Cancer and thrombosis
van Es, N.

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CHAPTER 14

SUMMARY AND PERSPECTIVES
SUMMARY

The central themes of this thesis are strategies for prevention, diagnosis, and treatment of venous thromboembolism in cancer patients. In Chapter 2, we provided a comprehensive overview of the current diagnostic and therapeutic management of venous thromboembolism, in which the different approach to patients with and without cancer is highlighted. Whereas diagnosis and treatment of venous thromboembolism was considered a one-size-fits-all approach until about two decades ago, physicians now increasingly acknowledge that clinical decisions should be tailored to the presence or absence of cancer. Yet, despite these advancements, improvements in the care for these patients are needed, since failures in prevention, diagnosis and treatment remain more frequent among cancer patients than in those without cancer.

Improvements in strategies for prediction

Part I was aimed at the evaluation of risk stratification for cancer-associated venous thromboembolism. In Chapter 3, we demonstrated that various currently available clinical prediction scores for venous thromboembolism in cancer patients perform poorly. A total of 876 patients with various types of advanced cancer were followed for 6 months, during which approximately 6% developed venous thromboembolism. None of the examined prediction scores, including the Khorana, Vienna CATS, PROTECHT, and CONKO scores, could identify a group of patients in whom the risk of venous thromboembolism was high enough to justify thromboprophylaxis. This led us to conclude that these scores are currently not suitable for use in clinical practice and that improvements are needed.

In Chapter 4, we reported on an evaluation of the performance of the Khorana score in cancer patients who are known to be at the highest risk of venous thromboembolism: those with pancreatic adenocarcinoma. In a retrospective cohort study of 178 ambulatory patients, the overall cumulative incidence of venous thromboembolism after 2 years of follow-up was 12%. Again, the Khorana score was not able to discriminate between low and high risk patients, which raises doubts about its validity in this patient group. Instead, the high risk of venous thromboembolism should invite physicians to maintain a low threshold of considering primary prevention, irrespective of the Khorana score.

The analysis in Chapter 5 combined patient-level data from seven randomized controlled trials in which the effect of prophylactic low-molecular-weight heparin on survival was
evaluated in patients with cancer. The performance of the dichotomous Khorana score for predicting venous thromboembolism appears to vary substantially across tumor types. This finding challenges the premise that the Khorana score can be used as a pan-cancer risk assessment tool, like it was introduced. Among patients with a high-risk Khorana score, thromboprophylaxis effectively prevented venous thromboembolism, while not being associated with a clinically or statistically significantly increased risk of major bleeding.

In Chapter 6, a plasma biomarker for venous thromboembolism in cancer patients was evaluated, namely the procoagulant activity of extracellular vesicles exposing tissue factor as measured by the in-house fibrin generation test. In a cohort of 648 patients with various types of advanced cancer, a high procoagulant activity of extracellular vesicles was associated with a two-fold higher risk of venous thromboembolism. The association was strongest in patients with pancreatic cancer, leading us to conclude that this biomarker may be a future candidate for prediction of venous thromboembolism in these patients, possibly in combination with other predictors.

Chapter 7 presented a derivation and external validation study of a novel, simple clinical prediction model for venous thromboembolism in ambulatory patients with cancer which only incorporates type of cancer and D-dimer levels. This model was able to accurately predict the risk of venous thromboembolism across a broad spectrum of cancer patients, thereby providing an individualized risk assessment tool that can aid physicians in deciding about who should receive thromboprophylaxis.

**Improvements in strategies for diagnosis**

Part II addressed the diagnosis of venous thromboembolism in cancer patients and the diagnosis of (occult) cancer in patients with venous thromboembolism. Chapter 8 presented a systematic review and meta-analysis of individual data on more than 7,000 patients who had been enrolled in six prospective management studies in which the performance of the widely used Wells rule and D-dimer testing in ruling out pulmonary embolism was evaluated. We showed that the proportion of patients in whom imaging can be withheld, based on a low Wells score and negative D-dimer, increased approximately 5% when the age-adjusted D-dimer threshold (i.e. age multiplied by 10 μg/L in patients older than 50 years) was used instead of the conventional fixed threshold. Although the yield of an age-adjusted D-dimer
threshold appeared to vary substantially across subgroups, it should be preferred over the fixed threshold in clinical practice, since it increases efficiency without jeopardizing safety.

In Chapter 9 we compared the performance of the original and simplified Wells scores in combination with the age-adjusted D-dimer threshold, again using the pooled data of six prospective management studies. The simplified version of the Wells score improves the clinical applicability of the decision rule, since physicians only need to evaluate whether two or more features are present for deciding when to refer a patient for imaging directly. We showed that the original and simplified Wells rules safely ruled out pulmonary embolism in a similar proportion of patients, which makes the latter rule the preferred option in clinical practice.

In Chapter 10, we evaluated screening for occult cancer in patients with unprovoked venous thromboembolism using individual patient data from ten recently published prospective studies. We concluded that one in every twenty patients with unprovoked venous thromboembolism will be diagnosed with cancer within a year. Physicians should have a low threshold of suspicion for cancer, especially in patients older than 50 years, since these patients were seven times more likely to be diagnosed with cancer than younger patients. Although extensive screening appeared to detect more cancers than a limited screening strategy at the time of venous thromboembolism diagnosis, it remains unknown whether this translates into patient benefits. Until this becomes clear, clinicians should refrain from extensive screening.

**Improvements in strategies for treatment**

Part III covered the treatment of venous thromboembolism in cancer patients. In Chapter 11, we demonstrated that direct oral anticoagulants are equally effective as but safer than vitamin K antagonists in the treatment of acute venous thromboembolism. In a meta-analysis of six phase 3 studies, no differences in the risk of recurrent venous thromboembolism were found, while direct oral anticoagulants were associated with a significant 40% lower risk of major bleeding, with an even greater reduction in intracranial hemorrhage. Given this superior safety profile, these new agents should be preferred for the majority of patients. In the subgroup of cancer patients, direct oral anticoagulants appeared to be associated with both a lower risk of recurrence and of major bleeding, although it has to be noted that this
selected group of trial patients is likely to have had a more favourable prognosis compared with the broader population of cancer patients with venous thromboembolism.

In Chapter 12 we reported a detailed analysis of the subgroup of cancer patients enrolled in the Hokusai-VTE study, a large randomized trial that compared the efficacy and safety of edoxaban with warfarin in the treatment of acute venous thromboembolism. Irrespective of the cancer definition used (i.e. history of cancer, active cancer as per the study physician, or a post-hoc classification of active cancer), edoxaban appeared to be as effective as warfarin, but associated with less clinically relevant bleeding. This is relevant in situations where low-molecular-weight heparin – the recommended treatment in cancer patients – is not available, too expensive, not preferred by the patient, or not tolerated.

Finally, in Chapter 13, the rationale and design of the Hokusai VTE-cancer study were described. This multinational study will be the first study to directly compare one of the direct oral anticoagulants, edoxaban, to low-molecular-weight heparin for treatment of acute, symptomatic or incidental venous thromboembolism in patients with active cancer. Some innovative design features are highlighted and substantiated with a scientific basis, using a post-hoc analysis from Hokusai-VTE and a network meta-analysis. This study will undoubtedly provide valuable information about the optimal treatment of venous thromboembolism in cancer patients and has the potential to change future guidelines.

**PERSPECTIVES**

Part I of this thesis illustrates that venous thromboembolism risk prediction in ambulatory cancer patient is challenging and far from optimal. Future improvements are likely to move into two potential directions: either refinement or replacement of current pan-cancer prediction tools, by using information on biomarkers, general cancer therapies, and patient-related factors, or the development of cancer-specific prediction models that incorporate information on mutations, classifications, and treatments specific to a single type of cancer. The initial results of the simple clinical prediction model introduced in Part I, which calculates a personalized risk of venous thromboembolism from tumor type and D-dimer level, are encouraging, but future intervention studies are needed to evaluate whether the use of this score to select ambulatory cancer patients for thromboprophylaxis translates into clinical benefit. Deciding on a more or less general incidence threshold at which oncologists
are willing to provide ambulatory cancer patients with thromboprophylaxis could help shape future guidelines and facilitate implementation of such a risk assessment tool.

As demonstrated in Part II of this thesis, the efficiency of current diagnostic strategies in cancer patients with suspected deep vein thrombosis or pulmonary embolism is suboptimal. A possible explanation, besides the lower specificity of D-dimer testing in this group, is the broad definition of active cancer once defined by Wells and colleagues as ‘malignancy with treatment within 6 months or palliative’, which does not appreciate the differences in pre-test probabilities across various types of cancer. A clinical decision rule targeted at cancer patients with cancer-specific information incorporated might increase the proportion of patients in whom deep vein thrombosis or pulmonary embolism can be ruled out without imaging, although it should perform substantially better than the current approach to eventually find its way into clinical practice.

Part II also demonstrated that extensive, imaging-based screening for cancer in patients with unprovoked venous thromboembolism does not appear to be beneficial. At the same time, a substantial proportion of the cancers are still missed by the currently suggested limited screening, fueling the search for alternative screening approaches in these patients. Novel, promising biomarkers for cancer, including tumor-educated platelets and circulating DNA, are now being evaluated in our recently started multinational PLATO-VTE study. The goal is to detect more cancers in an early, potentially curable stage, while these biomarkers in parallel might even direct targeted testing for cancer by predicting the actual type of cancer.

Several ongoing studies are comparing the efficacy and safety of edoxaban, rivaroxaban, or apixaban with low-molecular-weight heparin for venous thromboembolism in patients with active cancer. The first large randomized study that will be completed shortly is the Hokusai VTE-cancer study, of which the rationale and study design are reported in Part III. If non-inferiority of edoxaban is demonstrated with respect to the combined outcome of recurrent venous thromboembolism and major bleeding, oral treatment may soon be available for most cancer patients with cancer-associated venous thromboembolism.
CLOSING REMARKS

A shift towards a personalized approach in predicting, diagnosing, and treating cancer-associated venous thromboembolism is dawning, although many hurdles still need to be taken. Oncologists are increasingly aware of the substantial risk of (recurrent) venous thromboembolism in their patients, but thromboprophylaxis is still infrequently considered and treatment not always adequate. In the coming years, it’s the task of thrombosis specialists to develop accurate, valid, yet easy to use prediction tools that can guide clinical decisions based on personalized risks of a first or recurrent venous thromboembolism as well as bleeding. Large, high-quality administrative datasets with rigorously collected data may be perfectly suitable to fill this gap when used in combination with machine learning techniques.

The huge advances in DNA sequencing in combination with ever decreasing costs, will soon allow us to also use genetic information obtained from tumor material to predict venous thromboembolism, since it is not unlikely that specific mutations drive the thrombogenic potential of certain cancers. Once high-risk patients can be adequately identified, randomized studies should be initiated to evaluate the clinical benefit of these new prediction tools – an essential but often forgotten step before implementation in clinical practice. Together with the exciting development of novel anticoagulants that do not appear to be associated with bleeding, such as factor XI and XII inhibitors, we may finally move towards easy, safe, and clinically beneficial prevention and treatment of venous thromboembolism tailored to the individual cancer patient.