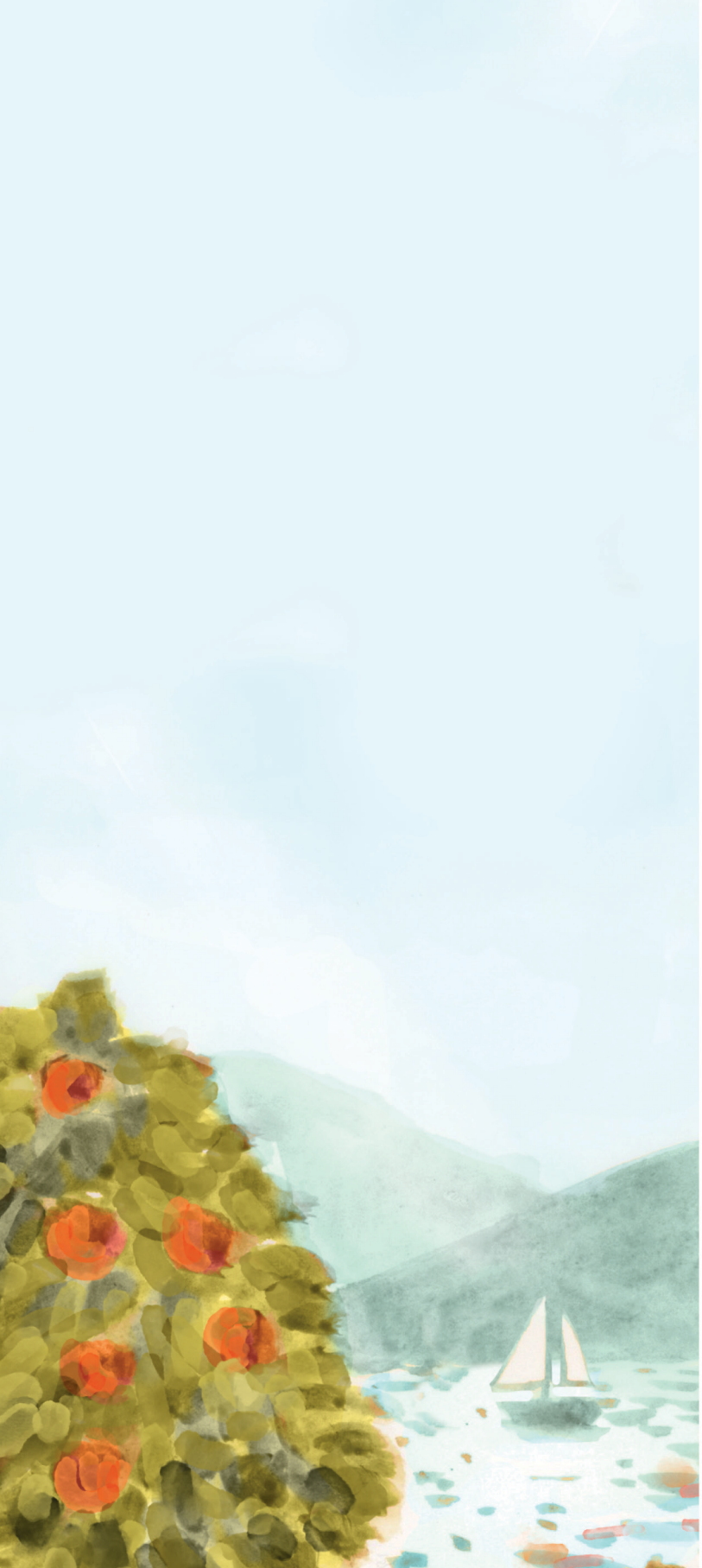
Capturing venous thromboembolism: imaging and outcomes of venous thromboembolism

Jong, C.M.M. de



CHAPTER 15

General discussion and summary

The studies described in the first part of this thesis focused on novel imaging techniques for diagnosing venous thromboembolism (VTE), specifically in clinical situations where the diagnosis is challenging. In the second part of this thesis, outcomes of care of VTE patients were evaluated, with an emphasis on the understanding and measurement of the impact of VTE on patients' lives.

Chapter 1 provides a general introduction to imaging of VTE and outcomes of VTE, introducing patient-centered outcomes and patient-reported outcome measures (PROMs), and gives an overview of the presented studies.

Part 1: Imaging of venous thromboembolism

Chapter 2 elaborates on modern, available and emerging imaging techniques for acute pulmonary embolism (PE) which extend beyond multidetector computed tomography pulmonary angiography (CTPA) – the current imaging method of choice. Several imaging techniques are promising, such as photon-counting computed tomography (PCCT), perfusion iodine maps based on subtraction of dual-energy acquisition, single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) techniques. However, their potential to improve diagnostic imaging for PE should be evaluated in prospective management outcome studies, focusing on the effect of using these techniques on relevant patient outcomes such as the impact on and satisfaction with management decisions and quality of life, in addition to evaluating their diagnostic accuracy. The same applies to artificial intelligence (AI). AI may improve the diagnostic management of PE and enable further innovation in various roles. Future studies should compare strategies involving AI to current standard radiological practice and determine which AI algorithms are feasible to implement and are viable in clinical practice.

In **chapter 3**, we have evaluated the clinical application of magnetic resonance direct thrombus imaging (MRDTI) as part of the diagnostic management of suspected thrombosis. Between 2015 and 2023, a total of 36 patients had been subjected to MRDTI at our centre. The main indication for MRDTI scanning was to differentiate between acute and chronic thrombosis, the majority having suspected recurrent ipsilateral deep vein thrombosis (DVT) with an inconclusive compression ultrasonography (CUS). Another indication to perform MRDTI was to confirm or rule out acute DVT of the extremities or iliac veins after other imaging tests (ultrasonography and/or CT scan) had not been conclusive. The technique has been increasingly used since 2019 at our practice. MRDTI indicated acute thrombosis in over a third of patients and guided treatment decisions in all except in two patients, confirming its impact on clinical decision making. Our findings also illustrate the feasibility of the use of the technique in daily practice.

In the context of non-diagnostic CUS in patients with suspected recurrent ipsilateral DVT, we have assessed the cost-effectiveness of performing an additional ultrasound at completion of anticoagulant treatment of a previous DVT that could serve as a baseline examination, referred to as a reference CUS. In a decision analytic model, described in **chapter 4**, health care costs and mortality were compared between different diagnostic scenarios for suspected recurrent ipsilateral DVT of the leg. Using patient-level data from the Theia study, which was a prospective diagnostic management study involving patients with suspected recurrent ipsilateral DVT, and claims data in the model, we found that scenarios that included reference CUS had higher estimated one-year costs than the scenarios without reference CUS, while estimated mortality was comparable. Therefore, from the economic perspective, the routine application of reference CUS is not supported based on this model. Additionally, we investigated a different decision context in a sensitivity analysis to analyse the clinical situation in which reference CUS examinations would already be performed and available. This analysis showed that scenarios which included the use of reference CUS had lower costs than scenarios without. Thus, from a cost-effectiveness perspective, if a reference CUS is already performed and available, the use of its results can be part of the diagnostic strategy. Current international guidelines do not consistently include the use of reference imaging, but our findings guide policymakers in formulating recommendations regarding the application of reference CUS during follow-up after DVT.

Part 2: Outcomes of venous thromboembolism

Chapter 5 explores outcomes of VTE care from different perspectives. In addition to the traditionally measured binary outcomes, i.e. recurrent VTE, bleeding, and mortality, outcomes of care should be measured from the patient perspective to capture patients' values and needs. Moreover, from the society perspective, additional outcomes are important to consider, such as health-care resource utilization, costs due to diagnosis and treatment of VTE, and indirect costs caused by patients' inability to work. The combination of conventional binary outcomes, patient-centered outcomes, and society-level outcomes paint the complete picture of outcomes of VTE care. A holistic view on outcomes of care of VTE patients aligns with the current transition toward patient-centered and outcome-driven care, with the objective of achieving the highest value for patients which is in agreement with the emerging concept of value-based health care. Measuring meaningful outcomes will improve understanding of the full impact of VTE on individual patients and can help identify patients' needs and preferences to facilitate tailored treatment.

To evaluate which outcomes matter most to patients and to support the use of patient-relevant outcomes in clinical practice, a standardised set of patient-centered outcomes was developed during the ICHOM-VTE project, which is described in **chapter 6**. During a modified Delphi consensus process, an international working group consisting of VTE experts and patient representatives selected outcomes that were considered most important to patients, along with the optimal instruments and relevant timepoints to measure these outcomes. Fifteen core outcomes were included in the standardised set, encompassing patient-reported outcomes, long-term consequences of VTE, disease-specific complications, and treatment-related complications. A core set of PROMs was selected and supplemented with a cascade opt-in system that enables further assessment using relevant additional PROMs if required, based on the presence of symptoms.

The ICHOM-VTE project was endorsed by the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease. **Chapter 7** provides recommendations for the use of PROMs during clinical follow-up of patients with VTE, proposed in an ISTH SCC communication, advocating the routine use of PROMs to enhance patient-centered care. The use of PROMs as defined by the ICHOM-VTE standard set was proposed. Furthermore, we advocated diligent preparation of the implementation of PROMs in daily clinical practice, with the suggested use of electronic tools to facilitate PROMs collection and interpretation to minimise the burden for patients and health-care professionals. Also, we advocated the application of PROMs to measure endpoints in clinical studies.

First experiences of patients and health-care professionals with the routine use of PROMs at our outpatient clinic were evaluated in **chapter 8**. The PROMs part of the ICHOM-VTE set were incorporated in daily care for VTE patients visiting the outpatient clinic, using a digital application which was integrated into the electronic health records system. Since the implementation, patients received invitations by email to complete PROMs ahead of the scheduled appointments. Interviews with patients and involved health-care professionals showed that their first experiences with the use of PROMs were neutral to -predominantly- positive. Health-care professionals believed that PROMs provided additional value, both during preparation for the visit and during the consultation. The completion of PROMs added to the feeling of being prepared for the visit in some patients, while other patients did not feel prepared for the outpatient clinic visit despite completing PROMs or felt prepared regardless of the PROMs. To optimise the use of PROMs, resources should be enhanced, including technical support for data processing and interpretation of PROM responses. Second, patients need to be better

informed about the relevance of PROMs. Health-care professionals should be trained to improve their ability of the interpretation of PROMs and translation of PROM results into actions, and could be supported to discuss individual PROM results with patients during the consultation. In addition, reduction of the question load may lead to a higher completion rate. Our findings can help improve PROMs application in practice and support further implementation in everyday thrombosis care.

In addition to the impact of the thrombo-embolic event itself on physical, mental, and social well-being, the treatment of VTE may impact patients' lives due to side effects that could be harmful. In women of reproductive age who are treated for VTE, there should be attention for their menstrual blood loss and awareness of the risk of heavy menstrual bleeding associated with anticoagulation. **Chapter 9** ends with the call to action to routinely assess menstrual blood loss during follow-up after VTE. In the TEAM-VTE study, we assessed menstrual blood loss in a cohort of 98 women who started with oral anticoagulants for acute VTE. Menstrual blood loss was measured using pictorial blood loss assessment charts during the last menstrual cycle before VTE diagnosis in retrospect, and prospectively for each menstrual cycle during 3-to-6-month follow-up. Two-thirds of women were found to experience abnormal menstrual blood loss after start of anticoagulant treatment. On top of defining abnormal menstrual bleeding according to pictorial blood loss assessment chart scores, we used a self-reported definition to capture the woman's perception of abnormal menstrual bleeding. During the study period, we observed a decrease in menstrual bleeding-related quality of life (QoL) over time which was most pronounced among women who experienced new-onset heavy menstrual bleeding, in other words, women who did not have heavy menstrual bleeding in the last menstrual cycle before diagnosis of VTE and initiation of anticoagulation. This study provided a first attempt to evaluate the risk of abnormal menstrual bleeding in this population as accurate as possible.

Measuring QoL offers the opportunity to assess and monitor the impact and consequences of a thrombo-embolic event that patients experience in their lives. **Chapter 10** delves into measurement of QoL after acute PE. By revealing the health domains and dimensions where improvement can be achieved, assessment of QoL may enable the initiation of tailored treatment. During the ICHOM-VTE project, QoL was selected as one of the outcomes most important to patients, which underscores why QoL should be measured during follow-up after acute PE. The use of generic or disease-specific PROMs, reflecting the patient's perspective, is the optimal approach for measuring QoL.

To assess the impact of VTE on daily functioning, the Post-VTE Functional Status (PVFS) scale was introduced in 2019 to meet the need for a reproducible instrument to measure and monitor functional status. This easy-to-use one-item tool focuses on relevant aspects of daily life and can be used to quantify and monitor functional limitations over time in patients who experienced VTE. The post-VTE functional status can be self-reported by patients through a questionnaire or flowchart and can also be assessed during a structured interview. The ordinal scale has been refined through a Delphi consensus process and patient focus groups, which resulted in good-to-excellent interrater agreement. Furthermore, the construct validity of the PVFS scale was demonstrated to be adequate. During the coronavirus disease 2019 (COVID-19) pandemic, the Post-COVID-19 Functional Status (PCFS) scale was proposed. The scale gained notable attention and several validation studies became available, including the validation of translated versions of the scale, which supported the use of the scale in clinical practice and in research. The PVFS scale and PCFS scale may be used to identify patients with incomplete recovery or poor functional outcome and may serve as relevant functional outcome measures in intervention studies. The usefulness of the scale in clinical practice is underlined by recommendations of its use in guidelines and position papers. Moreover, the PVFS scale was included in the ICHOM-VTE set as recommended instrument to measure functional limitations, which is one of the patient-important outcomes included in the standardised outcome set. The uptake of the PVFS scale and PCFS scale is described in **chapter 11**.

Subsequently, we formulated lessons that could be learned from use of the PCFS scale in research and clinical practice. Based on available literature, we have learned about the widespread adoption of the scale and learned lessons regarding the methodology behind the use of the scale that should be taken into account to optimise its application. The lessons learned from 2 years of use are summarised in **chapter 12**. An important lesson is to always report the full methodology, including method(s) and timing of assessment and analysis methods, which is crucial for interpretation. Standardised measurement plays a key role and allows for comparisons. Furthermore, scale grade 5 indicating "death" should be included to prevent bias, and the ordinality of the scale should be taken into account during statistical analysis. A survey conducted among users showed that the scale was considered a useful tool.

At our centre, the PCFS scale was applied to measure functional status at two timepoints during 12-month follow-up of COVID-19 survivors. In **chapter 13**, we studied the distribution of PCFS scale grades over time and the relation between post-COVID-19 functional status and other outcomes assessed with PROMs. Our study showed that

62% of the 79 included patients had a change in PCFS scale grade between 6 weeks and 12 months of follow-up, of whom almost two-thirds improved in functional status over time. More than half of the study patients had no, negligible, or slight functional limitations at 6 weeks post-discharge (PCFS grade 0, 1, or 2), which increased to two-thirds at 12 months. The individuals with stable PCFS scale grade at the two timepoints were distributed across the scale. One out of five had sustained moderate-to-severe limitations (PCFS grade 3 or 4) and 10% deteriorated from no, negligible, or slight functional limitations to moderate-severe limitations during the follow-up period – those patients may benefit from focused attention and potentially adequate treatment or rehabilitation. At 12-month follow-up, we observed that abnormal scores of PROMs for psychological symptoms were more frequent in patients with PCFS grade 2 or higher. Also, those patients seemed to have worse quality of life, dyspnea, and physical function scores. With increasing PCFS scale grades, we visually observed decreasing physical function and fitness outcomes and decreasing pulmonary function. These insights into the distribution of PCFS over time and how PCFS scale grades compare to other outcomes at 12-month follow-up may be valuable during application of the scale. Notably, the sample size did not allow for analyses beyond descriptive statistics. Further research is needed to evaluate whether changes in PCFS over time correspond to clinically relevant and meaningful changes for patients and correlate with quality of life and other outcomes.

To evaluate long-term complications after COVID-19-associated PE, we performed a multicentre cross-sectional study in **chapter 14**. A total of 299 COVID-19 patients, who had been diagnosed with acute PE and received follow-up after hospital discharge, were followed for a median duration of 19 months. Chronic thromboembolic pulmonary hypertension (CTEPH) was considered ruled out based on at least one of the following criteria and examinations: CTEPH prediction score, CTEPH rule-out criteria, echocardiography, ventilation-perfusion scintigraphy, CTPA, or right heart catheterization. In our study population, none of the patients was diagnosed with CTEPH. Moreover, no recurrent symptomatic VTE was diagnosed and thrombus resolution did not seem to be different than after non-COVID-19 associated PE. Although this study was conducted in a selected group of patients who received follow-up according to strategies that were not fully standardized across the participating centres, we provided important data on the occurrence of CTEPH after COVID-19-associated PE. Our findings suggest that CTEPH is not a more prevalent complication after COVID-19-associated PE than after PE unrelated to COVID-19, which is in line with other studies.

Future perspectives

To facilitate the use of PROMs in everyday clinical practice, their implementation in routine workflows is needed, although this comes with various challenges. Since the findings of trials are to be translated to daily practice, outcomes that are most important to patients should be used as primary or secondary outcomes of studies to evaluate effectiveness of interventions based on meaningful endpoints.

An opportunity to both support the use of PROMs in clinical trials and the adoption of PROMs in daily clinical practice may lie in creating a shorter all-encompassing disease-specific PROM without overlapping questions, that is easy to complete by patients, requires minimal effort to process, and whose results are straightforward to interpret by researchers and care providers. The introduction of a standardized valid and reliable patient-reported instrument would also address the lack of standardization of outcomes in clinical VTE trials and would align PROM data collection, allowing for better comparison of outcomes. To develop a PROM that is accessible to all patients, consideration should be given to specific patient groups such as patients with low literacy levels and patients who experience language barriers. Suggestions to improve accessibility could be to use simplified language, to provide the options of audio or video versions of the PROM or potentially the option to use an interactive digital tool, to include visual aids such as color-coding and icons that patients can select to respond, and to offer translated versions of the PROM.

A first step in the development of an overarching PROM could be to start with a currently available set of PROMs for VTE and remove the overlapping questions and items. For instance, the core set of PROMs included in the ICHOM-VTE standard set of outcomes, which was developed for use in clinical practice, could be used as a starting point. Then, focus group discussions and a Delphi consensus process among an expert panel with input from patient representatives should follow to further develop a draft PROM, that is to be thoroughly evaluated and validated for all relevant outcomes. The comprehensiveness of the instrument may determine the success of its implementation, considering the feasibility of PROM completion, data processing, and use of its results in daily practice.

The usefulness of PROM results may be enhanced when specifying threshold values such as a minimal detectable change, minimal important change, and minimal clinically important difference. The minimal detectable change, or smallest change in score that can be detected, helps to distinguish between actual change and random variation. Moreover, the smallest change or difference that is perceived as important by patients can be indicated by the minimal important change or minimal clinically

important difference. The first can be used to interpret changes in scores over time within one individual, while the latter can be applied to compare scores between individuals or groups. After development of a new PROM, it would be valuable to derive these values in representative samples of VTE patients.

Incorporation in routine workflows would be facilitated by the integration of PROM data into the electronic health records. The use of an integrated digital application can support the collection, processing, and presentation of PROM data. This would facilitate the practical use and monitoring of PROM results over time, both from individual patients and from groups of patients. Since PROMs are emerging in various fields beyond VTE care, their integration into widely used health record systems may potentially be established (inter)nationally. For patients who lack or have insufficient digital skills, the possibilities of PROM completion with support provided on-site could be explored, for instance the option of completing the questionnaire on a tablet at the outpatient clinic or at the health-care facility, possibly with the assistance of volunteers.