Cancer-associated thrombosis

Advances in diagnosis and treatment

Kraaijpoel, N.

Link to publication

Creative Commons License (see https://creativecommons.org/use-remix/cc-licenses):
Other

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 14

SUMMARY AND PERSPECTIVES
SUMMARY

The main subjects of this thesis concerned the diagnostic and therapeutic management of cancer-associated thrombosis, together with diagnosis of occult cancers in patients with unprovoked venous thromboembolism. In Chapter 2, an overview of recent advances in diagnosis and treatment of venous thromboembolism was provided, with a special focus on approaches applying to management of cancer patients. Whereas the diagnostic approach to patients with cancer has remained largely unchanged over the past few years, therapeutic management has made a major shift from subcutaneous therapy with low-molecular-weight heparins to oral therapy with direct factor Xa inhibitors. This novel therapeutic strategy is associated with a favorable efficacy at the expense of a higher risk of bleeding, primarily seen in patients with gastrointestinal cancer. Therefore, when considering a direct factor Xa inhibitor for the treatment of cancer-associated thrombosis, the bleeding risk should be assessed on an individual basis and carefully weighed against the preferable efficacy profile, patient preference for route of administration, and associated costs.

ADVANCES IN DIAGNOSIS OF CANCER-ASSOCIATED THROMBOSIS

Part I focused on improvements in the diagnostic management of venous thromboembolism in patients with and without cancer. Chapter 3 reported on a meta-analysis of individual patient data previously identified in a systematic review on the performance of the Wells rule and D-dimer in more than 7,000 patients with suspected pulmonary embolism. The performance of the original Wells rule, which assigns between one and three points to the different score items, was compared with that of the simplified Wells rule, which only assigns one point to each of the score items. The simplified version of the Wells score facilitates use of the score in practice, as the presence of only two positive items indicates that patients should be referred for imaging. Both scores were evaluated in combination with age-adjusted D-dimer testing. The diagnostic performance of both scores was shown to be comparable, indicating that the simplified score should be preferred in daily practice.

In Chapter 4, the diagnostic accuracy of single limited, serial limited, and whole-leg ultrasonography for suspected deep vein thrombosis were summarized and compared in a systematic review. The failure rates of the three strategies appeared to be comparable, although the failure rate of the
single limited approach was uncertain due to a lower prevalence of deep vein thrombosis in that group. Preference for one of the strategies in clinical practice should therefore be based on pretest probability assessment, feasibility, expertise, and perceived clinical relevance of deep vein thrombosis isolated to the distal veins.

**Chapter 5** presented the results of a systematic review summarizing the definitions used for pulmonary embolism-related death in recent clinical studies and assessed adjudication and reporting of this clinical outcome. Definitions for pulmonary embolism-related death were poorly reported and those reported were heterogeneous, which may be an important cause for the wide range of pulmonary embolism-related death rates among published studies. As pulmonary embolism-related death is often included in the primary outcome of clinical studies in the field of venous thromboembolism, standardization of its definition is needed to improve internal and external validity of study results.

**Chapter 6** describes the rationale and design of a large, international individual patient data meta-analysis of diagnostic management studies for suspected pulmonary embolism. The main objectives are to assess the optimal diagnostic strategy across different healthcare settings and the performance of these strategies in patients with specific comorbidities, including cancer. Finally, a novel clinical decision model will be developed including clinical items and quantitative D-dimer as a continuous variable. This tool is intended for use in both cancer and non-cancer patients with suspected pulmonary embolism, aiming at safely reducing the number of patients referred for imaging, with better accuracy than currently available tools.

**ADVANCES IN TREATMENT OF CANCER-ASSOCIATED THROMBOSIS**

**Part II** assessed improvements for treatment strategies in cancer-associated thrombosis. **Chapter 7** was a clinical review aiming to support physicians in their daily practice by providing an overview of available evidence and personal perspectives on challenging clinical problems. Three common scenarios of cancer-associated venous thromboembolism were discussed, including acute deep vein thrombosis for which extended anticoagulant treatment beyond 6 months was anticipated, incidentally detected pulmonary embolism, and central venous catheter-associated deep vein thrombosis of the upper extremity.
Chapter 8 was an aggregate post-hoc analysis of the large phase III trials comparing direct factor Xa inhibitors with vitamin K antagonists for the treatment of acute venous thromboembolism, totaling more than 20,000 patients. The severity of anticoagulant-related major bleeding events was compared between cancer patients and non-cancer patients. Although the group with cancer patients most likely included a selected group of patients, the results of this study suggested that the presentation and clinical course of major bleeding events is not worse in patients with cancer. These findings may be reassuring for physicians who treat cancer patients presenting with anticoagulant-related major bleeding.

In Chapter 9, the impact of anticoagulant-related bleeding in cancer patients was further evaluated in a post-hoc analysis of the Hokusai VTE Cancer trial. In this trial, edoxaban was noninferior to dalteparin for the composite outcome of recurrent venous thromboembolism and major bleeding. The risk of recurrent venous thromboembolism was lower with edoxaban, at the expense of a higher major bleeding risk. In the present analysis, the excess major bleeding events with edoxaban occurred mainly in the upper gastrointestinal tract in patients with all types of gastrointestinal cancer. In patients with cancer outside the gastrointestinal tract, the risk of major bleeding was similar for the two treatment regimens. These findings led to the conclusion that careful case-by-case consideration is needed when considering edoxaban in patients with gastrointestinal cancer.

In Chapter 10, the efficacy and safety of edoxaban in the Hokusai VTE Cancer trial was further assessed within important cancer type groups, including gastrointestinal, lung, urogenital, breast, hematological, and gynecological cancer. Apart from gastrointestinal cancer, edoxaban had a similar risk-benefit profile as dalteparin across the subgroups of interest, suggesting that edoxaban can be considered in most patients with cancer-associated venous thromboembolism. In patients with gastrointestinal cancer, the benefits of the lower risk of recurrent venous thromboembolism and the advantages of oral therapy should be weighed against the increased risk of major bleeding.

Chapter 11 presented the results of a prospective cohort study evaluating current treatment regimens for incidentally detected pulmonary embolism in cancer patients, as well as associated clinical outcomes. In addition, the risk of recurrent venous thromboembolism was compared between patients with pulmonary embolism confined to the subsegmental arteries and those with more proximal pulmonary embolism. Almost all patients were treated with anticoagulant therapy. The risk of recurrent venous thromboembolism was
found to be high, despite anticoagulant treatment, thereby strengthening current guideline recommendations to treat incidental and symptomatic pulmonary embolism similarly. Patients with isolated subsegmental and those with more proximal pulmonary embolism had a comparable risk of recurrent venous thromboembolism, which argues against a differential treatment regimen for cancer-associated incidental isolated subsegmental pulmonary embolism.

ADVANCES IN DIAGNOSIS OF OCCULT CANCER IN UNPROVOKED VENOUS THROMBOEMBOLISM

Part III was aimed at improving occult cancer detection in patients with unprovoked venous thromboembolism. In Chapter 12, the performance of the RIETE and SOME risk prediction scores for occult cancer was evaluated in patients with acute venous thromboembolism included in the Hokusai-VTE trial. These scores were designed to identify patients at high risk of a yet undetected cancer who might benefit from additional extended cancer screening tests. The overall discriminative performance of both scores was found to be poor. Although the dichotomous scores were able to discriminate between higher and lower risk patients, most cancers were found in the low risk groups. Therefore, the use of the RIETE and SOME scores in clinical practice cannot be recommended.

Chapter 13 describes the rationale and design of the ongoing PLATO-VTE study. This prospective multicenter cohort study compares the sensitivity of novel biomarkers for cancer with that of standard-of-care limited cancer screening in patients with unprovoked venous thromboembolism. The biomarkers assessed include platelet mRNA sequencing, circulating tumor DNA, and proteomics analysis, which may be associated with a superior cancer detection rate, while reducing radiation or invasive testing. In addition, some of these biomarkers may possibly also indicate the location of the tumor. The PLATO-VTE study has the potential to change cancer screening practice in unprovoked venous thromboembolism by using a biomarker-based approach improving or replacing current strategies, and the results are eagerly awaited.
PERSPECTIVES

Current diagnostic algorithms for venous thromboembolism perform worse in patients with cancer due to a lower specificity of clinical decision rules and D-dimer testing and a higher prevalence of venous thromboembolism among those assessed. As a result, use of these algorithms is infrequent in the oncology population, and imaging is the first-choice diagnostic test, leading to an increased pressure on emergency and radiology departments, unnecessary radiation exposure, and possible detection of clinically insignificant clots. Items of clinical decision rules used in clinical practice are mostly applicable to the general population and are less predictive in patients with cancer. Only a minority of patients included in the derivation studies had cancer, and potential score items did not account for individual differences in the risk of thrombosis within the heterogeneous cancer population. In addition, potential interactions between score items and cancer were not assessed, and for the purpose of simplicity, continuous variables and D-dimer levels were always categorized, thereby reducing statistical power. It is conceivable that clinical items specific to the cancer population, such as cancer type, cancer stage, and type of chemotherapy could improve the diagnostic performance of current models, as well as the use of continuous variables. Whereas in the past, prediction scores for suspected venous thromboembolism were designed for ease of use in busy emergency departments where score results had to be calculated by hand, the current widespread use of web and smartphone applications allows for the use of prediction scores that are calculated by software. Novel prediction models may therefore include a large variety of continuous and categorical variables, while incorporating continuous D-dimer and accounting for possible interactions. Furthermore, an absolute risk estimate can be provided instead of a probability range. It is to be expected that such prediction models will be developed and implemented in clinical practice in the forthcoming years, allowing for accurate risk prediction tailored to the individual cancer patient, thereby optimizing the proportion of patients managed without imaging.

Part I elaborated on a recently initiated systematic review and individual patient data meta-analysis, which will combine data of all diagnostic studies previously performed in the field of pulmonary embolism. This will allow for comparison of current diagnostic strategies in a large group of cancer patients, and assessment of the most predictive variables and optimal current strategy in this population. In addition, a novel prediction rule, which incorporates D-dimer
as a continuous parameter, will be developed, which will be validated for use in the cancer population as well. Future prospective studies may assess whether addition of cancer-specific variables improve the performance of the model in cancer patients.

**Part II** of this thesis illustrated the shift from low-molecular-weight heparins to direct oral anticoagulants for the treatment of cancer-associated thrombosis. Although the risk of recurrent venous thromboembolism is lower with the new regimen, the risk of bleeding appears to be higher, but only in patients with gastrointestinal cancer. Edoxaban and rivaroxaban are now suggested for the treatment of cancer-associated thrombosis when there are no drug-drug interactions and bleeding risk is considered low. To better tailor individual anticoagulant treatment regimens, future attempts should aim at discriminating between patients at high and low risk of bleeding with direct oral anticoagulants, taking into account site of the tumor, chemotherapy-related mucositis, and whether the primary tumor was resected. Despite anticoagulant treatment, the risk of recurrent venous thromboembolism is still high with the currently available treatment regimens. In the coming years, innovative therapies targeting the contact activation pathway should therefore be evaluated specifically for cancer-associated thrombosis, as these may possibly reduce the risk of recurrent venous thromboembolism, without increasing the risk of bleeding. Current guidelines recommend to continue anticoagulant treatment beyond the initial 3- to 6-month phase when the cancer is still considered to be active. The decision to extend treatment duration is now based on a balanced assessment of the benefit-risk ratio and patient preference. To better guide decisions regarding the extended treatment phase, standardized definitions for active cancer and data comparing different anticoagulant types and dosages in this period are required.

**Part II** also demonstrated that incidental pulmonary embolism in cancer patients was associated with a considerable risk of recurrent venous thromboembolism, despite anticoagulant treatment. Interestingly, patients with thrombi restricted to the subsegmental arteries had similar outcomes as those with more proximal pulmonary embolism, but whether these patients had concomitant deep vein thrombosis was not reported. An ongoing prospective cohort study in the non-cancer population assesses the safety of withholding anticoagulation in patients with subsegmental pulmonary embolism in whom deep vein thrombosis is excluded upon bilateral ultrasonography of the lower extremities. A similar intervention study is needed in patients with cancer to assess whether incidental subsegmental pulmonary embolism requires
anticoagulant therapy in the absence of deep vein thrombosis, possibly reducing overtreatment and its associated bleeding risk. Data on long-term treatment and associated clinical outcomes are also needed in the setting of incidentally detected splanchnic vein thrombosis, as the optimal management strategy for this disease remains a matter of debate.

Part III illustrated that the performance of current cancer screening strategies in patients with unprovoked venous thromboembolism is insufficient as a large proportion of cancers are still being missed. Attempts to discriminate between patients at high and low risk of cancer have not been successful so far. Advances in technology have allowed for detection of subtle alterations in the genome, epigenome, transcriptome, proteome, and metabolome in bodily fluids; these assays are referred to as liquid biopsies. Novel promising liquid biopsies for cancer are currently being evaluated in the ongoing PLATO-VTE study, which has the potential to improve cancer screening practice with a higher accuracy, possibly also identifying tumor location, while reducing radiation and invasive testing. If the good performance of these test is confirmed, further validation in a randomized trial will be needed to assess the clinical benefit of biomarker-based cancer screening. As liquid biopsies are being developed and improved at a rapid pace, next generation tests are expected to be introduced within the next decade, which should be considered candidates for subsequent evaluation in patients with venous thromboembolism. Although expectations are high, it is very likely that a combined rather than a single-biomarker approach will reach the highest detection rate for the different types of cancer seen in venous thromboembolism. Future efforts should therefore aim at validation of combined assays in this high-risk population.