Deep vein thrombosis : diagnostic and prognostic challenges

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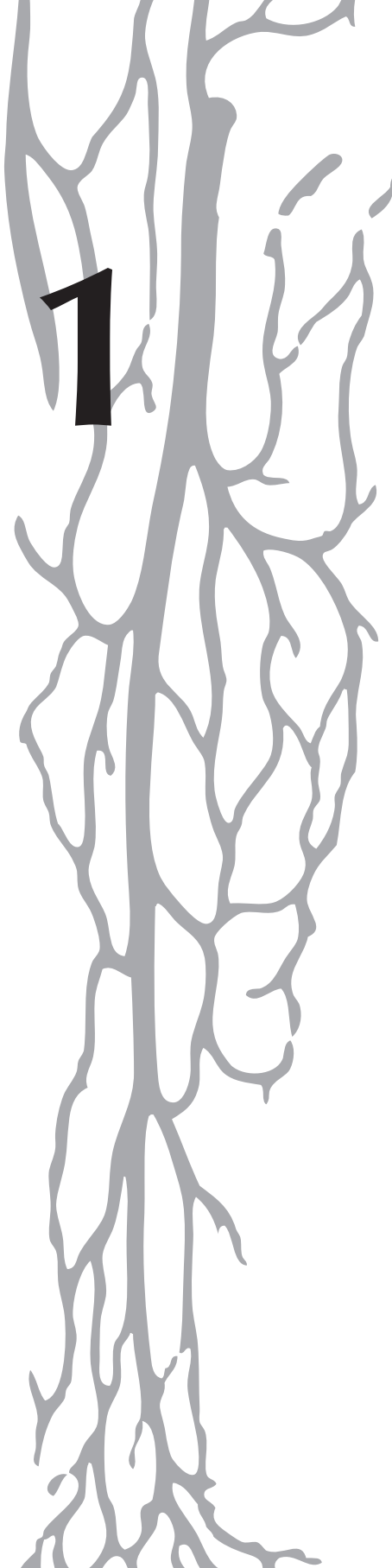
Introduction and outline of this thesis



Deep vein thrombosis (DVT) is characterized by the formation of a blood clot in one of the deep veins. DVT occurs most frequent in the deep veins of the lower extremities, but can also occur in one of the veins of the upper extremity, splanchnic veins or cerebral veins. When DVT detaches, it can embolise into the lungs, causing acute pulmonary embolism (PE), which is potential life threatening. DVT and acute PE are together defined as one disease: venous thromboembolism (VTE). The understanding of the pathophysiologic mechanism of VTE is still based on Virchow's triad described in 1856: venous stasis, vessel injury and hypercoagulability.[1] Signs and symptoms of VTE are nonspecific. Therefore diagnostic tests are needed in addition to questioning and physical examination to establish definite diagnosis.

Although VTE diagnostic management and imaging techniques have rapidly evolved over the past decades, a correct diagnosis remains challenging in many cases. **Chapter 2** provides an overview of the current challenges in the diagnostic management of suspected VTE, which are subsequently further discussed in the first part of this thesis. New, promising diagnostic management strategies are being developed all over the world, and continuously tested in diagnostic management studies. The safety threshold against which all this studies are evaluated is the failure rate of invasive venography, because this is still the 'golden standard' for DVT according to current guidelines. However, over the last years, the disease prevalence in DVT diagnostic management study populations has significantly decreased. In line with the association between disease prevalence and failure rate as proposed by Bayes in 1764, we aimed to develop a new disease prevalence dependent diagnostic safety threshold for future diagnostic management studies (**chapter 3**).[2]

The current favoured strategy of diagnostic management of a first DVT is the use of a diagnostic algorithm starting with a clinical decision rule to estimate the pre-test probability of having DVT.[3] The most widely used clinical decision rule is the Wells rule, consisting of 10 items with allocated different number of points to a total score.[4] In case of a low clinical probability (Wells rule < 2 points) combined with a negative D-dimer test, DVT can be ruled out without additional imaging tests such as compression ultrasonography (CUS). In clinical practice this decision rule is however often incorrectly used leading to unneeded excessive diagnostic tests and diagnostic failures.[5] In **chapter 4** we therefore aimed to design and test a simpler rule which consisted of only 4 items, the so-called 'I-DVT' score.

The diagnostic management of DVT is more difficult in specific patient groups, including pregnant women, patients with suspected ipsilateral recurrent DVT and patients with suspected upper extremity DVT (UEDVT). Magnetic Resonance Direct Thrombus Imaging (MRDTI), a non-contrast enhanced MRI technique, can be a potential solution in diagnosing DVT in these patients. With this technique a thrombus can be directly visualised, based on the oxygenation of haemoglobin when blood clots, which results

in the formation of methemoglobin. This acts as an endogenous contrast agent and appears as high/'white' signal when imaged using a T1-weighted MRI sequence.[6,7]

A DVT diagnosis in pregnant patients may be difficult because of the relatively high incidence of isolated pelvic vein thrombosis. For obvious reasons, compression ultrasonography is inadequate due to anatomical reasons.[8] Alternative conventional diagnostic tests include direct, CT- or MRI venography, that expose mother and foetus to ionizing radiation and/or contrast material. **Chapter 5** describes a case of a pregnant woman with suspected DVT in whom conventional diagnostic tests failed to establish a definite diagnosis. The diagnosis could however be finally confirmed by MRDTI.

The current strategy of diagnosing patients with a suspected ipsilateral recurrent DVT is also complicated, mainly because of highly prevalent chronic thrombus remains that are present in up to 50% of patients despite adequate anticoagulation. A distinction between residual vein thrombosis and acute recurrent DVT with CUS is impossible.[9] In a previous study, it was shown that MRDTI accurately distinguishes acute recurrent DVT from chronic thrombus remains.[10] An alternative direct thrombus imaging technique is the T1 weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery (TSE-SPAIR) sequence. This sequence is characterised by the visualisation of the vessel wall in a high resolution, which is not the case with MRDTI.[11] In **chapter 6** we investigate the additional value in diagnostic accuracy and diagnostic confidence of the TSE-SPAIR sequence on top of the MRDTI sequence in 15 patients with suspected recurrent ipsilateral DVT.

One other diagnostic challenge is the diagnosis of upper extremity deep vein thrombosis (UEDVT). Compression ultrasonography is often inconclusive because of overlying anatomic structures that hamper adequate compression of the veins. Contrast venography is needed in many cases, which is associated with complications due to exposure to radiation and contrast material.[12] In **chapter 7,** we explored the feasibility of the MRDTI and TSE-SPAIR sequences for diagnosing UEDVT.

The second part of this thesis focuses on the prognosis of patients diagnosed with and treated for DVT. To prevent complications as acute PE and the post-thrombotic syndrome (PTS), adequate anticoagulant treatment for DVT is required. The current treatment of choice is direct oral anticoagulants (DOACs).[13] The main advantage of DOACs over the more old-fashioned vitamin K antagonists is that they have a lower risk of bleeding. Moreover, neither monitoring nor dose titrations are needed.[14] A potential drawback of DOACs is a higher risk of decreased drug persistence, i.e. prematurely discontinuing treatment. In **chapter 8** we explored the incidence of prematurely cessation of anticoagulant therapy for incident venous thromboembolism based on Dutch pharmacy registry data.

Inadequate treatment of DVT is one of the main risk factors of PTS. PTS is a chronic complication occurring in 20-50% of patients with DVT, and is characterised by a spectrum of mild to severe symptoms of chronic venous insufficiency.[15] Several risk factors

for PTS at the time of the DVT diagnosis have been identified, such as more proximal DVT, older age, obesity and history of ipsilateral recurrent DVT.[16] Whether ultrasound-measured chronic vein obstruction by residual clots and/or valvular reflux may be helpful in better predicting PTS remains controversial. Therefore, the primary aim of **chapter 9** was to perform a systematic review and meta-analysis to identify ultra-sonographic parameters, assessed during or after treatment of proximal DVT of the leg, that predict post thrombotic syndrome.

It has been shown that elastic compression stocking (ECS) therapy may prevent PTS, but only in case patients are compliant to wearing the stocking on a daily base for 2 full years.[17-19] Importantly, stockings are costly, cumbersome to apply, and can be hot, constricting, and itchy. These factors are the main cause of the poor compliance of patients to ECS therapy in clinical practice. The primary aim of **chapter 10** was to find independent predictors for PTS development in patients who compliantly used ECS up to one year after DVT, to select patients who may safely stop ECS therapy.

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