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## Discussion and summary



The first aim of this thesis is to improve the diagnostic management of recurrent venous thromboembolism (VTE) by identifying clinical predictors of recurrent VTE in patients with suspected recurrent VTE and by evaluating the accuracy of a Magnetic Resonance Direct Thrombus Imaging (MRDTI) technique in the imaging of ipsilateral recurrent deep vein thrombosis (DVT). Secondly, the short term treatment of late recurrent VTE is discussed to minimize the duration of exposure to anticoagulant therapy for patients. Finally, this thesis has the aim to assess the incidence of recurrent VTE and the prognosis after a first VTE and the role of residual thrombosis after a first thrombosis in the recurrence risk. *Chapter 1* gives a general introduction to this thesis and *Chapter 2* gives an overview of the state of art of the diagnostic management of (recurrent) deep vein thrombosis.

## **PART I: DIAGNOSTIC MANAGEMENT OF RECURRENT VTE**

Many clinical decision rules have been established to stratify patients into a low and high risk of VTE. However these rules have limitations for patients with suspected recurrent VTE. Therefore *chapter 3* discusses the clinical predictors of confirmed VTE in patients with suspected recurrent VTE and shows that clinical predictors associated with a confirmed recurrent VTE diagnosis are different from clinical predictors in patients with a first suspected VTE, suggesting the clinical benefits of a separate clinical decision rule for patients with a suspected recurrent VTE.

The accurate imaging of recurrent thrombosis is challenging due to the presence of residual thrombosis after a first thrombosis. Therefore if a patient presents with a suspected recurrent DVT in the same leg as the previous DVT and an incompressible venous segment is seen on ultrasonography it could be unclear whether this presents old or new thrombosis, resulting in non-conclusive ultrasonography results. However, the prevalence of non-conclusive ultrasonography results is unknown. In *chapter 4* we show that in 58% of the patients with a suspected ipsilateral recurrent DVT the diagnosis was accurately ruled out and anticoagulant treatment was withheld and in 10% of the patients the diagnosis of ipsilateral recurrent DVT was established with predefined diagnostic criteria. However in the remaining 32% of patients, the ultrasonographies were non-conclusive, while all patients were still treated with anticoagulant therapy. This study shows that non-conclusive ultrasonographies are common in patients with a suspected ipsilateral recurrent DVT and furthermore that overtreatment of these patients exists. This high percentage of non-conclusive ultrasonographies demands for an objective imaging test that could accurately diagnose an ipsilateral recurrent DVT.

Magnetic Resonance Direct Thrombus Imaging has shown to be an accurate, non-invasive diagnostic method for a first DVT. This technique depends on the high signal

associated with the presence of methemoglobin in an acute thrombosis and could potentially be used in distinguishing an acute recurrent thrombosis from a residual thrombosis and therefore be of value in the diagnostic management of ipsilateral recurrent DVT. However before assessing whether MRDTI could be of value in the diagnostic management of ipsilateral recurrent DVT one should be certain that the high signal associated with the acute thrombosis extinguishes after a period of time. Therefore in *chapter 5* a study is discussed in which we enrolled 43 consecutive patients with a first acute DVT. All patients received an ultrasonography and MRDTI at the acute phase, after 3 months and 6 months. In all 39 patients available at 6 months follow-up the initially observed abnormal MR-signal had normalized, whereas in 12 of these patients (31 %) compression ultrasonography was still abnormal. On the basis of these results it was concluded that MRDTI is potentially of use in the diagnostic management of ipsilateral recurrent DVT.

Consequently *chapter 6* focuses on a multicenter prospective study to evaluate the accuracy of MRDTI in diagnosing clinically suspected recurrent DVT. Thirty nine patients with objectively proven ipsilateral recurrent thrombosis and 42 patients with residual thrombosis were enrolled. MRDTI demonstrated a sensitivity of 95% and a specificity of 100%. Furthermore the interobserver variability was excellent with a kappa statistic of 0.98. It was concluded that MRDTI is an accurate, highly reproducible diagnostic modality for the diagnosis of ipsilateral recurrent DVT.

## **PART II. THE TREATMENT DURATION OF RECURRENT VTE**

International guidelines recommend indefinite duration of anticoagulant treatment for a second venous thromboembolism (VTE). However, VTE recurrence risk diminishes over time while the risk of hemorrhage persists with continued anticoagulation. The Dutch guideline recommends to consider limited duration of treatment (i.e. 12 months) for a late second VTE, defined by a >1-year interval after discontinuing treatment for a first VTE, since the risks of continued anticoagulation might outweigh the benefits in those patients. *Chapter 7* evaluates this short term treatment duration of 12 months for patients with a late second VTE in daily practice. This study showed an incidence-rate of 9.4/100 patient-years (95%CI 6.1-14). An unprovoked second VTE was associated with a higher recurrence risk (Hazard ratio 2.0; 95%CI 0.85-4.8). The conclusion of this study was that short term treatment of 12 months should not be recommended in patients with a second late unprovoked VTE, due to the high recurrence risk.

### PART III: PROGNOSIS AFTER A VENOUS THROMBOEMBOLISM

There is a debate on whether the presence of residual thrombosis is a prognostic factor for recurrent VTE. In *Chapter 8* we show that majority of studies indicated a 1.5 - to 4-fold increased VTE recurrence risk associated with the presence of residual thrombosis, but that these risks are dependent on the method used for assessing residual thrombosis.

To evaluate whether assessing residual thrombosis has any clinical relevance it is important to know the interobserver reliability of the presence of this residual thrombosis. In *chapter 9* we evaluated the interobserver reliability of measuring residual thrombosis in the prognosis of recurrent VTE. This study showed an excellent interobserver reliability for the presence of residual thrombosis and a good interobserver reliability for the measurement of residual thrombosis with a limited number of patients being misclassified.

To assess the magnitude of a disease it is important to know the incidence of recurrent thrombosis. *Chapter 10* focuses on the incidence of recurrent VTE in the urban population. This study showed an incidence figure of recurrent VTE of 0.22 per 1000 inhabitants per year, compared to an incidence figure of 1.2-1.8 per 1000 inhabitants per year for patients with a first VTE.

Little is known on the prognosis after an upper extremity thrombosis. We performed a meta-analysis and systematic review on the early prognosis after a upper extremity DVT. *Chapter 11* shows that the rate of recurrent VTE in the first 3 months of anticoagulant therapy after an upper extremity DVT is similar to patients with a lower extremity proximal DVT; however the fatal bleeding rates (0.87%) are higher. These results suggest a less aggressive treatment strategy for patients with upper extremity DVT compared to patients with lower extremity DVT.

### FUTURE PERSPECTIVES

This thesis shows that future research is still needed to improve and enhance the knowledge of the clinical management of recurrent venous thromboembolism.

First the third chapter shows that clinical predictors for suspected recurrent venous thromboembolism might be different than clinical predictors for a suspected first VTE. A prospective multicenter study is planned to derive a new clinical prediction rule for patients with suspected recurrent VTE with the objective of enhancing the efficacy and efficiency of pre-testing of this group of patients.

Furthermore this thesis shows that MRDTI is an accurate and highly reproducible technique for the imaging of patients with suspected acute ipsilateral recurrent DVT. However before this technique could be used in the daily practice the safety of withholding anticoagulant therapy after a negative MRDTI should be evaluated. Therefore

a management outcome study in which patients are managed by MRDTI with the 3 months failure VTE rate as primary outcome is being planned.

Also the optimal therapy duration for patients with recurrent VTE is still debatable. Future studies should be performed to individualize the optimal therapy duration in patients and to minimize the risk of bleeding and pulmonary embolism.

The last part of the thesis shows higher fatal bleeding rates in the first three months of anticoagulant therapy after an upper extremity DVT. These results raise the hypothesis that a less aggressive treatment may be warranted in patients with upper extremity DVT compared to lower extremity DVT. Therefore we propose to perform a randomized controlled trial in which the current standard anticoagulant treatment is compared with a less aggressive treatment strategy in patients with a first upper extremity DVT.





