Diagnosis of venous thrombosis and the post-thrombotic syndrome

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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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