Chapter 1

INTRODUCTION AND GENERAL OUTLINE
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‘In the past century, some diseases have disappeared, others have remained, while a few have become more prevalent’- R.H. Rellub *

BACKGROUND

Venous thromboembolism is an increasingly common complication in cancer patients. Over the past decades, the incidence of venous thromboembolism among patients with cancer has continued to rise to almost 20 per 1000 person years (Figure). An important explanation for this observation may be the ever-improving cancer survival rate due to revolutionary developments in cancer treatment, thereby extending the course of the disease. Other factors may also play a role, such as the introduction of novel thrombogenic cancer therapies, increased use of central venous catheters, and technological improvements of imaging modalities enabling detection of small thrombi, which previously remained undetected. As the global cancer incidence was predicted to grow by 61% between 2008 and 2030 to a total 20,7 million per year, a major increase in the burden of cancer-associated venous thromboembolism is expected.

The risk of developing venous thromboembolism varies depending on tumor-, patient-, and treatment-related factors. For example, in breast or prostate cancer the annual incidence lays around 1-2%, whereas in pancreas or brain cancer, incidences over 10% have been observed. Besides intrinsic alterations in the hemostatic system leading to a pro-thrombotic state, immobilization, hospitalization, chemotherapy, and surgery further increase the risk of venous thromboembolism. When venous thromboembolism is diagnosed in cancer patients, prognosis is poor as two-thirds of these patients do not survive longer than 12 months. Whether the high mortality rate is caused by thrombotic disease or by aggressiveness of the cancer is not well studied, although the low frequency of fatal pulmonary embolism relative to the total number of deaths in clinical trials performed in this population suggest that cancer-related factors play the most prominent role. However, the burden attributable to venous thromboembolism can have a profound impact on quality of life, most notably due to distressing symptoms that are often present in the acute and chronic phase. Moreover, the risk of recurrent venous thromboembolism despite appropriate anticoagulant therapy is much higher in cancer patients than in those without cancer, as is the associated bleeding risk during treatment. While diagnostic algorithms for venous thromboembolism have improved over the years in patients without cancer, the performance of these strategies is still
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Further improvements are therefore needed in the diagnostic and therapeutic management of cancer-associated thrombosis. **Part I** of this thesis focuses on diagnostic approaches for venous thromboembolism in cancer and non-cancer patients, aiming at simple, patient-friendly, time-efficient, and safe methods to exclude venous thromboembolism while avoiding diagnostic imaging. **Part II** aims at improving therapeutic strategies tailored to the individual cancer patient by considering not only efficacy and safety, but also route of administration and patient preference. **Part III** revolves around the inverse clinical association between cancer and thrombosis, and targets improvements in detection of undiagnosed cancer in patients presenting with unprovoked venous thromboembolism.

**Figure** – Absolute rates of venous thromboembolism per 1000 person years in patients with cancer (cases; red line) and general population controls (blue line) between 1997 and 2006. Reprinted from Walker et al. European Journal of Cancer, 2013, with permission from Elsevier.
Chapter 2 provides an overview of recent advances in diagnosis and treatment of venous thromboembolism in patients with and without cancer.

**PART I – Advances in diagnosis of cancer-associated thrombosis**

Patients with clinically suspected venous thromboembolism should be managed with the use of a diagnostic algorithm, combining a clinical decision rule and D-dimer testing to determine which patients should be referred for imaging. With this approach, venous thromboembolism can be considered excluded without imaging in up to half of patients. Yet, in the oncology population, the proportion of patients that can be managed without imaging is much lower, while the false negative rate is higher. Likely explanations for these observations include the lower specificity of D-dimer due to elevated baseline levels in cancer patients, the lower specificity of clinical decision rules due to a poor predictive performance of the individual score items in patients with cancer, and the higher prevalence of venous thromboembolism among cancer patients. Given these drawbacks, physicians often decide to directly proceed to imaging in cancer patients with suspected venous thromboembolism. In the absence of a cancer-specific diagnostic management strategy, the optimal approach in these patients remains undetermined.

In Chapter 3, the diagnostic performance of the original Wells score for suspected pulmonary embolism was compared with that of the simplified Wells score in cancer and non-cancer patients. Chapter 4 reports on a systematic review summarizing and comparing the diagnostic accuracy of single limited, serial limited, and whole-leg ultrasonography for suspected deep vein thrombosis. Chapter 5 presents the results of a systematic review on definitions, adjudication, and reporting of pulmonary-embolism related death in recent clinical studies. Chapter 6 describes the rationale and design of an individual patient data meta-analysis of diagnostic management studies for pulmonary embolism, which aims at evaluating the performance of current diagnostic strategies across different health settings and specific subgroups, including cancer patients. In addition, the aim is to develop a novel clinical prediction model with improved accuracy compared to the current tools, both in patients with and without cancer.
PART II – Advances in treatment of cancer-associated thrombosis

For decades, venous thromboembolism in cancer patients has been treated similarly as in patients without cancer. The pivotal CLOT trial, published in 2003, changed practice as it was the first large trial introducing a different treatment regimen for cancer-associated venous thromboembolism. The results of this study showed that low-molecular-weight heparin (dalteparin) was associated with half the risk of recurrent venous thromboembolism compared to the standard-of-care treatment at that time, i.e. vitamin K antagonists. Although low-molecular-weight heparins became the recommended treatment in international guidelines, their use in clinical practice was not universally adopted because of the associated burden of daily subcutaneous injections and high costs.

After their introduction almost 10 years ago, direct oral anticoagulants soon became the treatment of choice for venous thromboembolism in the non-cancer population because of their similar efficacy as vitamin K antagonists, favorable safety, and ease of use due to a fixed-dose regimen. Recently, the direct oral factor Xa inhibitors edoxaban and rivaroxaban were compared with low-molecular-weight heparin for the treatment of cancer-associated venous thromboembolism in the Hokusai VTE Cancer trial and SELECT-D pilot trial, respectively. Both randomized studies showed a lower risk of recurrent venous thromboembolism and a higher risk of major bleeding, which was primarily observed in patients with gastrointestinal cancer. Taken together, edoxaban and rivaroxaban appear to be attractive alternatives for low-molecular-weight heparins for most types of cancer, thereby avoiding the need for daily injections and reducing the cost of treatment. International guidance now suggest these direct oral anticoagulants as treatment for venous thromboembolism in cancer patients who are considered to have a low risk of bleeding.

Chapter 7 provides a comprehensive overview of available literature to guide treatment decisions for common cases of cancer-associated venous thromboembolism. In Chapter 8, the severity of anticoagulant-related major bleeding was compared between patients with and without cancer, who were previously included in the large phase III trials comparing direct oral anticoagulants with vitamin K antagonists for treatment of acute venous thromboembolism. Chapter 9 further evaluates the clinical impact and course of major bleeding events occurring in patients enrolled in the Hokusai VTE Cancer trial, with a focus on patients with gastrointestinal cancer. Chapter 10 provides an in-depth analysis of the efficacy and safety of edoxaban and low-molecular-weight heparins in patient subgroups with different types of cancer.
Chapter 11 reports the results of a prospective cohort study evaluating treatment regimens for incidentally detected pulmonary embolism in cancer patients, with a special focus on the subgroup of patients with pulmonary embolism restricted to the subsegmental arteries.

PART III – Advances in diagnosis of occult cancer in unprovoked venous thromboembolism

Occult cancer is detected in up to 5% of patients presenting with unprovoked venous thromboembolism in the year following diagnosis. Currently, international guidance recommends a so-called ‘limited’ cancer screening strategy in these patients, comprising a medical history, physical examination, basic laboratory testing, chest X-ray, and age- and sex-specific testing, such as prostate specific antigen or mammography. Importantly, this strategy misses about half of the occult cancers. Several studies assessing more elaborate screening strategies including imaging scans, endoscopies, or biomarkers showed no benefit over a limited approach with regard to overall cancer detection rate. Novel blood-based biomarkers for cancer may be attractive alternatives or add-on tests for the current screening strategies, as they may be associated with a higher cancer detection rate, while avoiding radiation or invasive diagnostic procedures.

In Chapter 12, two risk prediction scores for occult cancer were evaluated in patients with acute venous thromboembolism. These scores were designed to select patients at high risk of cancer who might benefit from additional extended cancer screening tests. Chapter 13 describes the rationale and design of the ongoing PLATO-VTE study, in which the sensitivity of novel biomarkers for cancer is compared with that of standard-of-care limited cancer screening in patients with unprovoked venous thromboembolism.
REFERENCES


* Personal communication