Clinical aspects of venous thromboembolism in special patient populations

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**General Introduction**

Clinical research is a part of healthcare science that involves human participants. It studies the epidemiology and pathophysiology of disease, and it learns us how to most efficaciously and safely prevent, diagnose and treat illnesses (1–3). Two main types of clinical studies can be distinguished: interventional and observational studies (1). Interventional studies are experiments in which participants are assigned to specific interventions according to a pre-specified study protocol; interventions can be drugs, devices, or procedures. A new medical strategy may be compared to a standard-of-care strategy, but it may also be compared to placebo or to no intervention. Some clinical trials compare interventions that are already available in clinical practice. The safety and efficacy of the intervention is determined by measuring pre-specified outcomes. In clinical observational studies, outcomes are also assessed in (groups of) participants, but the participants are not assigned to specific interventions; instead, the participants undergo interventions or procedures as part of routine clinical care. Clinical studies are designed to answer specific questions and to translate basic research into new treatments, strategies and information to improve patient care.

The first known experiment resembling a clinical study is described in the “Book of Daniel” in the Bible, and was performed by Nebuchadnezzar II (634–562 B.C.), a military leader and king of Babylon for nearly 60 years (4,5). He put his people on a diet consisting of only meat and wine, which he believed would get them in better physical shape. Several men refused however, and preferred to eat only vegetables. The king approved their diet, but only for the duration of 10 days, after which he would assess everyone’s health condition. During this assessment the vegetarians appeared healthier than the carnivores, which led him to permit the vegetable lovers to continue their diet. In retrospect, this likely is the first recorded experiment that guided a (public) health decision in humans.

In the field of venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), incredible progression has been made throughout the centuries regarding our knowledge on the epidemiology, pathophysiology, prevention, diagnosis, treatment and prognosis of the disease in several settings. In 1271, the first case of DVT was reported in a 20-year old Norman cobbler (6). The man was advised by his physician to wait and see, but he subsequently developed an ulcer. According to the story, the ulcer was healed after applying dust from below a stone covering the tomb of king Saint Louis, and he still lived 11 years thereafter (6). In the era that followed, pregnancy was hypothesized to be the leading (and perhaps the only known) risk factor for DVT. It was thought that postpartum DVT was caused by accumulation of unconsumed breastmilk in the legs (“milk leg”), and in the late 1700s breast-feeding was encouraged to prevent DVT (7,8). Bloodletting was used to treat
DVT until the end of the 19th century (9). Because of fear for thrombus extension, strict bed rest was prescribed, and this constituted, at least from the end of the 19th century, the cornerstone of DVT treatment. In 1793, Hunter had started performing venous ligation above the level of the thrombus, to prevent migration of clots from the legs to the lungs (10). This technique became increasingly popular at the end of the 19th century, and was considered the only possible measure to prevent PE, even though it was associated with a high morbidity and mortality. This procedure was widely used until the mid-20th century. In the first half of the 20th century, anticoagulants were discovered, and in 1960 the first randomized controlled trial demonstrated that anticoagulant therapy strongly reduced the risk of recurrent VTE and mortality in patients with PE. Since then, numerous clinical studies have evaluated anticoagulants for the prevention and treatment of VTE, which have defined our current clinical practice (11,12).

Despite the progress that has been made in the past decades in the field of VTE, various clinical aspects of this disease have not been fully addressed. This thesis aims to evaluate several clinical elements of VTE in special patient populations, including pregnant patients and those with cancer. Furthermore, it aims to increase knowledge on the current treatment strategies and complications on the long-term for rare forms of VTE such as unsuspected pulmonary embolism (PE) and upper extremity deep vein thrombosis (UEDVT). Finally, insight is provided into the clinical impact of bleeding events with the use of oral factor Xa (fXa) inhibitors versus vitamin K antagonists (VKA) in patients with VTE.

Outline of the thesis

**Part I** describes several aspects of sex-specific VTE, in particular pregnancy, the use of hormonal contraceptives, and anticoagulant-associated vaginal bleeding. **Chapter 2** provides an overview of VTE risk factors for women, and how these interact with common types of hereditary thrombophilia. In **chapter 3** the rationale and design of the Highlow study are described. This randomized controlled trial evaluates two widely used doses of low-molecular-weight heparin (LMWH) for the prevention of pregnancy-associated recurrent VTE. Additionally, in **chapter 4** we present an interim report of the ongoing Highlow study. Finally, **chapter 5** focuses on vaginal bleeding in women with VTE, treated with apixaban or warfarin.

In **part II**, the relationship between cancer and VTE is addressed. **Chapter 6** summarizes the current understanding of the prevention and treatment of VTE in patients with cancer. In **chapter 7** we discuss the clinical and radiologic characteristics as well as the prognostic value of unsuspected PE in cancer patients. **Chapter 8** contains an interim
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report of a prospective registry, which evaluates the current treatment strategies and long-term clinical outcomes in cancer patients with unsuspected PE, and chapter 9 concerns the interobserver agreement on the diagnosis and extent of unsuspected PE in cancer patients.

Several aspects of UEDVT are discussed in part III of this thesis. First, in chapter 10 an overview of the clinical characteristics, risk factors, diagnosis, management, prognosis and prevention of UEDVT is provided. Chapter 11 includes the results of a systematic review on the clinical course of UEDVT in patients with and without cancer; chapter 12 contains the findings of our recent cohort study on the current management strategies and long-term clinical outcomes of UEDVT and upper extremity superficial vein thrombosis (UESVT).

The final part of this thesis, part IV, concerns the clinical impact of bleeding with oral fXa inhibitors and VKA. Chapter 13 provides the results of our study on the clinical presentation and course of bleeding events in patients with VTE, treated with apixaban or warfarin. The clinical impact of major bleeding events in patients with VTE treated with edoxaban or warfarin is reported in chapter 14. Chapter 15 presents the results of an individual patient data meta-analysis, comparing the clinical impact and course of major bleeds between patients treated with fXa inhibitors or VKA.
Chapter 1

References

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