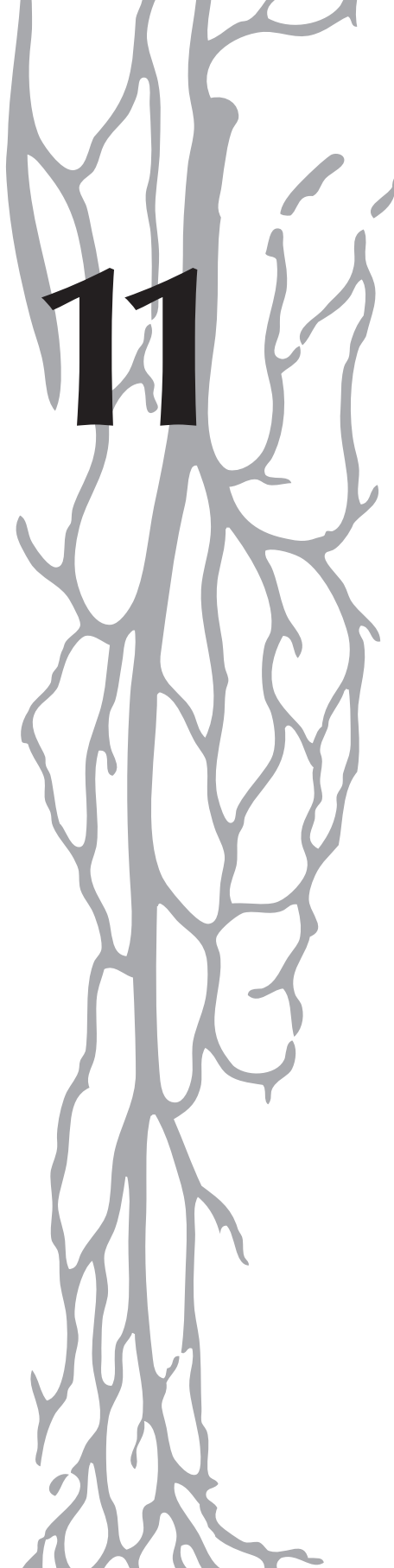
Deep vein thrombosis : diagnostic and prognostic challenges

Dronkers, C.E.A.

11

General discussion and summary



The studies described in the first part of this thesis aimed to improve the diagnostic management of deep vein thrombosis (DVT) in general, and in diagnostic challenging circumstances specifically. The second part of this thesis describes studies that aimed to improve the prognosis of DVT by evaluation of the persistence to prescribed therapy and predictors of the development of post thrombotic syndrome (PTS). **Chapter 1** provides a general introduction and overview of the presented studies.

PART I: CHALLENGES IN DIAGNOSTIC MANAGEMENT AND IMAGING OF DEEP VEIN THROMBOSIS

Chapter 2 gives first an overview of current and future perspectives in imaging of venous thromboembolism. The current favoured strategy for the diagnostic management of suspected first DVT is the combination of pre-test probability assessment by a clinical decision rule, D-dimer test and (serial) compression ultrasound (CUS). Notably, the 'gold standard' for a DVT diagnosis is still venography. The safety threshold against which all DVT diagnostic management studies are evaluated is therefore the known failure rate of venography, which has been shown to be 1.3% (upper limit 95% confidence interval 4.4%). This number represents the percentage of patients diagnosed with VTE (venous thromboembolism) during 3-month follow-up after a normal venography. The current used diagnostic strategy is much less invasive than venography, since no exposure to radiation and contrast material is needed. Therefore, the threshold for clinicians to order any test for DVT has become markedly lower, which has led to an even lower disease prevalence in study populations over the past years. Importantly, according to the theorem of Bayes, the failure rate, i.e. the post-test probability of having the disease, is associated with the disease prevalence in a population i.e. the pre-test probability of having the disease. In **chapter 3** we performed a systematic review and meta-analysis to evaluate the association between disease prevalence and failure rate over the last years in published studies on diagnosis of DVT, in order to propose a new diagnostic safety threshold for future studies on diagnostic management of suspected DVT. We selected all high quality DVT diagnostic management studies published since 1990. After plotting the published failure rates of all studies against the associated disease prevalence, we confirmed the association between both statistics with an absolute 1.0% higher DVT prevalence leading to a mean 0.026 percentage point's increase in failure rate. The formula of the upper level of the 95% CI of the reference line of this graph answered the formula: failure rate= 1.25 + 0.026*disease prevalence. We suggest that this formula should be incorporated in the power calculation of future studies. The adaption of the failure rate threshold by the expected disease prevalence in the studied population will prevent validation of insufficient diagnostic tests based on underpowered studies.

As discussed, the diagnostic workup of DVT ideally starts with calculating the pre-test probability of having DVT by a validated clinical decision rule. The most widely used rule is the Wells rule, but this rule consists of no less than 10 items with allocated different numbers of points. In clinical practice, this decision rule is therefore often incorrectly used leading to unneeded diagnostic tests and diagnostic failures. In **chapter 4,** we have developed a simpler rule by selecting the 4 items of the Wells rule which were - according to an expert panel - most predictive of DVT. These items were **I**mmobilization, >3 cm **D**ifference in calves circumferences, prior **V**enous thromboembolism (VTE) and active malignant **T**umor. This new clinical decision rule with one point for each variable was named the 'I-DVT score'. When both the Wells rule and I-DVT-score were applied to patients with clinically suspected DVT, the areas under the ROC curves (AUC) were 0.70 (95%CI 0.66-0.74) and 0.65 (95%CI 0.61-0.70) respectively, showing comparable accuracy. Notably, before the I-DVT score can be used in clinical practice, it has to be tested and validated in a prospective clinical management study.

Magnetic Resonance Direct Thrombus Imaging (MRDTI) is a non-contrast enhanced MRI technique which has already been shown to accurately diagnose a first DVT and to distinguish acute thrombosis from chronic thrombus remains. This technique is based on the different paramagnetic properties of methemoglobin, which is formed in a fresh blood clot by the oxidation of hemoglobin, i.e. Fe^{2+} converted to Fe^{3+}. We hypothesized that this MRDTI technique can be a helpful solution in specific patient populations with suspected DVT, i.e. pregnant woman, patients with suspected ipsilateral DVT and patients with suspected upper extremity DVT (UEDVT).

The diagnostic management of pregnant woman is challenging mainly because there is a higher incidence of pelvic vein thrombosis than in the non-pregnant population. Pelvic vein thrombosis is very difficult to diagnose with compression ultrasound due to obvious anatomic reasons. In **chapter 5,** we have described the case of a 29 year old woman who was pregnant of a dichorionic diamniotic twin and presented with a high clinical suspicion of DVT. Repeated CUS was not diagnostic for DVT but showed reduced flow over the left external iliac vein, common femoral vein and superficial femoral vein. In pursue of a definite diagnosis, Magnetic Resonance Direct Thrombus Imaging (MRDTI) was performed showing a clear high signal in the left common iliac vein which was diagnostic for acute thrombosis in this venous segment. By performing MRDTI in this patient, we prevented exposure of the patient and her babies to ionizing radiation and contrast material. In **chapter 6** we discussed the additional value of a comparable direct thrombus imaging technique, the so called T1 weighted Turbo Spin-echo Spectral Attenuated Inversion Recovery (TSE-SPAIR) sequence, in the diagnostic work-up of suspected ipsilateral recurrent DVT. This is a very challenging diagnosis because it is not possible with CUS to distinguish acute recurrent DVT from chronic thrombus remains. Residual thrombosis is present in up to 50% of patients after a first DVT and a definite

diagnosis cannot be made in ~30% of patients with CUS alone. We showed that the addition of the TSE-SPAIR sequence led to a higher diagnostic confidence of the radiologist when analysing the TSE-SPAIR sequence on top of the MRDTI sequence, most probably caused by the higher spatial resolution of the vessel wall. Although this study was not powered to analyse diagnostic accuracy, the sensitivity and specificity for proximal DVT was not changed by adding the TSE-SPAIR sequence to MRDTI. Therefore, there are no arguments to use the TSE-SPAIR sequence standardly in combination with the MRDTI sequence, although the extra TSE-SPAIR sequence may help to increase diagnostic confidence in case of uncertain diagnosis.

Upper extremity deep vein thrombosis (UEDVT) is very challenging to diagnose as well, especially when located in the subclavian vein. The main reasons for this are the overlying anatomic structures in the shoulder, such as the clavicle, hamper proper diagnosis with CUS. Since the MRDTI technique already showed to accurately diagnose DVT of the leg, we hypothesised that it should also be possible to diagnose UEDVT with MRDTI. In **chapter 7** we applied the two direct thrombus imaging techniques MRDTI and TSE-SPAIR in 3 patients who were already diagnosed with UEDVT by conventional techniques. In all three patients, UEDVT could be visualised successfully by the MRI.

PART II: PROGNOSTIC CHALLENGES OF DEEP VEIN THROMBOSIS

Adequate anticoagulant treatment is important to secure a favourable prognosis of DVT. Over the last years the treatment of choice shifted from vitamin K antagonists (VKAs) to direct oral anticoagulants (DOACs). DOACs have been shown to be equal in efficacy but have a lower bleeding risk than VKAs. Another advantage of DOACs is that regularly monitoring is not needed, since they have a more stable pharmacokinetic and pharmacodynamic profile than VKAs. A disadvantage of not monitoring the anticoagulant therapy however is a potential decrease in drug persistence. Adequate treatment is especially important in the first months as the risk of recurrence is higher after prematurely stopping anticoagulation treatment within 1 or 1.5 months after the VTE event than after 3 months. In **chapter 8** we found that, based on Dutch pharmacy registry data, 20% (95% CI 18-24) of patients stopped prematurely with their DOAC within the first 2 months from the DVT diagnosis. This stopping rate was comparable with drug persistence of treatment of other cardiovascular diseases such as oral antiplatelet therapy after acute coronary syndrome or secondary prevention treatment (statins, blood pressure lowering medication) after acute stroke. In patients who were taking VKA, and who were closely monitored by the anticoagulation clinic in Leiden, the stopping rate was much lower: 9.1% (95%CI 8.3-9.9). This study should therefore be used as a warning that

further investigation on the incidence and consequences of non-persistence in DOAC patients is urgently needed.

Post-thrombotic syndrome (PTS) is an important chronic complication after DVT. Elastic compression stockings (ECS) have been suggested to prevent PTS when they are compliantly used. ECS therapy is however notoriously uncomfortable and compliance is poor in clinical practice. Therefore, identification of predictors for PTS may help doctors to select patients who have a high risk for PTS and whom should be advised to wear their stockings compliantly for at least 2 years. In **chapter 9** we performed a systematic review and meta-analysis of all studies that included consecutive patients with DVT who received standardized anticoagulant treatment and had an ultrasonography assessing vascular damage after DVT during at least 6 months follow-up and were followed for the occurrence of PTS. We found that residual thrombosis and venous reflux were both predictive for PTS, for pooled Odds Ratios (OR) of 2.17 (95%CI 1.79-2.63) and 1.34 (95%CI 1.03-1.75) respectively. To select patients who could safely stop ECS therapy after one year we performed a pre-defined endpoint analysis of the Octavia study in **chapter 10.** The Octavia study was a multicentre single blind non-inferiority randomized controlled trial. Adequately anti-coagulated patients who were compliant to compression therapy for 12 months after a symptomatic, ultrasound proven proximal DVT were randomized between continuation and cessation of ECS therapy. Patients were followed for 12 months with as primary endpoint the incidence of PTS at the end of follow-up period. We found that thrombus score ≥3 (≥3 vein segments with residual thrombosis), BMI ≥26, duration of complaints before DVT diagnosis ≥8 days and a Villalta score of 2-4 points were independent significant predictors of PTS. When selecting patients without any of these predictors in the patient group that stopped ECS use after 1 year, 3.2% (95%CI 0.08-18) were diagnosed with mild PTS during follow-up and none with moderate or severe PTS. These findings suggest that after one year of compliant ESC use, stopping ECS treatment can be discussed in individual patients without any of the predictors present.

FUTURE PERSPECTIVES

With the MRDTI technique, a new era of diagnostic possibilities for suspected deep vein thrombosis has begun. Instead of diagnosing a thrombus indirectly by incompressibility of a venous segment via ultrasound or filling defects via venography, a thrombus can now be visualised directly.

The solution for accurately diagnosing patients with a suspected ipsilateral recurrent DVT is nearby with the on-going Theia study. This is a diagnostic management study, in which patients with a suspected ipsilateral recurrent DVT are managed based on the results of the MRDTI scan only. When this study successfully proofs the safety of

this strategy, MRDTI can be directly implemented in clinical practice. The use of MRDTI for diagnosing UEDVT needs two extra steps before it can be used in clinical practice. The accuracy of MRDTI and TSE-SPAIR for diagnosing UEDVT will be explored with the MAGNITUDE/Selene study, and thereafter a diagnostic management study has to be performed as well. Moreover, MRDTI is a very promising technique to diagnose thrombosis in other difficult to image venous segments in the future. For instance, studies to test the feasibility of MRDTI to diagnose thrombosis in the splanchnic veins and cerebral veins are being planned.

The introduction of DOACs has largely changed the treatment landscape of VTE. However, there are still challenges to overcome. Large prospective studies are needed to study the efficacy in daily clinical practice where the risk of non-persistence due to lack of monitoring consists. On the other hand, when DOACs are adequately taken, some studies reported that DOACs can potentially lower the incidence of PTS because of the more constant anticoagulation level compared with VKAs. New studies are needed to proof this effect. Also, the effectiveness and optimal treatment duration of elastic compression stockings remains a point of discussion. Recent studies suggested tailoring ECS therapy per individual. However it remains to be determined which clinical, radiological and biochemical variables form the optimal risk stratification tool to select patients who can safely stop wearing ECS. A large patient-level database is needed to derive this tool and could for example be formed by pooling the results of 3 most recent large ECS studies: the Octavia, IDEAL and SOX trial. Thereafter, a randomized controlled trial should be performed to test a strategy that allows for the identification of low risk patients who can safely stop ECS after the first three to six months.