study (19,21,22). Furthermore, we did not show a predictive value of the non-invasive examination of calf muscle pump function and venous outflow resistance in the univariate analysis. Adding these tests to the multivariate model showed only a minor improvement of

the ROC area-under-the-curve. This is in contrast to previous studies that identified venous outflow resistance as a predictor of the post-thrombotic syndrome (15,20).

The overall risk of 49% post-thrombotic syndrome that we observed after one year, is comparable with the incidence of the post-thrombotic syndrome after one to two years reported in other studies that used the CEAP classification (15,16,20). Studies that used the Villalta scale to classify the post-thrombotic syndrome, observed a lower incidence of 20 to 40% (7,9,18,22). The Villalta scale uses symptoms and signs whereas the CEAP classification uses clinical signs that represent a progressive gradation of disease severity. A higher incidence of the post-thrombotic syndrome using the CEAP score in comparison to the Villalta scale was also shown in a study that compared the different classifications for the post-thrombotic syndrome (28). Until uniform diagnostic criteria for the post-thrombotic syndrome are defined, the ability to compare results from different studies will remain limited.

None of the patients in our study had a CEAP classification 5 or 6. The use of immediate short-stretch elastic bandages followed by class III elastic therapeutic stockings probably reduced the development of the post-thrombotic syndrome and may be the explanation for the absence of venous ulceration (8,9,20,29).

The true time of onset of the post-thrombotic syndrome after an objectively diagnosed first deep venous thrombosis is uncertain. Earlier studies, one with a follow-up of twenty years, suggested a gradual increase in incidence of the post-thrombotic syndrome over the years (7,29,30). More recent studies with a follow-up period of five years showed that the post-thrombotic syndrome develops within two years (8,9,20,31). Our results show that the post-thrombotic syndrome is established within one year after deep venous thrombosis, without an increase in the incidence or severity of the post-thrombotic syndrome after one up to two years, in patients treated with immediate adequate compression therapy.

A strength of this study is the high percentage of complete follow-up. Our study shows that one year follow-up allows sufficient time for the post-thrombotic syndrome to become apparent. Hence, future

studies focusing on the development of post-thrombotic syndrome, can be limited to a one-year follow-up duration.

A possible clinical implication of our findings is that a simplified duplex scanning should be performed in all patients six weeks after deep vein thrombosis to identify patients at high risk for the post-thrombotic syndrome. This syndrome developed within one year in 88% of patients who were treated with compression therapy with a duplex scanning at six weeks that showed combined residual proximal thrombosis and superficial valvular reflux.

Another important reason to implement non-invasive examination with duplex scanning six weeks after diagnosis is to differentiate between symptomatic recurrent thrombosis and residual thrombosis with post-thrombotic complaints during follow-up. In patients with recurrent thrombosis treatment should be focused on anticoagulation therapy, whereas compression therapy is the treatment strategy in patients with residual thrombosis and post-thrombotic complications. Recurrence rate after a symptomatic first deep venous thrombosis is high with 5% after 2 years up to 25% after 5 years (7,25-27,32). Patients with residual thrombus have an increased risk of recurrence and the post-thrombotic syndrome (15,17,18,20,32). Duplex scanning six weeks after diagnosis elucidates the changes of the thrombus in the individual patient and enables the physician to compare residual thrombus with recurrent thrombus when a patient returns with symptoms after a deep venous thrombosis.

The results of this study may have implications for the advised duration of elastic compression stockings. We identified that men over 50 years with proximal deep venous thrombosis and residual proximal thrombosis or superficial valvular reflux six weeks after diagnosis were at increased risk of developing the post-thrombotic syndrome. These high-risk patients are candidates for long term compression therapy. A question that remains to be answered is how long patients with an indication for long term compression therapy should continue this therapy: two years, or even longer. In patients without these predictors or signs of the post-thrombotic syndrome, compression therapy could be stopped after adequate treatment and recovery of deep venous thrombosis in the first three to six months. Prospective studies should confirm whether it is safe to withhold compression therapy in these patients.

We conclude that the post-thrombotic syndrome develops in one half of all patients within one year, with no increase in incidence or severity up to two years of follow-up. Male sex, age over 50 years, proximal localisation of thrombus at diagnosis, residual thrombosis in the proximal veins and valvular reflux in the superficial veins six weeks after diagnosis are predictors of the development of the post-thrombotic syndrome in patients with a first episode of deep venous thrombosis. A simplified duplex scanning six weeks after diagnosis of deep venous thrombosis enables the identification of patients at high risk of the post-thrombotic syndrome.

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Summary

Venous thrombosis is a common disorder with an incidence of 1 to 3 individuals per 1000 per year[1]. Most often venous thrombosis occurs in the deep veins of the leg but other locations are also possible, e.g. upper extremities or hepatic veins. Pulmonary embolism occurs when part of the blood clot dislodges and migrates via the bloodstream through the heart into the lungs. Deep venous thrombosis is a serious disorder because of its potential complication the post-thrombotic syndrome[2]. Pulmonary embolism is a potentially fatal disease in which early recognition and institution of anticoagulant therapy can prevent death[3]. A large proportion of patients with clinically suspected venous thrombosis do not have the disease[4]. Therefore it is important to accurately exclude or confirm the diagnosis in patients with suspected venous thrombosis.

Diagnosis of Venous Thrombosis

In the first part of this thesis two new diagnostic strategies are described to safely and efficiently exclude or confirm deep venous thrombosis and pulmonary embolism in patients in whom this disease is suspected.

The imaging test of choice in the diagnosis of deep venous thrombosis is the highly specific ultrasonography. Due to the less than optimal sensitivity for calf vein thrombosis, ultrasonography requires serial testing which is often difficult to implement in busy clinical care systems[5-7]. For all diagnostic tests regardless their accuracy, the post-test probability of disease is highly dependent on the pretest probability. The combination of clinical pretest probability assessment, D-dimer test and ultrasonography increases the predictive value and reduces the need for repeat ultrasonography. In **Chapter 2** we report the findings of 811 patients with clinically suspected deep venous thrombosis using a diagnostic management strategy that combined ultrasonography with clinical probability[8] and measurement of D-dimers[9,10]. To assess the safety of this algorithm we assessed the incidence of symptomatic venous thrombosis during 3-months of follow-up as the primary endpoint. In 280 patients (35% of the study population) the clinical probability of deep venous thrombosis was considered low; in 30 of these 280 patients (11% prevalence) a thrombosis could be demonstrated with an abnormal initial ultrasonography. Of the other 250 patients with low clinical probability and a normal ultrasonography who remained untreated, 5 patients (2%; 95% confidence interval [CI]: 1-5%) developed a nonfatal venous thrombosis during follow-up. In 531 patients (65% of the study

population) the clinical probability of venous thrombosis was classified as intermediate to high; in 300 of these 531 patients (56%) the diagnosis was made with an abnormal initial ultrasonography. Of the remaining 231 patients with a normal ultrasonography, 148 had a normal D-dimer test; these were left untreated and none of them developed deep venous thrombosis during follow-up (0%; 95%CI: 0-3%). Of the 83 patients with an abnormal D-dimer test, 77 underwent repeat ultrasonography about 1 week later; none of the 64 patients with a second normal ultrasound, who were left untreated, developed symptomatic deep vein thrombosis during follow-up (0%; 95% CI: 0-6%). The need for repeat ultrasonography was reduced by 85% (from 250 + 231 = 481 patients to 83 patients). This study shows a practical and safe management strategy in ruling out deep vein thrombosis in patients with clinically suspected thrombosis.

There are many different diagnostic strategies to exclude or confirm pulmonary embolism. These diagnostic algorithms are usually complicated and therefore not easily implemented in clinical practice[11]. It is important to develop a simple but effective management strategy in the diagnosis of pulmonary embolism. In **Chapter 3** the safety of a simple diagnostic algorithm, combining clinical probability[12], D-dimer testing and computed tomography[13] in patients with suspected pulmonary embolism was assessed. Pulmonary embolism was classified as "unlikely" or "likely" using a dichotomized clinical decision rule with a cutoff level of ≤ 4 points. In patients with unlikely pulmonary embolism and a normal D-dimer test result (< 500 ng/ml), the diagnosis was considered excluded and anticoagulation treatment was withheld. All other patients underwent computed tomography. The primary outcome of this study (named the Christopher study) was the incidence of symptomatic venous thrombosis during 3 months of follow-up. Of the 3306 included patients pulmonary embolism was classified as unlikely in 2206 patients (67%). Pulmonary embolism was excluded in 1057 patients (32%) with the combination of an unlikely clinical probability and a normal D-dimer test. Subsequent nonfatal venous thrombosis, during 3-month follow-up, occurred in 5 patients (0.5%, 95% CI: 0.2-1.1%). In 2249 patients computed tomography was performed which showed pulmonary embolism in 674 patients (20% of the study population). Computed tomography excluded pulmonary embolism in 1505 patients with a subsequent 3-month incidence rate, without treatment, of 1.3% (95%CI: 0.7-2.0%). The algorithm was completed and allowed a management decision in 98% of patients. These results showed us that the diagnostic algorithm is easy to use and as effective as other more complex strategies in the management of patients with clinically suspected pulmonary

embolism. This algorithm is associated with low risk for subsequent fatal and nonfatal venous thrombosis.

Whether the clinical utility of this diagnostic strategy in excluding pulmonary embolism could be further optimized by varying the cutoff levels of the clinical decision rule as well as the D-dimer test, without jeopardizing safety, was evaluated in **Chapter 4**. For this study we performed a post-hoc analysis of the Christopher study. Pulmonary embolism was excluded in 29.3% of the population with the combination of an unlikely clinical probability (clinical decision rule ≤ 4) and a D-dimer test below 500 ng/ml. In these patients no additional imaging tests were necessary. The overall incidence of symptomatic venous thrombotic events during 3 months of follow-up was 0.9% (95%CI: 0.3-2.4%). This did not exceed the generally accepted safety upper limit of 2.7%, which is the upper limit of the 95% confidence interval of the 3-month thrombotic rate after a normal pulmonary angiography[14]. By increasing the cutoff level of the clinical decision rule from 4 to 5 points, pulmonary embolism could be ruled out in an additional 4% of the study population (from 29.3% to 33.3%) at the expense of an increased 3-month venous thrombotic rate of 1.5% (95%CI: 0.6-3.0%). By increasing the D-dimer cutoff level from 500 to 600 ng/ml, pulmonary embolism could be ruled out in an additional 3% of the study population but the 3-month thrombotic rate increased to 2.2% (95%CI: 1.1-4.0). This study demonstrates that the cutoff levels of the clinical decision rule as well as the the D-dimer test should be kept at the original cutoff levels, respectively 4 points and 500 ng/ml, in order to prevent the 3-month thrombotic rate exceeding that of a normal pulmonary angiography.

These previous studies showed that D-dimer levels below 500 ng/ml have a high sensitivity in ruling out pulmonary embolism. The specificity of D-dimer levels below 500 ng/ml is not high enough to accurately confirm this diagnosis. However, by increasing the D-dimer cutoff levels it is possible to increase the specificity of the D-dimer test. Studies with increased D-dimer cutoff levels were restricted to populations with a low risk for venous thrombosis[15,16]. In **Chapter 5** we assessed the clinical consequences of high quantitative D-dimer levels combined with clinical probability score in the management strategy in patients with suspected pulmonary embolism. We included patients with a high risk for venous thrombosis, i.e., hospitalized patients, patients older than 80 years and patients with a malignancy or previous surgery. The overall prevalence of pulmonary embolism was 21%. The pulmonary embolism prevalence was strongly associated with the the D-dimer level, and increased

fourfold (from 15% to 61% prevalence) with D-dimer levels greater than 4000 ng/ml compared to levels between 500 and 1000 ng/ml. In patients with unlikely pulmonary embolism and D-dimer levels greater than 2000 ng/ml, the prevalence of pulmonary embolism increased to 36% which is similar to the overall prevalence in the likely pulmonary embolism group. These results allowed us to conclude that strongly elevated D-dimer levels substantially increase the likelihood of pulmonary embolism, even in patients with a high risk for venous thrombosis. Whether this should translate into more intensive diagnostic and therapeutic measures in patients with high D-dimer levels, irrespective of clinical probability, remains to be studied.

Post-thrombotic Syndrome

The second part of this thesis addresses the incidence, risk factors and early predictors of the post-thrombotic syndrome (PTS).

PTS is a chronic complication that develops in 20 to 50% of patients after deep venous thrombosis[2]. The clinical features vary from mild oedema to chronic pain and venous ulcers in the affected limb. There is no 'gold standard' test for the diagnosis of PTS and the diagnosis is primarily based on clinical features. In contrast to the many identified risk factors for deep venous thrombosis[17], the only identified risk factors for PTS so far are recurrent, ipsilateral deep venous thrombosis and a high body mass index[18-21]. We performed a large follow-up study to assess acquired and genetic risk factors for the development of PTS after a first deep venous thrombosis. In **Chapter 6** we report the findings of 1668 patients of the Multiple Environmental and Genetic Assessment (MEGA) study. The one-year cumulative incidence of PTS was 25%, with a cumulative incidence of 7% for severe PTS. The one-year cumulative incidence of PTS in women was 31% compared to 17% in men. Women had a 1.5-fold higher risk of developing PTS than men (risk ratio (RR) 1.5, 95%CI 1.3-1.8). Similarly, obese patients had a 1.5 fold increased risk of PTS compared to patients with normal weight (RR 1.5, 95%CI 1.2-1.9), with a one-year cumulative incidence of 34% compared to 22%. Varicose veins were present in 28% of patients prior to the deep venous thrombosis, and in these patients the one-year cumulative incidence of PTS was 30%. These patients had a 1.5-fold increased risk of PTS compared to patients without varicose veins (RR 1.5, 95%CI 1.2-1.8). Proximal localization of thrombosis in the femoral and iliac vein was associated with a 1.3-fold increased risk of PTS compared to popliteal vein thrombosis (RR 1.3, 95%CI 1.1-1.6). Calf vein thrombosis conferred a

similar risk for PTS as popliteal vein thrombosis. Patients over 60 years were less likely to develop PTS than patients below the age of 30 (RR 0.6, 95%CI 0.4-0.9). Malignancy, surgery, minor injury, plaster cast, pregnancy or the use of female hormone did not influence the risk of PTS, nor did the factor V Leiden or prothrombin 20210A mutation. This study shows that PTS is a frequent complication of deep venous thrombosis despite the widespread use of elastic compression stockings. The results of this study led to the identification of new risk factors for PTS; women, obese patients, patients with proximal deep venous thrombosis and those with varicose veins have an increased risk of PTS, whereas the elderly appeared to have a decreased risk.

The pathogenic mechanism underlying PTS is venous hypertension caused by venous valvular reflux with diminished calf muscle pump function and persistent venous obstruction. This high venous pressure leads to alterations of the skin microcirculation and morphological skin changes[22]. These skin changes can be classified with the clinical score of the Clinical, Etiologic, Anatomic, and Pathofysiologic (CEAP) classification[23]. Venous hypertension will be present before clinical symptoms are manifest. With duplex scanning it is possible to measure the extent of the initial thrombus, residual thrombosis and valvular reflux, while strain gauge plethysmography quantifies venous outflow resistance and calf muscle pump function[24,25]. These non-invasive venous examinations can be useful to predict the development of PTS. **Chapter 7** assesses the predictive value of non-invasive venous examination in a 2-year follow-up study in 111 patients with a first deep venous thrombosis of the leg. The cumulative incidence of PTS was 49% after one year, and the incidence and severity did not increase afterwards. Men were at increased risk of PTS compared to women (RR 1.4, 95% confidence interval (CI) 0.9-2.2), as were patients over 50 years compared to younger patients (RR 1.4, 95%CI 0.9-2.1). Patients with thrombosis localized in the proximal veins at diagnosis had an increased risk of PTS compared to patients with distal thrombosis (risk ratio (RR) 2.3, 95% confidence interval (CI) 1.0-5.6). PTS developed in 32 out of 52 patients (62%) with residual thrombosis in the proximal veins six weeks after diagnosis, compared to 17 out of 45 patients (38%) without residual proximal thrombosis, leading to a 1.6-fold increased risk (RR 1.6, 95%CI 1.0-2.5). The presence of valvular reflux in the superficial veins was a predictor of PTS with a 1.6-fold increased risk (RR 1.6, 95%CI 1.1-2.3). A multivariate analysis of these predictors yielded a ROC area-under-the-curve of 0.72 (95%CI: 0.62-0.82). We found that PTS develops in half of all patients within one year after a first deep venous thrombosis, with no increase up to two years of follow-up.

This study identified five predictors of PTS: male sex, age over 50 years, proximal localization of the thrombus, residual proximal thrombosis and superficial valvular reflux at six weeks. Duplex scanning six weeks after diagnosis of deep venous thrombosis appears to be clinically useful to identify patients at risk of the PTS.

Conclusions

In the first part of this thesis we investigated two new diagnostic algorithms for patients with clinically suspected deep venous thrombosis and pulmonary embolism. These management strategies include both pretest clinical probability and D-dimer assay, and reduce the need for non-invasive imaging tests. These novel strategies are safe in excluding deep venous thrombosis and pulmonary embolism. The results of the first part of this thesis led to a different, more simple diagnostic strategy in patients with venous thrombosis. The diagnostic algorithm for the diagnosis of deep vein thrombosis led to a reduction of the need of serial ultrasonography. The use of D-dimer in patients with a low clinical probability can give a further reduction in the need of initial ultrasonography. A systematic review showed that in low clinical probability patients with negative D-dimer results, diagnosis of deep vein thrombosis can be safely ruled out without performing an ultrasonography[26]. The question of which D-dimer assay to use is another matter. The SimpliRED red cell agglutination assay that we used for the diagnosis of deep vein thrombosis has a lower sensitivity than rapid enzyme-linked immunosorbent assays (ELISAs)[10]. Indeed high sensitivity assays such as the rapid ELISA miss fewer venous thromboses than other tests. Conversely, the SimpliRED assay may reduce the need for imaging tests because of higher specificity. Nowadays, rapid ELISAs are being used frequently, and avoiding missed diagnoses is preferred over reducing imaging tests. Finally, it is important that D-dimer tests should only be employed if the physician is convinced that venous thrombosis is a diagnostic possibility and not as a screening test. The challenge for future studies is to provide new algorithms, which can safely provide a further reduction of the number of patients undergoing imaging tests for the diagnosis of venous thrombosis.

In the second part of this thesis we described two follow-up studies which led to the identification of new risk factors and early predictors for PTS. At present, the results of these studies enable us to provide individualized information to patients with a first deep venous thrombosis about their risk for the development of PTS. Future research should focus on validating and standardizing diagnostic

criteria for PTS. A standardized diagnosis is necessary to improve the uniformity of the diagnosis and to enhance the ability to compare results of different studies. Moreover, objective diagnosis of PTS will allow physicians to monitor the development and course of PTS in their own patients.

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Samenvatting

Veneuze trombose is een aandoening waarbij er een stolsel ontstaat in een bloedvat. Dit betreft meestal de diepgelegen vaten in het been of bekken (diep veneuze trombose). Wanneer er een deel van dit stolsel loslaat, kan dit via de bloedstroom meegevoerd worden, waarna het stolsel blijft steken in de bloedvaten van de long. Dit wordt een longembolie genoemd. Patiënten met een diep veneuze trombose lopen het risico op een chronische complicatie: het posttrombotisch syndroom. Een onbehandelde longembolie kan fatale gevolgen hebben, en het tijdig herkennen van de aandoening en het starten van behandeling met bloedverdunners is dan ook van groot belang. Bij een groot deel van de patiënten met een klinische verdenking op veneuze trombose is de ziekte niet aanwezig. Het is daarom belangrijk om de diagnose nauwkeurig uit te sluiten of te bevestigen bij patiënten met een klinische verdenking op veneuze trombose.

Diagnose Veneuze Trombose

De diagnose diep veneuze trombose wordt meestal door middel van echografisch onderzoek gesteld. Echter, dit onderzoek kan kleine stolsels in de kuit missen. Daarom wordt na een week een tweede echografie verricht om het kleine aantal patiënten, bij wie de kuitvene trombose verder is toegenomen, ook te detecteren. Het herhaald verrichten van een echografie van de beenvaten is een veilige, maar inefficiënte methode bij de diagnostiek van diep veneuze trombose.

Patiënten met diep veneuze trombose of longembolie kunnen zich met zeer uiteenlopende klachten presenteren en lange tijd werd gedacht dat deze klinische presentatie geen waarde had bij het stellen van de diagnose. In de jaren 90 heeft de introductie van een klinische beslisregel ervoor gezorgd dat artsen in staat zijn om patiënten met verdenking op veneuze trombose, in verschillende risicogroepen in te delen met een bijbehorend lage of hoge kans op de diagnose.

Verder is het meten van D-dimeer concentraties een belangrijk hulpmiddel in de diagnostiek van zowel diep veneuze trombose als longembolie. Een stolsel bestaat voornamelijk uit fibrine en D-dimeren zijn afbraakproducten van fibrine. Het testen van D-dimeer is dus een manier om de aanwezigheid van een stolsel in de bloedvaten te bepalen.

Het is dan ook belangrijk om een 'management strategie' toe te passen bij patiënten met verdenking op een veneuze trombose, die beeldvormend onderzoek combineert met een klinische beslisregel en D-dimeer test om het aantal noodzakelijke beeldvormende onderzoeken te verminderen.

Het eerste deel van dit proefschrift beschrijft twee nieuwe, veilige en efficiënte diagnostische strategieën bij patiënten met een klinische verdenking op diep veneuze trombose en longembolie.

In **hoofdstuk 2** bestuderen wij de waarde van de combinatie van echografie met een klinische beslisregel en D-dimeer bij de beoordeling van 811 patiënten met een verdenking op diep veneuze trombose. Met een klinische beslisregel werden patiënten ingedeeld in twee categorieën met een lage en een gemiddelde-tot-hoge waarschijnlijkheid op diep veneuze trombose. Diep veneuze trombose werd uitgesloten met één normale echografie bij patiënten met een lage waarschijnlijkheid en bij patiënten met een gemiddelde-tot-hoge waarschijnlijkheid in combinatie met een normale D-dimeer. Bij patiënten met een gemiddelde-tot-hoge waarschijnlijkheid en een afwijkende D-dimeer was een tweede normale echografie nodig om de diagnose uit te sluiten. De belangrijkste uitkomst van het onderzoek was de incidentie van veneuze trombose tijdens de drie eerstvolgende maanden. Bij 280 patiënten (35% van de onderzoeksgroep) was een lage waarschijnlijkheid voor diep veneuze trombose; 30 van deze 280 patiënten (11%) bleek toch trombose te hebben bij echografisch onderzoek. De overige 250 patiënten met een lage waarschijnlijkheid en een normale echografie werden niet behandeld en 5 patiënten (2%; 95% betrouwbaarheids interval [BI]: 1- 5%) ontwikkelden veneuze trombose tijdens de drie volgende maanden. Bij 531 patiënten (65% van de studie populatie) was een gemiddelde-tot-hoge waarschijnlijkheid op diep veneuze trombose en bij 300 van deze 531 patiënten (56% prevalentie) bleek bij echografie inderdaad een trombose aanwezig. Van de overige 231 patiënten met een normaal echografie onderzoek, hadden 148 patiënten een normale D-dimeer test en geen van deze patiënten ontwikkelde, zonder verdere behandeling, een diep veneuze trombose (0%; 95%BI: 0-3%). Bij patiënten met een afwijkende D-dimeer test werd de echografie na 1 week herhaald en bij geen van de 64 patiënten met een tweede normale echografie, ontstond een veneuze trombose (0%; 95% BI: 0-6%). De strategie resulteerde in een afname van 85% van de noodzaak tot herhaalde echografie (van 250 + 231 = 481 patiënten naar 83 patiënten). Dit onderzoek toont een praktisch en veilig algoritme om diep veneuze trombose uit te sluiten op basis van de combinatie van klinische beslisregel, echografie en D-dimeer.

Er zijn verschillende strategieën om de diagnose longembolie te stellen. Deze diagnostische algoritmes zijn vaak complex en moeilijk te implementeren in de kliniek.

In **hoofdstuk 3** is de veiligheid van een eenvoudig diagnostisch algoritme, bestaande uit een combinatie van klinische waarschijnlijkheid, D-dimeer test en computed tomografie (CT), onderzocht bij patiënten met een klinische verdenking op longembolie. Met een klinische beslisregel werden patiënten ingedeeld in twee categorieën waarbij longembolie onwaarschijnlijk of waarschijnlijk was. Een longembolie werd uitgesloten geacht wanneer de klinische beslisregel onwaarschijnlijk voor longembolie was en de D-dimeer test normaal. Alle overige patiënten ondergingen een CT scan. De belangrijkste uitkomst van dit onderzoek, de Christopher studie genaamd, was de incidentie van veneuze trombose tijdens de drie eerstvolgende maanden. Van de 3306 patiënten was het bij 2206 patiënten (67%) vanwege de klinische beslisregel onwaarschijnlijk dat zij een longembolie hadden. In 1057 patiënten (32%) met de combinatie onwaarschijnlijke longembolie en een normale D-dimeer test werd de diagnose uitgesloten geacht. De incidentie van veneuze trombose in deze groep was, gedurende drie maanden zonder behandeling, 0.5% (95%BI: 0.2-1.1%). Bij 674 van de 2249 patiënten die een CT ondergingen werd de diagnose longembolie gesteld (20% van de populatie). In 1505 patiënten toonde CT geen longembolie aan, bij 1.3% (95%BI: 0.7-2.0%) werd gedurende de drie daaropvolgende maanden alsnog een veneuze trombose vastgesteld. Het algoritme werd bij 98% van de patiënten gevolgd. Geconcludeerd kan worden dat deze strategie eenvoudig te gebruiken is en net zo veilig en effectief is als de complexere algoritmes.

In **hoofdstuk 4** wordt besproken of de efficiëntie van het algoritme om longembolie uit te sluiten verder kan worden verbeterd, zonder daarbij de veiligheid op het spel te zetten. Bij 29% van de populatie werd longembolie uitgesloten middels een klinische beslisregel ≤ 4 punten (longembolie onwaarschijnlijk) in combinatie met een normale D-dimeer test (< 500 ng/ml). Bij deze patiënten werd geen aanvullende beeldvormende diagnostiek verricht. De incidentie van veneuze trombose tijdens de drie daaropvolgende maanden was 0.9% (95%BI: 0.3-2.4%). Als veiligheidsgrens van het 95% betrouwbaarheidsinterval wordt 2.7% aangehouden. Dit komt overeen met de bovenste grens van het 95% betrouwbaarheidsinterval van de incidentie van veneuze trombose na een normale pulmonalisangiogram. Door het afkappunt van de klinische beslisregel van 4 naar 5 punten te

verhogen, kon de diagnose longembolie bij 4% meer patiënten worden uitgesloten. Dit ging echter ten koste van de veiligheid met een toegenomen incidentie van veneuze trombose tot 1.5% (95%BI: 0.6-3.0%). Door het verhogen van het afkappunt van de D-dimeer test van 500 naar 600 ng/ml, was het mogelijk om bij een extra 3% van de populatie een longembolie uit te sluiten, maar wederom met een verhoogde kans op veneuze trombose, van 2.2% (95%BI: 1.1-4.0). Om patiënten niet bloot te stellen aan een hoger veiligheidsrisico dan bij een normale pulmonalisangiografie, dienen de afkappunten van zowel de klinische beslisregel als de D-dimeer test te worden gehandhaafd op de oorspronkelijke waarden, namelijk 4 punten en 500 ng/ml.

Deze onderzoekingen hebben laten zien dat D-dimeer waarden onder de 500 ng/ml een hoge sensitiviteit hebben om longembolie uit te sluiten. De specificiteit is echter niet hoog genoeg om de diagnose nauwkeurig vast te stellen. Door het afkappunt van de D-dimeer test te verhogen is het mogelijk om de specificiteit van deze test te verbeteren. Dit is alleen bestudeerd in populaties met een lage kans op veneuze trombose. In **hoofdstuk 5** bestuderen we de klinische consequentie van hoge kwantitatieve D-dimeer waarden, in combinatie met klinische waarschijnlijkheid, bij patiënten met een klinische verdenking op longembolie. Patiënten met een hoge kans op veneuze trombose zoals patiënten die zijn opgenomen in een ziekenhuis, patiënten ouder dan 80 jaar en patiënten met een kwaadaardige aandoening of recente operatie, namen deel aan het onderzoek. Bij 21% van de patiënten werd een longembolie vastgesteld. De hoogte van de D-dimeer waarden hing sterk samen met het vóórkomen van longembolie. Patiënten met D-dimeer waarden boven de 4000 ng/ml hadden 4 maal vaker longembolie (61% in plaats van 15%) dan patiënten met D-dimeer waarden tussen 500 en 1000 ng/ml. Bij patiënten met een klinische beslisregel die onwaarschijnlijk was voor longembolie en D-dimeer waarden boven de 2000 ng/ml had 36% een longembolie. Dit is vergelijkbaar met het aantal longembolie in de klinische beslisregel waar longembolie waarschijnlijk is. Deze resultaten tonen aan dat sterk verhoogde D-dimeerwaarden de kans op longembolie aanzienlijk vergroten, zelfs bij patiënten met een hoge kans op veneuze trombose. Het is nog onduidelijk of bij patiënten met hoge D-dimeerwaarden intensieve diagnostiek moet worden verricht.

Posttrombotisch Syndroom

Het tweede deel van dit proefschrift behandelt de incidentie, risicofactoren en vroege voorspellers van het van het posttrombotisch syndroom (PTS).

PTS is een chronische complicatie die bij 20 tot 50% van de patiënten ontstaat na een diep veneuze trombose. De klinische verschijnselen variëren van mild oedeem tot chronische pijn en ulcera aan het aangedane been. Er is geen 'gouden standaard' test om de diagnose PTS te stellen en de diagnose is vooral gebaseerd op klinische kenmerken. In tegenstelling tot de vele risicofactoren die bekend zijn voor veneuze trombose zijn slechts weinig risicofactoren bekend voor PTS. De twee bekende risicofactoren voor PTS zijn recidiverende diep veneuze trombose aan hetzelfde been en een verhoogde body mass index. We hebben een groot vervolgonderzoek uitgevoerd om de verworven en genetische risicofactoren voor het ontstaan van PTS na een eerste diep veneuze trombose in kaart te brengen. In **hoofdstuk 6** tonen we de resultaten van 1668 patiënten uit de Multiple Environmental and Genetic Assessment (MEGA) studie. De cumulatieve incidentie van PTS was 25% na één jaar, met een cumulatieve incidentie van 7% voor ernstige PTS. De cumulatieve incidentie na één jaar was 31% voor vrouwen ten opzichte van 17% voor mannen. Vrouwen hadden een 1.5 keer verhoogde kans om PTS te ontwikkelen ten opzichte van mannen (relatief risico (RR) 1.5, 95%BI 1.3-1.8). Patiënten met overgewicht hadden een 1.5 keer verhoogde kans op PTS ten opzichte van met patiënten met een normaal gewicht (RR 1.5, 95%BI 1.2-1.9), met een cumulatieve incidentie na één jaar van 34% ten opzichte van 22%. Bij 28% van de patiënten waren spataderen aanwezig voor de diagnose diep veneuze trombose, en bij deze patiënten was de cumulatieve incidentie van PTS na één jaar 30%. Patiënten met spataderen hadden een 1.5 keer hogere kans op het ontwikkelen van PTS dan patiënten zonder spataderen (RR 1.5, 95%BI 1.2-1.8). Een trombose in de aderen van het bovenbeen en in de lies was geassocieerd met een 1.3 maal verhoogde kans op PTS ten opzichte van een trombose in de knieholte (RR 1.3, 95%BI 1.1-1.6). Trombose in de kuitvenen gaf dezelfde kans op PTS als trombose in de knieholte. Patiënten die ouder dan 60 jaar waren, hadden minder vaak PTS dan patiënten jonger dan 30 jaar (RR 0.6, 95%BI 0.4-0.9). Kanker, operatie, klein trauma, gips, zwangerschap of het gebruik van hormonen hadden geen invloed op de kans op PTS. De genetische risicofactoren zoals de factor V Leiden of de prothrombine 20210A mutatie hadden evenmin invloed. Deze studie toont aan dat PTS een veel voorkomende complicatie is na diep veneuze trombose, ondanks het uitgebreide gebruik van therapeutische elastische kousen.

De resultaten van dit onderzoek hebben er voor gezorgd dat nieuwe risicofactoren voor het ontstaan van PTS zijn ontdekt. De risicofactoren die een verhoogde kans op PTS geven zijn; vrouwelijk geslacht, overgewicht, spataderen en trombose in het bovenbeen of in de lies. Terwijl oudere leeftijd een verlaagde kans op PTS lijkt te geven.

De pathologie die ten grondslag ligt aan PTS is hypertensie van de aderen die wordt veroorzaakt door reflux van het bloed in de aderen bij een verminderde kuitspierpompfunctie en blijvende obstructie van de aderen. Deze hoge druk in de aderen leidt tot veranderingen in de microcirculatie van de huid en huidafwijkingen. Deze huidafwijkingen kunnen worden ingedeeld met de klinische score van de CEAP-classificatie. Hypertensie van de aderen zal aanwezig zijn voordat de klinische symptomen verschijnen. Met duplex-onderzoek is het mogelijk om de grootte van de trombus te meten, blijvende obstructie en reflux van de kleppen in de aderen, terwijl met rekstrookplethysmografie-onderzoek de weerstand in de aderen en de kuitspierpompfunctie gemeten kan worden. Deze niet-invasieve onderzoeken van de aderen kunnen behulpzaam zijn in het voorspellen van de ontwikkeling van PTS. **Hoofdstuk 7** beschrijft de voorspellende waarde van niet-invasief onderzoek van de aderen bij 111 patiënten met een eerste diep veneuze trombose van het been die gedurende twee jaar werden gevolgd. De cumulatieve incidentie van PTS was 49% na één jaar en nam niet toe in frequentie of ernst in het tweede jaar. Mannen hadden een verhoogde kans op PTS ten opzichte van vrouwen (RR 1.4, 95%BI 0.9-2.2). Patiënten ouder dan 50 jaar hadden een 1.4-maal verhoogde kans in vergelijking met jongere patiënten. Patiënten met een trombose in de aderen van het bovenbeen hadden een hogere kans op PTS dan patiënten met een trombose in het onderbeen (RR 2.3, 95%BI 1.0-5.6). Patiënten met resttrombose in de aderen van het bovenbeen zes weken na de diagnose hadden een 1.6 maal verhoogde kans op het krijgen van PTS ten opzichte van patiënten zonder resttrombose in deze aderen (RR 1.6, 95%BI 1.0-2.5). De aanwezigheid van reflux in de oppervlakkige aderen leidde tot een 1.6-maal verhoogde kans op PTS (RR 1.6, 95%BI 1.1-2.3). Multivariaat analyse van deze voorspellende factoren toonde een ROC waarde van 0.72 (95%BI: 0.62-0.82). Dit onderzoek heeft laten zien dat binnen één jaar na een eerste diep veneuze trombose PTS ontstaat bij de helft van alle patiënten. We hebben vijf voorspellende factoren voor PTS gevonden: mannelijk geslacht, leeftijd boven de 50 jaar, trombose in de aderen van het bovenbeen, resttrombose in de vaten van het bovenbeen en reflux in de aderen

na zes weken. Een duplex scan zes weken na de diagnose diep veneuze trombose lijkt klinisch relevant om te kunnen voorspellen welke patiënten een verhoogde kans hebben op PTS.

Conclusies

In het eerste deel van dit proefschrift hebben we twee nieuwe algoritmes beschreven voor de diagnostiek van patiënten met een klinische verdenking op diep veneuze trombose en longembolie. Beide strategieën, die bestaan uit een combinatie van klinische waarschijnlijkheid en D-dimeer test verminderen de noodzaak voor beeldvormende diagnostiek en zijn veilig in het uitsluiten van diep veneuze trombose en longembolie. De resultaten van het eerste deel van dit proefschrift dragen bij aan een nieuwe, eenvoudigere diagnostische strategie voor patiënten met veneuze trombose. De management strategie voor de diagnostiek van diep veneuze trombose beperkt het aantal tweede echografieën. Het gebruik van D-dimeer test bij patiënten met een lage klinische waarschijnlijkheid kan het aantal eerste echografieën verder reduceren. Een overzicht van de literatuur heeft aangetoond dat bij patiënten met een lage waarschijnlijkheid en een normale D-dimeer test de diagnose diep veneuze trombose veilig kan worden uitgesloten, zonder een echografie te verrichten. Welke D-dimeer test het beste gebruikt kan worden is een heel ander onderwerp. De SimpliRED test die we hebben gebruikt voor de diagnostiek van diep veneuze trombose, heeft een lagere sensitiviteit dan de snelle ELISA test. De hogere sensitiviteit van de ELISA test zorgt ervoor dat minder veneuze tromboses worden gemist. Aan de andere kant, zorgt de hogere specificiteit van de SimpliRED test ervoor dat er minder beeldvormende diagnostiek gedaan hoeft te worden. Tegenwoordig wordt de snelle ELISA test vaker gebruikt en het vermijden van een gemiste diagnose is belangrijker dan het vermijden van een paar beeldvormende testen. Tenslotte is het belangrijk dat D-dimeer niet als screenende test wordt gebruikt, maar alleen wanneer de arts overtuigd is dat veneuze trombose een waarschijnlijke diagnose is. De uitdaging voor toekomstig onderzoek is om een verdere afname te bereiken van het aantal patiënten dat beeldvormende diagnostiek nodig heeft voor de diagnose veneuze trombose.

In het tweede deel van dit proefschrift beschrijven we twee vervolgonderzoekingen waarin nieuwe risicofactoren en voorspellende factoren voor PTS zijn geïdentificeerd. De resultaten van deze onderzoekingen stellen ons in staat om specifieke informatie aan patiënten met een eerste diep veneuze trombose te geven over hun risico op het ontwikkelen van PTS. Toekomstig onderzoek zou

zich moeten richten op het valideren en standaardiseren van de diagnostische criteria voor PTS. Een gestandaardiseerde diagnose is noodzakelijk om de eenduidigheid van de diagnose te verbeteren en maakt het mogelijk om de resultaten van verschillende onderzoekingen te vergelijken. Bovendien stelt een objectieve diagnose artsen in staat om het ontstaan en het beloop van PTS bij hun eigen patiënten in kaart te brengen.

Nawoord

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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 16 april 1972 te Gouda. In 1990 behaalde zij het diploma Voorbereidend Wetenschappelijk Onderwijs aan het Rhedens Lyceum te Rozendaal. In het volgende jaar behaalde zij haar propedeuse Medische Biologie aan de Universiteit van Utrecht en werd een aanvang gemaakt met de studie Geneeskunde. Tijdens haar studie heeft zij stage gelopen aan de Medical University of South Carolina en bij de African Medical Research and Education Foundation (AMREF Flying Docters) in Kenia. Haar neurologie coschap volgde zij in het Brigham and Womens Hospital verbonden aan Harvard Medical School in Boston. In 1998 behaalde zij haar artsexamen, waarna zij als arts-assistent Interne Geneeskunde ging werken in het Meander Medisch Centrum te Amersfoort. In deze periode werd het in dit proefschrift beschreven onderzoek gestart onder leiding van prof. dr M.H.H Kramer en prof. dr W.R. Faber, in samenwerking met de afdeling Klinische Epidemiologie van het Leids Universitair Medisch Centrum (prof. dr F.R. Rosendaal). In 2000 startte zij in het Meander Medisch Centrum de opleiding tot internist (opleider: Dr. A. van de Wiel) welke in 2004 werd voortgezet op de afdeling hematologie van het Leids Universitair Medisch Centrum (opleiders: Prof. dr J.A. Romijn, Interne Geneeskunde, en Prof. dr R. Willemze, Hematologie). In 2005 werd zij geregistreerd als internist en in 2006 als hematoloog waarna zij als chef de clinique hematologie en beenmergtransplantatie van het Leids Universitair Medisch Centrum werkzaam was. Sinds maart 2008 is zij werkzaam in het Antoni van Leeuwenhoek Ziekenhuis voor het aandachtsgebied Medische Oncologie (opleider: Prof. dr S. Rodenhuis). Vanaf 1 januari 2009 zal zij werkzaam zijn als internist-hematoloog in het Máxima Medisch Centrum, Eindhoven-Veldhoven.

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