Clinical aspects of venous thromboembolism in special patient populations

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Summary
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This thesis focuses on several clinical aspects of venous thromboembolism (VTE) in special patient populations. In the first part, we address several elements of sex-specific VTE. Part two describes the relationship between cancer and VTE, with a focus on unsuspected pulmonary embolism (UPE). The third part concerns clinical aspects of upper extremity deep vein thrombosis (UEDVT), and the last part focuses on the clinical impact of bleeding with factor Xa (fXa) inhibitors and vitamin K antagonists (VKA).

Part 1: Sex-specific venous thromboembolism

Chapter 2 is a review of the literature describing the pathophysiology and magnitude of risk factors for VTE that are related to female sex, including the use of several types of hormonal contraception, hormone replacement therapy, pregnancy and the postpartum period. Due to these risk factors, during reproductive age women have a two-fold higher risk of developing VTE compared to men. When adjusting for the use of hormonal contraceptives and pregnancy, men seem to have a higher risk of developing VTE than women. The mechanism explaining the intrinsic higher risk of VTE in men has yet to be elucidated.

The presence of thrombophilia, i.e. a genetic variation causing a prothrombotic phenotype interacts with women-specific risk factors for VTE. The clinical implications of the presence of these factors are discussed.

Women with a history of VTE have a 2% to 10% absolute risk of developing a VTE recurrence during subsequent pregnancies. Therefore, the evidence-based guidelines recommend antepartum and postpartum pharmacological thromboprophylaxis for all pregnant women with a history of VTE and a moderate or high risk of recurrent VTE. The optimal dose of low-molecular-weight heparin (LMWH) to prevent a recurrence in these women is unknown. To study which one of two widely used doses of LMWH is most efficacious and safe in preventing pregnancy-related recurrent VTE, we designed the Highlow study, a randomized controlled trial (RCT) of which the protocol is detailed in Chapter 3. Chapter 4 contains an interim report of the Highlow study, and describes the study status as of June 2016, including baseline characteristics of 181 enrolled patients. This report presents the largest number of pregnant women with a history of VTE participating in a RCT to date. The enrolment rates show that recruitment of these women is feasible. Final outcome results are expected in 2020, and are very likely to impact current clinical practice and modify evidence-based guidelines. In Chapter 5 we studied the characteristics of vaginal bleeding in women with VTE receiving apixaban, an oral fXa inhibitor, or LMWH followed by VKA. Even though the absolute number of vaginal bleeding events seems comparable between apixaban and VKA recipients, the proportion of vaginal bleeding events is higher in women treated with
apixaban. The characteristics and severity of vaginal bleeding events were comparable in both treatment arms. Our study demonstrates that anticoagulant therapy in women with VTE can be complicated by vaginal bleeding, and physicians should be vigilant of the occurrence of vaginal bleeds in women using anticoagulants, especially in the reproductive phase of life. Future studies should focus on the impact of vaginal bleeding during the use of anticoagulants on quality of life, and preferably validated blood loss scores should be applied to better evaluate the severity of vaginal bleeding events.

**Part 2: Cancer and venous thromboembolism**

VTE is a common complication in cancer patients. Chapter 6 reviews the use of anticoagulant drugs for the prevention and treatment of symptomatic and incidental cancer-associated VTE. The use of anticoagulants in cancer patients can be challenging due to concomitant use of antineoplastic drugs, the frequent need of diagnostic or therapeutic interventions, and the susceptibility to nausea and vomiting. LWMH is currently the recommended type of anticoagulant for treatment of cancer-associated VTE because it was found to be superior to VKA in the prevention of recurrent VTE, with a similar risk of major bleeding complications. Ongoing trials are evaluating the effectiveness and safety of direct oral anticoagulants (DOACs) in patients with cancer and VTE. Primary VTE prophylaxis is currently not routinely recommended in ambulant cancer patients due to the high number needed to treat.

In Chapter 7 several recent studies on UPE in cancer patients are summarized. The reported incidence ranges from 1% to 5% and probably reflects an underestimation. The current evidence on radiologic and clinical characteristics, symptoms and prognosis of UPE is detailed. Major guidelines suggest similar initial and long-term anticoagulant therapy as for cancer patients with symptomatic PE, but direct evidence is scarce. To evaluate current treatment approaches and to prospectively assess the occurrence of major clinical outcomes such as recurrent VTE, bleeding and mortality, we are currently conducting an international, observational, prospective cohort study on cancer patients with UPE. An interim report of the study is provided in Chapter 8. Up to June 2016, 490 patients were enrolled in the registry, and this preliminary report demonstrates that cancer patients with UPE have a substantial risk of both recurrent VTE and bleeding during anticoagulant therapy. The risk of recurrent VTE is possibly lower for patients with subsegmental (i.e. most distal) UPE compared to those with more proximal clots. This finding suggests that in cancer patients with subsegmental UPE, the benefits of anticoagulant therapy may not outweigh the risks, but this suggestion needs to be confirmed in larger sample sizes and preferably in a randomized controlled trial. In a substudy, reported in Chapter 9, we investigated the interobserver agreement among radiologists on the diagnosis of distal UPE and the actual radiologic extension of UPE. The interobserver agreement between radiologists regarding most proximal location
Summary of UPE in cancer patients appears fair, but decreases for more distally located clots. Following our findings in chapter 8, knowing the extent of UPE may have therapeutic consequences, and extra dedicated reading of CT scans in cancer patients with UPE should be considered.

Part 3: Upper extremity deep vein thrombosis

Chapter 10 provides an overview of the available evidence on the incidence, clinical characteristics, risk factors, diagnosis, treatment and prognosis of UEDVT. UEDVT accounts for 4% to 10% of all DVT and is an increasingly frequent clinical problem which is mainly due to the more widespread use of central venous catheters (CVCs) that carry a high risk of VTE. Several diagnostic strategies have been tested in order to improve the diagnostic efficacy in patients with suspected UEDVT, but they are currently not in use and at present objective imaging is the cornerstone of diagnosis. Treatment recommendations for patients with UEDVT are largely extrapolated from studies on lower extremity DVT. Chapter 11 summarizes the clinical evidence on long-term clinical outcomes of UEDVT in terms of recurrent VTE, mortality and anticoagulant-related bleeding, with a special focus on patients with or without concomitant cancer. We found that studies were very heterogeneous in terms of study design, study populations and treatment approaches, and we concluded there is a need for large prospective studies to provide information on the clinical outcomes and best management of UEDVT. Subsequently, in Chapter 12 we assessed the current treatment strategies for patients with UEDVT and upper extremity superficial vein thrombosis (UESVT) in clinical practice and prospectively studied the long-term clinical outcomes for both diseases, including a separate assessment of the prognosis of cancer patients with UEDVT. Anticoagulant therapy was started in 98% and 73% of patients with UEDVT and UESVT, respectively. The risk of recurrent VTE seems low in patients with UEDVT and negligible for UESVT, but cancer patients with UEDVT have a significant risk of developing recurrent VTE. Post-thrombotic symptoms were infrequent and, if present, mild for both diseases.

Part 4: Bleeding with fXa inhibitors and vitamin K antagonists

Oral FXa inhibitors have been introduced for several indications including treatment of VTE and are now widely used. In the AMPLIFY trial, the FXa inhibitor apixaban proved to be non-inferior to enoxaparin followed by warfarin (i.e. the old treatment standard) in preventing recurrent VTE, and was associated with significantly less bleeding. To provide information on how bleeding events with apixaban present and develop, we blindly classified the clinical presentation and course of all major and clinically relevant non major (CRNM) bleeding events in the AMPLIFY trial in Chapter 13. The clinical presentation and course of major and CRNM bleeds were found to be similar in both treatment groups. In Chapter 14 we assessed the clinical relevance and management
of bleeding events with edoxaban, another fXa inhibitor, that was found to be non-
inferior and safer than VKA in the treatment of VTE in the Hokusai-VTE study. In a post-
hoc analysis of the Hokusai-VTE study we demonstrate that edoxaban associated major
bleeds have a comparable clinical presentation and course of major bleeds as with
VKA in patients treated for VTE. Chapter 15 aimed to combine the previously classified
severity of clinical presentation and course of all major bleeding events from the major
trials comparing fXa inhibitors to VKA for the treatment of VTE. fXa-inhibitor associ-
ated major bleeding events were found to have a significantly less severe presentation
and a similar course compared to VKA, and this finding was consistent for intracranial,
gastrointestinal and other types of bleeding. These findings should reassure physicians
and patients that fXa inhibitors are a convenient and safe choice for VTE treatment.