Diagnosis, treatment and long-term effects of venous thromboembolism
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Chapter 14

Summary
This thesis aimed to address the diagnosis, treatment and long-term effects of venous thromboembolism (VTE). In the first part, two studies were described in which we aimed to optimise the diagnostic workup of patients with suspected pulmonary embolism (PE). In the second part, the treatment of VTE in special patient groups was investigated. In the third part, we focused on the management of direct oral anticoagulant (DOAC)-associated bleeding complications with non-specific reversal agents. Finally, aspects regarding the etiology and treatment of the post-thrombotic syndrome (PTS) were studied.

**Part I – Diagnostic management of PE**

Although improvements have been achieved in the diagnostic management of VTE, using clinical decision rules combined with D-dimer testing followed by computed tomography pulmonary angiography (CTPA) when indicated, it has been shown that in clinical practice adherence to these recommended strategy is poor leading to overuse of CTPA. Since D-dimer levels increase with age the clinical usefulness of the D-dimer test in elderly with suspected PE is reduced. Chapter 2 evaluated the clinical utility and safety of an age-adjusted D-dimer cut-off for patients 50 years or older (patient age x 10 μg/L) and concluded that the combination of the clinical decision rule with an age-adjusted D-dimer cut-off was associated with a 12% reduction of CTPA compared to conventional cut-off levels, with a low likelihood of subsequent clinical VTE. Chapter 3 presented a management study of patients with suspected PE using a simplified algorithm including a D-dimer test in every patient at presentation, and thus avoiding delay in the emergency room. The clinical decision rule consisted of three items of the original Wells rule, now called YEARS items (clinical signs of deep venous thrombosis (DVT), haemoptysis, ‘PE most likely diagnosis’). In patients without any of the YEARS items and a D-dimer level lower than 1000 μg/L, and in patients with ≥1 item(s) and a D-dimer level lower than 500 μg/L, PE was considered excluded without CTPA. Our study showed that the YEARS algorithm reduces the number of CTPA with 14% as compared to the original Wells rule, with a low risk for fatal and non-fatal VTE during 3-month follow-up.

Results from these two management studies showed that both algorithms effectively and safely reduce the number of necessary CTPA to rule out PE, with a low risk of recurrent VTE, which can now be implemented in clinical practice.

**Part II – VTE treatment in special patient groups**

Since the risk of both thrombosis and bleeding rise with advancing age, Chapter 4 presented a subgroup analyses of the phase 3 randomised controlled
trials comparing DOACs with vitamin K antagonists (VKA) for the treatment of VTE and stroke prevention in atrial fibrillation. We showed that the favorable balance between risk and benefits of DOACs is preserved in the elderly population. Moreover, observed relative benefits of DOACs over VKA therapy can lead to larger absolute risk reductions, due to the higher event rates in elderly patients. **Chapter 5** described the treatment and clinical course of breakthrough events, i.e. recurrent thromboembolic events in patients who are on anticoagulants as treatment for VTE. This registry concluded that there is a wide practice variation in the management of breakthrough events during anticoagulant treatment reflecting the heterogeneous and complex nature of this clinical situation. Breakthrough events often develop in patients with cancer or antiphospholipid syndrome, or in patients receiving subtherapeutic anticoagulation. The risk of a second breakthrough event in this high-risk population is 5-7%. **Chapter 6** described the management and short-term prognosis of breakthrough events in anticoagulated patients with cancer. This observational study showed that in accordance to the current guidelines, the recommendation to prescribe LMWH rather than VKA as VTE treatment in patients with cancer also pertains to patients with breakthrough events. Furthermore, breakthrough events were accompanied by high morbidity and mortality in patients with cancer. Interestingly, increasing anticoagulant intensity in patients already receiving LMWH did not reduce the risk of second breakthrough events, whereas switching from VKA to LMWH did. **Chapter 7** investigated the pharmacokinetics and –dynamics of rivaroxaban and dabigatran in patients with short bowel syndrome and concluded that both rivaroxaban and dabigatran can be considered as alternatives to VKA and LMWH in selected patients. Although rivaroxaban seemed to be a better alternative with a higher oral bioavailability as compared to dabigatran etexilate. In this pilot study large inter-individual variability was observed which is likely caused by the small sample size and heterogeneity of the enrolled patients which reflects the clinical challenges physicians face treating this patient population. Hence, in clinical practice initial monitoring might be required to assure adequate absorption.

**Part III – Treatment of DOAC-associated bleeding complications**

Despite the fact that VKA and DOACs are very effective in the treatment of VTE and stroke prevention, use of anticoagulants leads to an increased risk of bleeding. **Chapter 8** reviewed the different treatment options of DOAC-associated bleeding complications. This narrative review emphasised that according to data from phase 3 trials including patients with atrial fibrillation and VTE - despite lacking a specific reversal agent for DOACs - the clinical outcome
of DOAC-associated bleeding complications is similar to VKA-associated bleeding complications. In the absence of a reversal agent for DOACs, the initial approach to patients with bleeding should consist of local haemostatic options combined with supportive measures. These supportive measures will be sufficient in the majority of patients with DOAC-associated bleeding complications. In case of life-threatening bleeding or necessity of immediate surgical interventions, non-specific prohaemostatic agents such as prothrombin complex concentrate (PCC) should be considered. Chapter 9 and 10 investigated, in healthy non-bleeding volunteers, an intermediate (37.5 IU/kg body weight) and low (25 IU/kg body weight) dose of four-factor PCC as potential reversal agent for apixaban- and rivaroxaban-associated bleeding complications. Both studies showed that four-factor PCC in these doses immediately increases endogenous thrombin potential and normalises prothrombin time in healthy volunteers treated with rivaroxaban and apixaban. The effect of PCC was sustained over a 24 hour period. However, a complete normalisation of thrombin generation beyond baseline values, as found in a prior study with 50 IU/kg four-factor PCC, was not observed, thus suggesting that in life-threatening bleeding, 37.5 or 25 IU/kg PCC will not suffice.

Part IV – Long-term effects of DVT: Post-thrombotic syndrome

The post-thrombotic syndrome is a frequent but poorly understood chronic complication of DVT and occurs in up to 50% of the patients. Chapter 11 investigated the potential benefit of rivaroxaban as compared with VKA in the development of PTS. In this post-hoc subgroup analysis of the Einstein DVT trial we assessed the incidence of PTS development in the enoxaparin/VKA-treated patients versus the rivaroxaban-treated patients. The results of this study showed that rivaroxaban-treated patients might have a lower risk of developing PTS as compared with enoxaparin/VKA-treated patient. Chapter 12 evaluated the role of toll-like receptor 9 (TLR9) in the development of PTS, residual thrombosis and recurrent DVT. Animal models suggest that impaired innate immunity leads to less thrombus resolution with adequate TLR9 expression being essential in promoting thrombus resolution after acute DVT. We assessed whether less thrombus resolution was associated with a lower expression of TLR9 and consequently higher risk of PTS development. In this study, TLR9 expression seemed lower in individuals with DVT and residual thrombosis, however no significant difference in TLR9 expression was found between DVT patients with or without PTS and healthy individuals without a history of VTE. Unexpectedly, TLR9 might play a role in recurrent DVT, as the TLR9 expression was significantly higher in patients with recurrent DVT. The pathophysiology behind TLR9 expression and recurrent DVT is uncertain and further investigation is needed to elucidate this finding and to evaluate
whether TLR9 could play a role in the prediction of recurrent DVT. Chapter 13 presented the results of a case-control study. In this study a panel of biomarkers was measured in patients with prior DVT who had developed PTS, in patients with prior DVT who did not develop PTS, and in healthy individuals without a history of VTE. This study did not find enhanced inflammation in patients with PTS, as levels of CRP, IL-6, and IL-8 did not differ between the three groups. However, patients with PTS were found to have a more pronounced coagulation activity, as suggested by higher levels of D-dimer and TAT.

**General discussion and future perspectives**

In the last decades many improvements have been made in the diagnostic workup of suspected PE. Large management studies supported a standardised strategy consisting of a clinical decision rule, D-dimer test and imaging. Despite these improvements, still in only 20-30% of patients who have an indication for CTPA, the diagnosis of PE is confirmed. Moreover, CTPA may also cause adverse effects such as contrast nephropathy and increased risk of cancer from radiation exposure. Therefore, further optimalisation of the diagnostic workup of suspected PE is needed. Moreover, in clinical practice adherence to the recommended, sequential algorithms and pre-test probability scores is poor. Since inappropriate use of the algorithm is associated with increased recurrence of VTE and overuse of CTPA, it is important that the implemented strategies are adhered to. Therefore future algorithms should be easy to remember and simple to apply, leading to increased adherence and consequently reduction of unnecessary CTPAs and less VTE recurrences. The two studies presented in this thesis are an important step forward. Both the ADJUST and YEARS algorithm showed a substantial reduction of CT-scans without the risk of increased recurrent VTE. The ADJUST algorithm is a modification of the current Wells algorithm in patients older than 50 years. The YEARS algorithm is simpler than the current Wells algorithm and has two major advantages over the current Wells and ADJUST algorithm. Firstly, the simultaneous assessment of the clinical items (YEARS items) and D-dimer test will avoid delay in the emergency room. Secondly, the YEARS algorithm also reduces CT-scans in patients less than 50 years old. In the future, a combination of the ADJUST and YEARS algorithm might be evaluated, in which the D-dimer cut-off in elderly patients could be increased within the YEARS algorithm.

Although many achievements have been made in the treatment of VTE, conducting clinical studies in special patient groups is challenging and needs collaboration of different disciplines. Until now, solid evidence for the best practice on anticoagulation treatment in patients with breakthrough events (i.e. recurrent VTE while using therapeutic dose anticoagulant therapy) and in patients with short bowel syndrome is lacking, making clinical care in such
patients complex and heterogeneous. Therefore, large management studies are essential to address the clinical outcome of different regimens in patients with breakthrough events. In the meanwhile physicians should carefully evaluate the benefits and risks of increasing anticoagulation intensity in case of breakthrough events as the risk of bleeding is considerable. Moreover, the dose and type of anticoagulant should be individualised as well as the duration of the treatment. Patients with short bowel syndrome requiring long-term nutrition represent a rare and heterogeneous population, consequently conducting large clinical randomised trials might be unachievable. Hence, future observational studies should focus on identifying patient characteristics that are important in selecting the most suitable anticoagulant in case long-term anticoagulation is required.

Despite the fact that DOACs are as effective as VKA in the treatment of VTE and for stroke prevention in atrial fibrillation, bleeding complications will remain an important issue. Our findings together with other in vivo research suggest that PCC, if dosed adequately, can overcome the anticoagulant effect of direct oral factor Xa-inhibitors and might be used as option for managing direct oral factor Xa-inhibitors-associated bleeding complications. However, these results should be interpreted with caution and confirmed in future studies in acutely bleeding patients. Specific reversal agents for oral factor Xa-inhibitors are currently under clinical evaluation. These studies in acutely bleeding patients will establish the effect of these specific antidotes as reversal agent for oral factor Xa-inhibitors, whether in vitro coagulation assays correlate with clinical haemostasis and what the effect of these reversal agents is on the clinical outcome of acute bleeding and on thrombotic events. Until such agents become available in routine clinical care, international guidelines recommend supportive measures and local source control followed by non-specific reversal agents such as PCC in case of severe or life-threatening factor Xa-inhibitor-associated bleeding complications.

Post-thrombotic syndrome is a common, but poorly understood complication of DVT. As all DOACs have a stable pharmacological profile DOACs might play a role in the prevention of PTS. Since recent guidelines recommend DOACs as first choice for the treatment of DVT, a randomised phase 3 trial to investigate the effect of DOACs versus VKA on the development of PTS will likely not be performed and post-hoc analyses of previously performed trials or observational studies will be needed to assess the effect of DOACs on PTS prevalence. Our group is undertaking a large study assessing PTS in patients treated with another DOAC. Regarding the pathophysiology of PTS, large prospective cohort studies measuring different biomarkers during several years of follow-up should elucidate which processes are crucial in the development of PTS.
Reference list
