# Diagnosis of venous thrombosis and 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.

## References


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