Treatment of venous thromboembolism: focus on patient characteristics and bleeding complications
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Summary and future perspectives
This thesis focused on various aspects of the treatment of patients with venous thromboembolism (VTE), both with vitamin K antagonists (VKA) as well as with direct oral anticoagulants (DOACs). The overall aim was to improve the treatment and management of VTE and to lower the patients' burden on treatment complications.

Part I: Patient characteristics in relation to treatment and outcome of venous thromboembolism

Chapter 2 is a review of the literature describing the epidemiology of VTE. The incidence rate of a first VTE is 1-2 per 1000 per year. Many risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE) are known, including cancer, immobilization and medical illnesses; but idiopathic VTE is found in half of the patients. Women are at higher risk of developing VTE during their life span than men, mainly due to hormonal factors, and 5-10\% of all patients experience a recurrent event within one year. The post-thrombotic syndrome is a frequent complication of DVT and occurs in 20-50\% of patients. Chronic thromboembolic pulmonary hypertension affects 0.4-4\% of patients with PE. Socio-economic consequences, i.e. the costs of and disability related to VTE are substantial and associated with a significant burden on the health care system.

In Chapter 3 we studied the importance of right ventricular dysfunction (RVD) on recurrent VTE in the Hokusai-VTE study. The Hokusai-VTE study was a randomized double-blind study comparing edoxaban with VKA in patients with acute symptomatic VTE. All patients received initial treatment with low-molecular-weight or unfractionated heparin for at least 5 days. In Hokusai-VTE two different indicators for RVD, N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥500 pg/mL and right to left ventricular (RV/LV) diameter ratio on computed tomography ≥0.9, were assessed. The rate of recurrent VTE was found to be lower in patients treated with edoxaban in comparison to VKA. In a post-hoc analysis of the PE population of the Hokusai-VTE, we demonstrated that edoxaban is superior to VKA in the treatment and prevention of recurrent VTE in PE patients with evidence of RVD. Since the advantage of edoxaban could not be explained by differences in baseline characteristics or bleeding complications between the treatment groups, suboptimal treatment with VKA, or differences in duration of initial heparin treatment, it is most likely that edoxaban has intrinsic characteristics that lead to a more constant protective anticoagulant effect than VKA. Therefore, edoxaban might be used in all PE patients eligible for anticoagulant treatment, and is a user friendly and more effective option than VKA in patients with RVD.

There are two possible regimens for treatment with a DOAC; the DOAC can be started after initial therapy with heparin for ≥5 days, or an all-oral DOAC regimen can be used. There
is no evidence comparing both options directly. **Chapter 4** investigated 1) the potential benefit of initial heparin therapy prior to DOAC use on recurrent VTE; 2) the characteristics of PE patients across the DOAC trials; and 3) the importance of anatomical extent of the presenting PE on RVD, cause of PE and recurrent VTE. First, we performed an indirect meta-analysis comparing recurrent VTE rates with DOACs with or without initial heparin to VKA therapy and showed a potential benefit of heparin lead-in before DOACs. Second, the comparison of PE patients from the different DOAC trials showed many similarities among the baseline characteristics, but a remarkable difference in the proportion of PE patients with extensive disease at presentation. And third, an in-depth analysis of the Hokusai-VTE study revealed an association between the anatomical extent of PE and elevated NT-proBNP levels, and recurrent VTE risk; the risk was almost 2 times higher in patients with extensive compared to those with limited disease in both treatment groups. The extent of PE was independent of the cause of PE (provoked or unprovoked). This study may help in the management of PE patients, but further research is warranted to investigate the role of initial heparin in PE patients with extensive disease.

The risk of developing VTE differs between men and women; women have a higher risk during reproductive age, men at older ages. **Chapter 5** focussed on differences between men and women in the presenting location of a VTE. Data from three large independent studies revealed that there was a difference between the sexes in the distribution of the presenting location of a first VTE, as PE was more often observed to be the presenting location of VTE in women, whereas this was DVT in men. These findings were consistent in different age groups and most prominent amongst patients with unprovoked VTE. It is unclear what the underlying mechanism is. Further research should explore this difference in presenting VTE location in different cohorts in order to provide insight in the aetiology.

DOACs offer major simplification of the treatment and management of VTE and are currently the recommended treatment option. However, a lot of patients in the Netherlands are still treated with VKA and in many cases, the patient’s opinion or preference are very often not considered in the decision making process of which anticoagulant to start. In **Chapter 6** we assessed whether patients with VTE prefer a DOAC or a VKA. A random sample of 200 patients treated with a VKA for VTE at the Thrombosis Service Amsterdam received a questionnaire using the treatment trade-off technique. Approximately two-thirds of the patients preferred a DOAC over a VKA after being presented with the advantages of DOACs in four scenarios of the questionnaire. The most important arguments to switch to a DOAC were the lack for regular laboratory monitoring, low bleeding risk and reduced interactions with food and other drugs. Younger patients, patients with higher educational level and patients less satisfied with their current VKA treatment were more likely to prefer a DOAC over a VKA. It is important for clinicians to involve patients in the decision making process to improve satisfaction with the treatment and therapy adherence, and to increase the quality of life.
Factor Xa (fXa) inhibitors have been developed as an alternative for VKA in the prevention of stroke in patients with atrial fibrillation and the treatment and prevention of VTE. In large phase 3 randomized trials, fXa inhibitors were shown to be as effective as VKA in the treatment of VTE and were associated with a reduced risk of major and clinically relevant non-major (CRNM) bleeding. However, there still remain concerns about the clinical impact and management of those bleeding events. To provide information on differences in bleeding pattern and severity of clinical presentation and course between fXa inhibitors and VKA, we performed an individual patient data meta-analysis of all major bleeding events from the randomized controlled fXa inhibitor trials (i.e. Einstein, AMPLIFY and Hokusai-VTE studies) in Chapter 7. All major bleeding events were blindly classified regarding severity of clinical presentation and subsequent clinical course. The clinical presentation of major bleeding events in patients treated with fXa inhibitors was less severe than in patients receiving VKA, whereas the clinical course was comparable between both treatment groups. These findings were consistent in different types of bleeding complications, such as intracranial haemorrhages and gastrointestinal bleeds. Therefore, fear of uncontrolled bleeding complications is not a reason to withhold fXa inhibitors in the treatment of patients with VTE. **Chapter 8** provided an in-depth analysis of the clinical impact, development, management and treatment of major bleeding events with edoxaban, one of the fXa inhibitors, in comparison to VKA. The Hokusai-VTE study showed that edoxaban was non-inferior in efficacy and superior in safety compared to VKA. In a post-hoc analysis of this study, major bleeding events with edoxaban were at least similar and potentially milder in clinical presentation and course compared to VKA-associated major bleeds. There were no differences in the treatment and management of the bleeding events in both treatment arms. In **Chapter 9**, we presented an overview of the incidence, characteristics, diagnostics, treatment and outcome of abnormal vaginal bleeding events in women receiving apixaban, another fXa inhibitor, and enoxaparin followed by a VKA. The overall occurrence of abnormal vaginal bleeds was comparable between women treated with apixaban and VKA. But within the group of women experiencing a bleeding event, vaginal bleeds were more frequently observed than other types of bleeding in women treated with apixaban. Consequently, there was a difference in the pattern of bleeding sites between the two groups. The characteristics, treatment and outcome of abnormal vaginal bleeding events were comparable in both treatment arms. In **Chapter 10** we investigated the occurrence, characteristics and clinical outcome of abnormal vaginal bleeding events in women receiving edoxaban or VKA. Abnormal vaginal bleeding occurred more frequently in women treated with edoxaban compared with VKA. Almost all events were characterized by heavy menstrual bleeding, and the majority of the abnormal vaginal bleeds had a
mild clinical impact and outcome. These two studies (Chapter 9 and 10) indicated that abnormal vaginal bleeding events are a frequent complication of anticoagulant treatment in women with VTE, and physicians should be aware of this since these bleeding events can decrease the quality of life. In most cases preventative or therapeutic measures can be installed to prevent temporary or permanent cessation of anticoagulant treatment.

With respect to the treatment of anticoagulant-related bleeding episodes, Chapter 11 summarized the findings from a systematic review and meta-analysis on the efficacy and safety of prothrombin complex concentrate (PCC) in patients with acute bleeding events related to VKA use. Major bleeding events affect 1-3% of patients treated with VKA per year and immediate reversal of the anticoagulant effect of VKA can be achieved by the administration of PCC. Our analysis showed that PCC is a faster and more effective method for international normalized ratio (INR) correction in patients with VKA-associated bleeding compared to treatment with fresh frozen plasma (FFP) or no treatment, without increasing the risk of thromboembolic complications or mortality. These findings support the current guideline recommendations of management of anticoagulant-related bleeding complications. Although there is ample evidence on the effectiveness and safety of PCC in bleeding complications, data on functional outcomes and haemostatic efficacy are limited. A couple of years ago, a new classification scheme has been developed to assess haemostatic efficacy of reversal agents in bleeding complications associated with anticoagulant use. Chapter 12 aimed to evaluate clinical outcome parameters, including haemostatic efficacy, and severity of clinical presentation and course, of patients receiving PCC for VKA-associated bleeding events. We performed a retrospective cohort study of 100 patients with a VKA-related bleeding treated with PCC in five Dutch hospitals and collected data from medical charts and discharge letters. Effective haemostasis (i.e. bleeding control over 24 hours) was achieved in 68% of patients, and two-thirds of the patients with major VKA-associated bleeding had a severe clinical presentation, and half also had a severe clinical course. A limitation of this study is the small sample size and the results should therefore be interpreted with caution. Nevertheless, the findings do provide inside in the new standard endpoint of haemostatic efficacy to which reversal agents for anticoagulant drugs are currently tested. This is the first study to assess this outcome accurately in VKA bleeding events and provides the opportunity to compare the results with ongoing studies investigating specific antidotes for reversal of DOACs. Chapter 13 addressed the management and clinical outcome of DOAC-related emergencies. In this report of an ongoing multi-centre cohort study, we analysed all consecutive patients enrolled between December 2014 and August 2017. In total 70 patients were included; 62 with a DOAC-associated bleeding event and 8 who underwent an emergency intervention while using a DOAC. Half of the patients with a bleeding event received PCC for anticoagulant reversal and effective haemostasis was achieved in 81% of those patients. Of the 9 patients receiving
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idarucizumab, 100% achieved effective haemostasis. Approximately a third of the patients needed an additional procedure of intervention to control the bleeding. One patient had a major bleed within 7 days after an emergency procedure. The results were compared to the previously described retrospective cohort study with VKA-associated bleeding events (Chapter 12). Effective haemostasis after PCC administration was higher in the DOAC compared with the VKA cohort, albeit not significantly. No differences were observed in thromboembolic events or mortality between the cohorts. This is the first study that makes a comparison between DOAC- and VKA-related bleeding events treated with PCC using haemostatic efficacy possible. Due to the small sample size, further studies are needed to confirm our results, although they provide some insight and reassurance in the effectiveness of PCC for DOAC-related bleedings.

Future perspectives

This thesis illustrated that VTE treatment in patients with PE and extensive disease is challenging and heterogeneous. Despite new developments over the years and the growing amount of evidence in the treatment of VTE, solid evidence on the role of a heparin lead-in prior to DOAC therapy in patients with PE, and on the effect of RVD and anatomical extent of PE in VTE treatment, is lacking. This complicates clinical care for patients with PE and evidence of extensive disease. Therefore, large studies in clinical practice are essential to evaluate the clinical outcome of different treatment regimens in these patients. In the meantime, physicians should carefully consider the risks and benefits of initial heparin therapy prior to DOACs, and provide individualized treatment plans.

We also demonstrated that the majority of VTE patients prefer treatment with a DOAC over VKA therapy when informed about advantages and risks of both. In clinical practice, more and more attention is given to shared decision making and involving the patient in the care process. Since VTE treatment can be chronic and the benefits are not always (directly) noticeable, it is essential to increase patient awareness of the importance of therapy adherence. Physicians are responsible to provide evidence-based background information on the disease and treatment options, and should encourage patients to participate in shared decision making. Nevertheless, future studies are needed to assess the effect of shared decision making on treatment satisfaction, therapy adherence and quality of life of patients.

Bleeding complications are less common in patients treated with DOACs compared with VKA, but they remain an important concern. As demonstrated in this thesis, the clinical outcome of major bleeding episodes with fXa inhibitors was comparable to those with VKA. This provides reassurance to physicians in prescribing these agents, because even without
the availability of reversal agents for fXa inhibitors, bleeding events were not uncontrollable or more severe than with VKA. Nevertheless, the impact of specific reversal agents on clinical outcome of major bleeds needs to be investigated once these agents become available. One might speculate that administration of a specific reversal agent can contribute to a preferable clinical outcome and prognosis, since it reverses the anticoagulant effect and therefore restores normal haemostasis.

Severe or life-threatening bleeding and urgent interventions require immediate reversal of oral anticoagulants. Major bleeding associated with VKA should be managed with PCC, as our findings support. For patients receiving dabigatran a specific antidote (idarucizumab) is now available, and another antidote is under development for reversal of fXa inhibitors (andexanet alfa). Until andexanet alfa is available in clinical practice, guidelines recommend supportive measures and local bleeding control in addition to PCC administration. Our findings, together with small cohort and healthy volunteer studies, provide evidence for the effectiveness of PCC in managing bleeding complications with DOACs. As specific antidotes for DOACs become more and more available, the treatment of those bleeds will shift and more data is warranted on the efficacy and clinical outcomes related to the use of DOAC specific antidotes.