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General outline and introduction

Venous thromboembolism (VTE) constitutes of deep vein thrombosis (DVT) and pulmonary embolism (PE). Deep vein thrombosis occurs most commonly in the leg(s), but could also be present in the veins of the arms, and in the mesenteric and cerebral veins. The formation of thrombosis depends on a triad of hypercoagulability, stasis and interruption of the integrity of the vein wall.

Venous thromboembolism is a common disorder and the annual incidence is estimated to be 67 per 100 000 in the general population.[1,2] A DVT could develop into a PE and despite adequate anticoagulant therapy this condition can be fatal in 1-8% of the patients.[3-5] Also, patients may experience long-term complications including post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension, compromising the quality of life. Anticoagulant therapy decreases the risk of recurrence and long-term complications, but this treatment is associated with the risk of (fatal) bleeding. Approximately 50% of the patients present with suspected recurrent VTE after a median time of 1 year after discontinuing anticoagulant therapy and in 27% of these patients the diagnosis is confirmed.[6] These patients are commonly treated with indefinite duration of anticoagulant therapy.[7]

Patients with suspected VTE usually present with dyspnea, shortness of breath, chest pain, swelling of the leg(s), muscle cramps, warmth and redness of the leg(s). Since these clinical symptoms are not specific of VTE clinical scoring systems and objective diagnostic tests have been developed. These scoring systems and diagnostic tests have been widely evaluated in patients with a suspected first thrombosis, however limited studies have been performed in patients with suspected recurrent VTE. This thesis therefore has its focus on the diagnostic management of recurrent VTE.

After a VTE has been diagnosed the prognosis of a patient is important to consider for making clinical decisions such as the duration of anticoagulant therapy and the intensity of this treatment. This thesis discusses whether short term anticoagulant (i.e. one year) treatment for late second VTE would potentially be beneficial.

Finally it is clinically important to identify potential predictors that could influence the prognosis after a first venous thromboembolism. Therefore another aim of this thesis is to assess the recurrence risk after a confirmed DVT and the role of residual thrombosis.

C*hapter 2* gives an overview of the diagnostic management of deep vein thrombosis. The state of the art for the use of clinical decision rules, D-dimer testing and imaging are discussed in patients with clinically suspected (recurrent) DVT.

Clinical decision rules are the first step in the diagnostic algorithm of acute clinically suspected VTE. These rules stratify patients into a low or high risk for VTE according

to clinical signs and symptoms. The most common used clinical decision rule for first suspected DVT is the Wells rule and for first suspected PE are the Wells and Geneva rules. However these rules were not developed specifically for patients with suspected recurrent VTE.[8-10] Due to different pre-test probability and the presence of chronic symptoms after the previous event, it could be assumed that a separate clinical decision rule for patients with suspected recurrent VTE would increase the diagnostic yield in this group of patients. Therefore, *chapter 3* will focus on potential clinical predictors for confirmed VTE diagnosis in patients with suspected recurrent VTE.

The imaging of recurrent VTE poses a clinical challenge. The base of this challenge is the presence of residual thrombosis in up to 80% of the patients after three months and 50% after one year after the first DVT, making it difficult to differentiate whether the thrombosis seen on imaging by compression ultrasonography or contrast venography - the current standard imaging tests- represents old or new thrombosis.[11] This differentiation is important, since residual thrombi don't require treatment and new thrombi are often treated with indefinite anticoagulant therapy with the associated bleeding risks.[7] *Chapter 4* evaluates the frequency of non-diagnostic ultrasonographies in daily clinical practice and estimates the clinical consequence (i.e. the decision to commence treatment or to withhold treatment) of these non-diagnostic ultrasounds.

Magnetic Resonance Direct Thrombus Imaging (MRDTI) has been shown to be a highly accurate diagnostic method for a first DVT of the legs.[12] The method is based on measurement of the T1 signal which shortens as a result of the formation of methemoglobin in a fresh thrombus. This technique does not require the administration of gadolinium and the acquisition time is short, making it a safe and patient-friendly test. Hypothetically this technique could be of value in the imaging of patients with a suspected ipsilateral recurrent DVT, since a high signal could represent a recurrent acute thrombosis, while a low signal would represent an old residual thrombosis. *Chapters 5 and 6* discuss this simple, non-invasive MRI technique which has the potential to accurately diagnose recurrent DVT, thus preventing patients from being unnecessarily treated with indefinite anticoagulant therapy or exposed to extension of DVT or (fatal) pulmonary embolism.

Besides the challenges of the diagnostic management of recurrent thrombosis, another challenge exists in the treatment of patients with recurrent VTE. An important balance between bleeding risk and risk of recurrence should be considered before commencing anticoagulant therapy. This is especially important for patients with recurrent VTE, since these patients are often subjected to indefinite treatment with the associated risk of (fatal) bleeding. *Chapter 7* will therefore discuss the risk of bleeding and recurrences after a short term treatment period (i.e. 1 year) in patients who have a second venous thromboembolism more than 1 year after their first one.

An important clinical field is the prognosis of a patient after an objectively diagnosed VTE. One essential factor of the prognosis is the recurrence risk. To assess the recurrence risk of patients, it is important to also consider the factors which could potentially influence this risk. When these predictors are known, a well-balanced individual decision could be made to continue or withhold anticoagulant therapy. In this way patients are not unnecessarily exposed to a long-term risk of PE or bleeding. One of the potential clinical predictors currently mentioned is the presence of residual thrombosis, however studies contradict whether residual thrombosis could be considered as a predictive factor for recurrence. *Chapter 8 and 9* discuss the role of residual thrombosis in patients with lower extremity DVT in predicting future recurrences and also the role of interobserver reliability in assessing the presence of residual thrombosis.

Furthermore, in order to understand the magnitude of a disease and the impact it has on society, it is important to know the incidence of this disease. Therefore *chapter 10* discusses the incidence of recurrent VTE in the urban population.

The recurrence and bleeding risk after a lower extremity thrombosis and PE have been well studied. However, little is known about the prognosis of patients after suffering from an upper extremity DVT. Upper extremity DVT accounts for 4-11% of all thromboses in the deep veins.[13-19] There are a number of notable differences between upper and lower extremity DVT, including the predisposing risk factors and populations most commonly affected, the overall incidence, and the presence of concomitant PE, which could influence the prognosis.[19] *Chapter 11* discusses the recurrence and bleeding risks of patients with upper extremity DVT during the first 3 months of anticoagulant therapy.

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