Capturing venous thromboembolism: imaging and outcomes of venous thromboembolism

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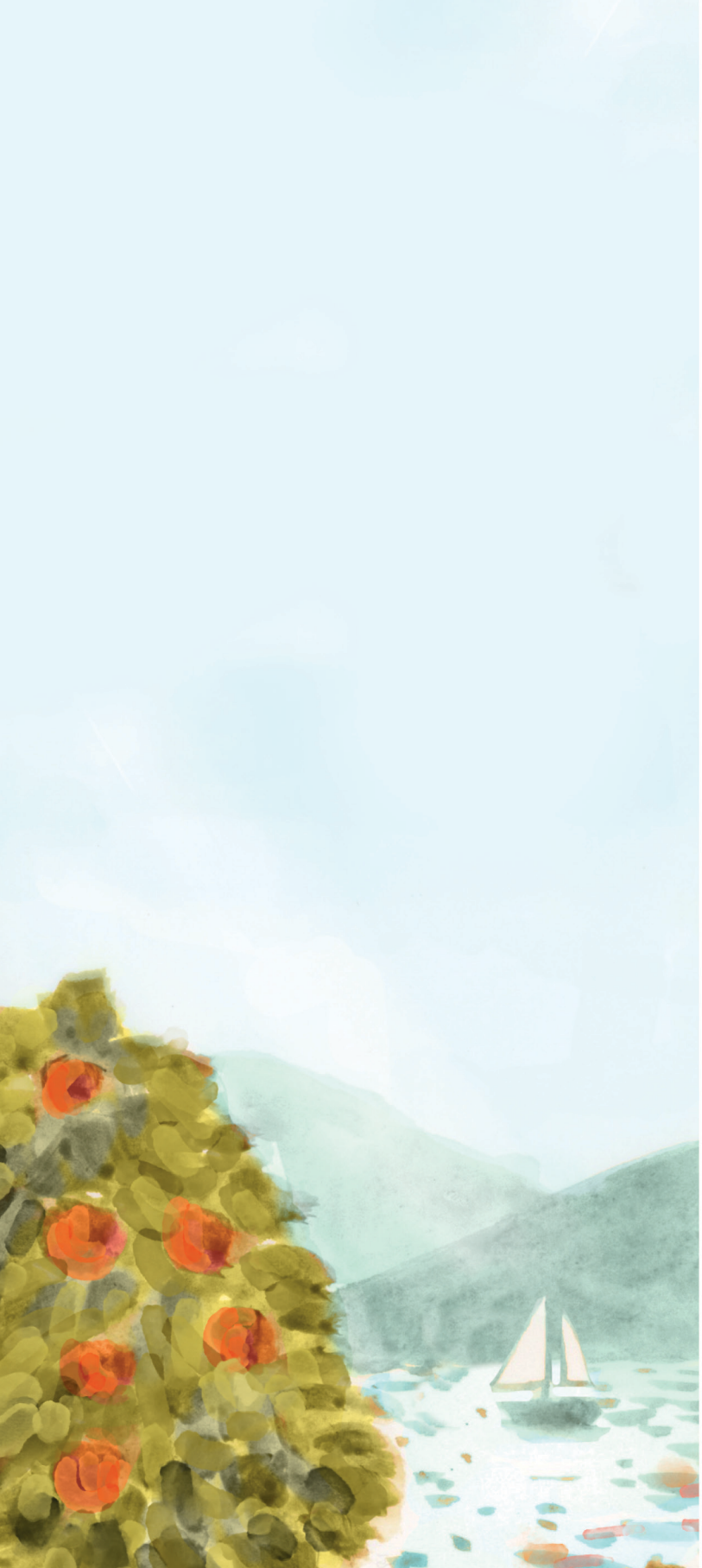

CHAPTER 1

Introduction and outline of this thesis

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially severe condition that may have a major impact on patients' lives. Despite anticoagulant treatment, which is the cornerstone of the treatment, up to half of the survivors of acute PE may experience persistent dyspnea, exercise intolerance, and/or functional limitations, referred to as the post-PE syndrome.[1] The post-PE syndrome can be diagnosed after at least 3 months of adequate anticoagulant treatment to differentiate from symptoms associated with the acute event. Its most severe manifestation is chronic thromboembolic pulmonary hypertension (CTEPH), characterized by unresolved thrombi in the pulmonary arteries as well as vascular remodelling in unaffected arteries, both causing increased pulmonary vasculature resistance, which could lead to right ventricle dysfunction and eventually heart failure. Moreover, 20-50% of patients who experienced DVT may develop post-thrombotic syndrome (PTS), which is caused by residual venous obstruction, local inflammatory response, and damage to vein walls and venous valves.[2] PTS is characterized by a range of symptoms associated with chronic venous insufficiency, such as pain, swelling, and fatigue or heaviness in the affected limb. Both the post-PE syndrome and PTS are associated with poorer outcomes and reduced quality of life (QoL), and may be prevented by adequate therapeutic interventions.[3-5] Early diagnosis of VTE and its long-term consequences is therefore of crucial importance. This thesis focuses on capturing VTE, both in a more literal and a more figurative sense: capturing VTE with diagnostic imaging tests, and capturing outcomes of VTE.

In the first part of this thesis, novel imaging techniques for diagnosing venous thrombosis are discussed. The imaging test of choice for suspected acute PE is multidetector computed tomography pulmonary angiography (CTPA) – a widely available technique, which has been validated in prospective management outcome studies.[6] CTPA is routinely performed when diagnostic imaging is indicated based on validated diagnostic algorithms that combine clinical decision rules (CDR) and D-dimer testing. Technological advancements over the years have led to the introduction of alternative imaging techniques for diagnosis of VTE. Moreover, artificial intelligence (AI) holds the potential to further innovate the diagnostic management. **Chapter 2** of this thesis discusses modern imaging techniques for acute PE including CTPA techniques, single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) techniques, and describes possible roles for AI.

Using conventional ultrasonography and computed tomography (CT) techniques, difficulties may arise in situations where deep veins are inaccessible or difficult to visualize, or when patients have allergies or contra-indications to contrast agents.

Magnetic resonance direct thrombus imaging (MRDTI) could overcome those challenges. MRDTI is a novel non-invasive MRI technique which is based on direct thrombus detection by visualization of the metabolism of a fresh thrombus, and does not require intravenous contrast or ionizing radiation.[7] In fresh thrombus, methaemoglobin is formed which causes shortening of the T1 relaxation time and leads to the generation of a high signal from the intravenous thrombus against the suppressed background on a T1-weighted sequence. The high signal intensity has been described in cases within hours after clot formation and has been observed to normalize during a period of 6 months, which may allow for the estimation of thrombus age.[8,9] The imaging technique could be of value in specific situations, such as suspected thrombosis in the deep veins within the pelvis (whether or not during pregnancy), suspected upper extremity DVT where diagnosis with ultrasonography is complex due to the local anatomy, and to differentiate between acute and chronic or residual thrombosis, for instance in patients with suspected recurrent ipsilateral DVT of the leg.[10-12] As MRDTI scanning is being performed in clinical practice at our centre, we evaluated its use by reviewing the indications, test results, impact on treatment decisions, and patient outcomes, of which the results are presented in **chapter 3**.

The first-line imaging test for diagnosis of DVT is venous ultrasonography, which should be performed based on clinical probability assessment and D-dimer testing.[13] However, in patients who have experienced a previous DVT and present with suspected recurrent ipsilateral DVT, residual venous obstruction may complicate the diagnosis of recurrence, leading to non-diagnostic inconclusive compression ultrasonography (CUS) in up to one third of patients.[14] In addition to the MRDTI technique, the application of reference compression ultrasonography could help preventing uncertainties. A reference CUS is an additional ultrasound performed at or after completion of anticoagulant treatment for DVT and provides a baseline examination that can be used for future comparison, in case the patient returns with suspected ipsilateral recurrence. We performed a cost-effectiveness analysis of different scenarios (with and without reference CUS; with and without MRDTI) for the diagnostic management of suspected recurrent ipsilateral DVT of the leg, which is described in **chapter 4**.

The second part of this thesis elaborates on outcomes of care for VTE patients, and the impact of VTE on patients' lives. Following a VTE diagnosis, patients may face a wide spectrum of health effects and long-term consequences. The thrombotic event and its sequelae can affect both physical and psychosocial functioning, considerably limiting patients' daily functioning, ability to work, psychological well-being, and quality of life.[3,15-18]

The impact of VTE on individual patients goes beyond the conventional binary outcomes (i.e. recurrent VTE, bleeding, and mortality) which are traditionally measured. The complete picture of outcomes of VTE care is discussed in **chapter 5**, along with future directions to shift the focus to outcomes that matter most to patients.

To identify all relevant aspects that matter to patients with VTE, we collaborated with the International Consortium for Health Outcomes Measurement (ICHOM) in the multidisciplinary ICHOM-VTE project with the aim to develop a standardised set of patient-centered outcome measures for use in clinical practice. **Chapter 6** provides details on the process and presents this standardised set. Patient-reported outcomes measures (PROMs) were included in the ICHOM-VTE set, and are ideal to measure patient-perceived health outcomes and disease impact by assessing self-reported health status, symptom burden and well-being through validated questionnaires. Based on the results of the project, recommendations for the use of PROMs during clinical follow-up of patients with VTE were formulated in a communication of the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease, presented in **chapter 7**. After incorporation of the PROMs part of the outcomes set in routine care at our centre, we performed a mixed-methods study to evaluate the first experiences of patients and health-care professionals with the routine use of PROMs for VTE patients visiting the outpatient clinic. The results are described in **chapter 8**.

During follow-up after VTE, care providers should be aware of side effects of the treatment. In the TEAM-VTE study, an international multicentre prospective cohort study, we evaluated menstrual blood loss among women of reproductive age who were treated with oral anticoagulants for acute VTE. The incidence of abnormal menstrual bleeding and results regarding menstrual bleeding-related QoL are presented in **chapter 9**. Assessment of QoL in general can identify limitations in health domains and may therefore contribute to better understanding of disease impact as perceived by individual patients. **Chapter 10** focuses on why, how, and when to measure QoL after acute PE.

While validated questionnaires to measure generic and disease-specific QoL have been available for some time, there was a clear need for a reproducible tool to measure functional outcomes after VTE and to better capture the consequences of VTE to daily life. What started as a call to action led to the development of the Post-VTE Functional Status (PVFS) scale.[19, 20] The ordinal PVFS scale assesses functional outcomes across six scale grades, covering limitations in usual activities and duties, as well as changes in lifestyle. Its development and introduction in VTE research and clinical practice are

described in **chapter 11**. Early in the coronavirus disease 2019 (COVID-19) pandemic, the scale was also considered useful in COVID-19 patients, given the high incidence of acute PE and the cardiovascular complications reported in COVID-19.[21] The Post-COVID-19 Functional Status (PCFS) scale was proposed to monitor functional recovery over the course of the disease. **Chapter 12** discusses the lessons learned after 2 years of use of the PCFS scale based on evaluation of the literature and experiences of users. Furthermore, in **chapter 13**, characteristics of the PCFS scale were assessed based on its application during 12-month follow-up of COVID-19 survivors.

Finally, the pathophysiology of PE in COVID-19 may be unique, leading to the hypothesis that thrombus resolution may be less effective and that the prevalence of CTEPH may be higher compared to non-COVID-19-associated PE populations.[22, 23] We studied COVID-19 patients who had been diagnosed with acute PE to examine the prevalence of CTEPH and recurrent VTE and to evaluate thrombus resolution. **Chapter 14** provides the findings regarding these long-term complications after COVID-19-associated PE.

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