Capturing venous thromboembolism: imaging and outcomes of venous thromboembolism

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PART 2

Outcomes of venous thromboembolism

CHAPTER 5

Outcomes of venous thromboembolism care: future directions

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Abstract

The complete picture of the outcomes of venous thromboembolism (VTE) care consists of conventional binary clinical outcomes (death, recurrent VTE and bleeding), patient-centered outcomes, and society-level outcomes. Combined, these allow for the introduction of outcome-driven patient-centered health care. The emerging concept of valuing health care from such a holistic point of view, i.e. value-based health care, holds a huge potential to revolutionize -and improve- the organization and evaluation of care. The ultimate goal of this approach is to achieve high value for patients, i.e. the best possible clinical outcomes at the right cost, providing a framework for evaluation and comparisons of different management strategies, patient pathways, or even complete health care delivery systems. To facilitate this, outcomes of care from a patient perspective, such as symptom burden, functional limitations, and quality of life need to be routinely captured in clinical practice and trials, complementary to conventional clinical outcomes, to fully capture patients' values and needs. The aim of this review was to discuss relevant outcomes of VTE care, explore value in VTE care from different perspectives, and propose future directions to inspire change. This is a call to action to shift the focus to outcomes that matter and make a larger difference in the lives of patients.

Introduction

Health care is rapidly changing as a result of technological advancements, aging populations, changing disease patterns, new discoveries for the treatment of diseases, political reforms, and changes in laws and regulations.[1, 2] Although each of these changes has the potential to revolutionize the way patient care is organized, one of these stands out: the modern concept of valuing health care. The future of care delivery is fundamentally evolving to become more patient-centered and outcome-driven. In addition to health-care indicators such as time in therapeutic range, anticoagulant therapy adherence, or the incidence of bleeding complications, the term outcomes also captures the results of care from the patient's perspective, i.e. what patients value most, such as quality of life or symptom burden. The notion of value is defined as achieving the best possible clinical outcomes for patients at the right cost, providing a framework for performance improvement, and is determined by comparing patient health outcomes against the costs of achieving these outcomes over the entire cycle of care.[3, 4] Maximizing the value for patients is the central goal of the concept of value-based health care, a rapidly emerging radically new approach to the evaluation of health care. The paradigm shift from the current supply-driven health-care system organized around what physicians do, volume of procedures, and fee for service into a patient-centered system organized around patients' outcomes and values will lead to a more sustainable and equitable health-care system and increased patient empowerment.[1, 3-7] This shift, however, requires a collective reset of mindset.

This next frontier of care delivery applies to venous thromboembolism (VTE) as it has with any other condition. In this review, we discuss the current outcomes of VTE care, explore different perspectives playing a role in determining value in VTE care, and propose future directions aiming to inspire change.

Conventional outcomes

Both deep vein thrombosis (DVT) and pulmonary embolism (PE) are highly incident conditions that make a considerable impact on patients' lives, in view of life-threatening complications early in the course of the disease and burdensome long-term sequelae.[8-16] These difficulties cause a considerable psychosocial impact, lead to impaired quality of life (QoL) and are a burden to the society because of the associated health care costs and loss of societal productivity owing to subsequent work-related disabilities.[17-25]

Until recently, VTE clinical trials typically focused on just the following three objective binary outcomes: death, recurrent VTE, and bleeding.[26] As such, the primary efficacy outcomes of the landmark trials in VTE performed in the past decades consisted of (a composite of) asymptomatic and confirmed symptomatic VTE or death from any cause, whereas major bleeding was the primary safety outcome; the same three outcomes are used when it comes to the evaluation of quality of care.[27] Mortality is definitely an important outcome. Treatment interventions leading to a survival benefit should be rapidly adapted and are the most important driver of evolving guideline recommendations. Interestingly, it has been reasoned that a large focus on survival in (critical care) studies may place too much emphasis on survival at any cost, which is not always a satisfactory outcome for many patients because it does not take QoL or functional outcomes of those who survive into account.[28] The same reasoning applies to a certain degree to recurrent VTE and bleeding: both are indisputable relevant consequences of the quality (i.e. efficacy and safety) of VTE treatment but do not take the actual consequences of these complications into consideration. The use of mortality or other binary endpoints, therefore, does not fully align with what patients find most important and should be complemented with outcomes that capture the patients' values and experience of care. Notably, the use of a so-called net clinical benefit endpoint of clinical trials has gained popularity in recent years. In VTE trials, net clinical benefit usually refers to the sum of major bleeding and thrombotic complications, which sometimes results in net clinical harm.[29] Although the term net clinical benefit suggests a quantitative framework that accurately compares the benefits and risks of an intervention with a comparator, the current definition actually ignores the very different consequences of thrombotic and bleeding complications. Regarding major bleeding, for instance, bleeding complications that meet different criteria of the definition of major bleeding, such as bleeding requiring blood transfusion versus intracranial haemorrhage, may have a different impact. Thus, in its current form, the net clinical benefit is not a valid overarching outcome and neither does fulfil the promise of its name nor does provide an adequate surrogate outcome for mortality.[30] With an improved understanding of the consequences and impact of complications, this definition may be refined.

In recent years, post-thrombotic syndrome (PTS) and post-PE syndrome (PPES) have been included as secondary outcomes of trials that were not specifically designed to impact these outcomes.[31, 32] These outcomes are long-term complications of VTE, requiring long-term follow-up to be captured. Although these outcomes have a clinical definition and are mostly health-care professional-reported, the diagnosis partly relies on patient-reported symptoms and correlates better with QoL than recurrent VTE or bleeding. Outcomes capturing the life impact of VTE, symptom burden, influence on activities, ability to return to work, and treatment satisfaction are still hardly -or rather not at all- reported in VTE trials.[26]

The results of clinical trials determine guideline recommendations and guide clinical practice, by informing which management options are most effective and safe. Because the current trials mostly evaluate the objective binary clinical outcomes of treatment from the perspective of health-care professionals, these outcomes offer only a limited picture by not considering the individual needs, values, and preferences of patients. Indeed, evaluating the effect of treatments on outcomes that matter most to patients may reveal differences between treatments and enable meaningful comparisons. Thus, although overall highly relevant, reporting only mortality, recurrent VTE, and bleeding complications is insufficient to evaluate the full spectrum of outcomes of VTE care.

The patient perspective

Improving care requires a common goal that unites interests from all perspectives, including that of the patient.[4] The ultimate goal of health care delivery is undoubtedly to achieve high value for the patient, expressed in QoL, functional abilities, and symptom burden. Following this, the drivers of impaired or enhanced QoL will determine the success and value of delivered care, at least from the patient perspective, and consequently qualify as relevant outcomes in VTE trials and care. We summarize all consistently reported determinants of QoL in VTE survivors below, as reported in the current literature.

For DVT patients, PTS has been shown to be associated with physical, mental, and social disabilities and has a large impact on QoL: large cohort studies have reported that patients who developed PTS have worse Short-Form Health Survey-36 (SF-36) and disease-specific VEINES-QOL/Sym questionnaire (both validated and reliable measures of health) determined QoL than both patients who did not develop PTS and population controls without VTE.[33,34] The same is true for PPES after acute PE.[35,36] Patients subjected to cardiopulmonary exercise testing (CPET) after one year of follow-up who had exercise limitations have poorer generic and disease-specific QoL measured using SF-36 and PEmb-QoL questionnaires than patients without exercise limitations.[37] Other studies have showed that PE survivors who report persistent dyspnea have poorer QoL based on the PEmb-QoL questionnaire compared with patients without dyspnea[38] and that post-PE impairment is associated with lower QoL as reflected by the EQ 5-dimension (EQ-5D) 5-level index, the EQ-visual analogue scale (VAS) and the PEmb-QoL questionnaire.[39] The most severe presentation of PPES is chronic thromboembolic pulmonary disease (CTEPD) with or without pulmonary hypertension (PH). Although chronic thromboembolic pulmonary hypertension (CTEPH) is clearly associated with worse SF-36 and EQ-5D-VAS scores [40,41,42], CTEPD without PH also causes impaired QoL.[43,44]

Moreover, VTE, in general, has a negative psychosocial impact. It has been shown that the indicators of mental health are worse in VTE survivors than in the general population.[18, 45-48] Patients experience the VTE event and its treatment as life changing, and they recall the VTE event as a defining moment in their life.[49] They believe that their lives have been changed by the VTE building on the first period following VTE diagnosis and how this change results in a so-called 'post-VTE identity'.[20] In addition, the fear of VTE recurrence, distrust of the medical establishment if the VTE diagnosis was missed or delayed, uncertainty about health and symptoms, and frank panic triggered by physical sensations or reminders of the VTE are reported, putting a burden on the participants' daily lives by limiting their physical and social activities.[20, 49, 50] Depression has been reported to occur in up to 15% of VTE survivors and further impair QoL.[21, 51, 52] Overall, patients experience changes in physical activity, social relationships, and the way they look at themselves, and develop the need to redefine life.[21, 22, 50, 53, 54]

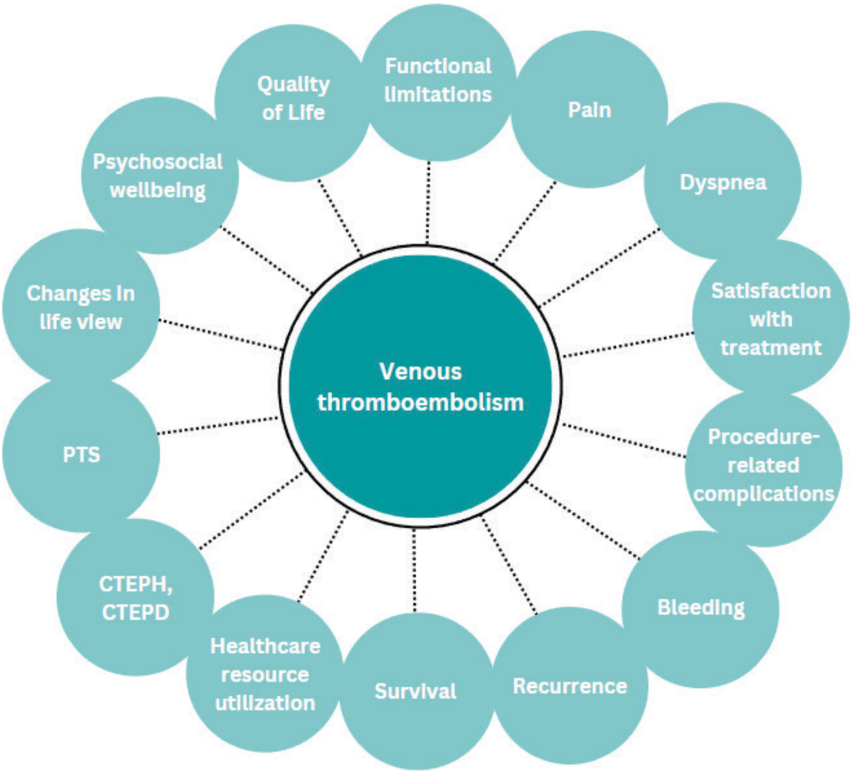
Several high-quality instruments have been developed to capture the full impact of VTE in a valid way, often self-reported. The 2 main instruments available for capturing disease-specific quality of life are the VEINES-QOL/Sym and PEmb-QoL questionnaires.[17,55-57] Functional outcomes and ability to work can be measured using the Post-VTE Functional Status scale.[58-60] There is a plethora of instruments available to measure psychosocial impact, i.e. depression, anxiety, and post-traumatic stress syndrome, many of which have been used in VTE cohort studies, e.g. the Hospital Anxiety and Depression Scale (HADS), Patient-Reported Outcomes Measurement Information System (PROMIS®) tools, mental component summary scores of SF-36 or its 12-item version (SF-12), Patient Health Questionnaire (PHQ-9), and Generalized Anxiety Disorder scale (GAD-7 or GAD-2).[61-66]

The society perspective

From the society-level point of view, additional outcomes are considered important, foremost population health and resource utilization with associated costs. Health-care resource utilization includes hospitalizations, visits to the (outpatient) clinic or general practitioner, and the use of anticoagulation. The initial diagnosis and treatment of VTE is responsible for the majority of costs, but health care utilization is increased for at least a year.[67, 68] In a multicenter observational study in seven European countries, the burden of PE related to resource utilization during follow-up was quantified: the overall VTE-related rehospitalization rate within the first 12 months after PE was 19% (ranging from 12-26% between countries) and 89% of the patients visited a physician during 12 months of follow-up, with on average 7.5 visits.[24] It takes on average 13 consultations of four different physicians to diagnose CTEPH.[69] A study investigating the health care costs attributable to incident VTE in the United States reported estimated overall incremental direct medical costs for the treatment of acute VTE amounted to 12,000 to 15,000 dollars per adult survivor of incident VTE in the first year after the VTE.[70] Surprisingly, the use of health-care resources is hardly mentioned in VTE trials.[26]

Indirect costs should also be taken into account. These are caused by the inability to work and loss of productivity when patients are not able to participate in the labour market (at their pre-existing level) after the VTE. In Scandinavian nationwide studies, individuals with an incident VTE had a 1.4-fold to 2.3-fold higher risk of subsequent work-related disabilities, after adjustment for comorbidities such as cancer and cardiovascular disease.[23,25] Evaluating medical consumption and productivity cost starts with collecting the total costs of health-care services and activities, provided during the entire cycle of care for the patient's medical condition.[4] Overall productivity can be measured by the work productivity loss index.[71]

Figure 1: Core outcomes included in the ICHOM core set of outcomes for patients with VTE.[72]

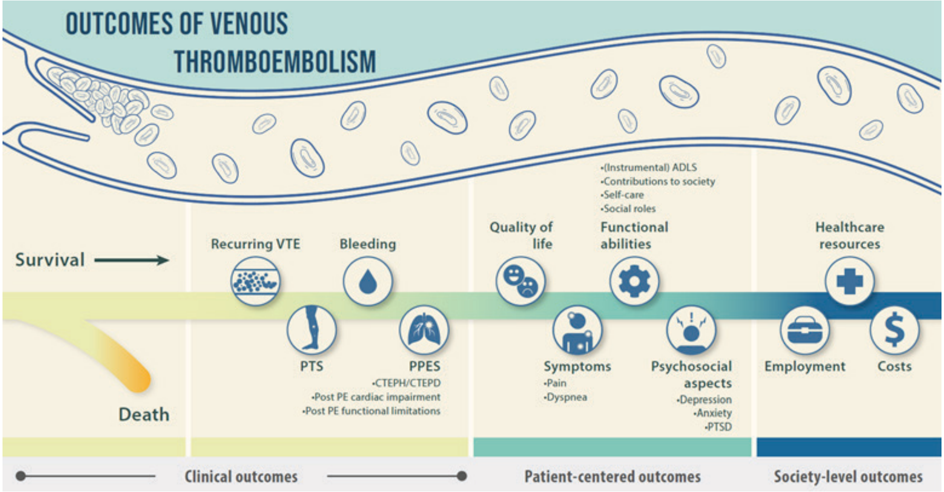


Abbreviations ICHOM: International Consortium for Health Outcomes Measurement, VTE: venous thromboembolism, PTS: post-thrombotic syndrome, CTEPH: chronic thromboembolic pulmonary hypertension, CTEPD: chronic thromboembolic pulmonary disease.

ICHOM-VTE

To establish a full overview of important outcomes of VTE care, a multidisciplinary project in collaboration with the International Consortium for Health Outcomes Measurement (ICHOM) was started in 2021. The aim of this project was to develop a set of patient-centered outcome measures for patients with VTE that would cover all important aspects of VTE care, including those that matter most to patients.[72] For this purpose, an international, multidisciplinary, working group of patients, physicians, advanced practitioners, nurses, and researchers was assembled. After extensive literature searches, focus groups and a modified Delphi process, core outcomes of VTE care were selected. The recommended core outcomes, as part of the standardized set, are shown in **Figure 1** and involve the traditional binary outcomes, economic outcomes, and QoL, symptom burden, and functional outcomes, explicitly including the ability to work, covering the perspective of the health-care professional, the patient, and society (**Figure 2**).[72]

Figure 2: Outcomes of venous thromboembolism.



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Post-thrombotic syndrome (PTS) is a long-term complication of deep vein thrombosis that manifests as a spectrum of symptoms, ranging from leg swelling to chronic pain, and signs of chronic venous insufficiency.[13]

Post-pulmonary embolism syndrome (PPES) is a long-term consequence of acute pulmonary embolism, defined by limitations in cardiopulmonary function in combination with dyspnea, reduced functional status or quality of life without an alternative explanation.[74]

Abbreviations VTE: venous thromboembolism, PTS: post-thrombotic syndrome, PPES: post-pulmonary embolism syndrome, CTEPH: chronic thromboembolic pulmonary hypertension, CTEPD: chronic thromboembolic pulmonary disease, ADLS: activities of daily living, PTSD: post-traumatic stress syndrome.

During the development of the standardized set for VTE, existing outcome measures were extracted from the literature to select those that best captured the identified core outcomes. These instruments were included in the consensus recommendation (**Table 1**). Notably, following the engagement of patient representatives during the decision-making process, additional outcomes that are currently not studied or measured in a standardized way, such as changes in life view, were considered 'must-have outcomes' and captured in the set.

Table 1: Suggested instruments to capture the patient-reported outcomes included in the ICHOM core set of outcomes for VTE.[72] The clinical outcomes are health-care professional-reported, and primarily defined according to the International Society on Thrombosis and Haemostasis (ISTH) VTE Common Data Elements.[75]

Patient-reported outcome	Patient-reported outcome measure
Quality of life	PROMIS Scale v1.2 - Global Health PEmb-QoL questionnaire VEINES-QOL questionnaire
Functional limitations (including ability to work)	Post-VTE Functional Status scale
Pain (including symptom severity)	PROMIS Short Form v2.0 - Pain Intensity - 3a
Dyspnea (including symptom severity)	PROMIS Short Form v1.0 - Dyspnea Severity - 10a
Psychosocial wellbeing	Patient Health Questionnaire (PHQ-9) Generalized Anxiety Disorder (GAD-7)
Satisfaction with treatment	Single question: "Are you satisfied with your VTE treatment?" If required: Anti-Clot Treatment Scale (ACTS)
Changes in life view	Single question: "Have you experienced a change in your expectations, aspirations, values, or perspectives on life opportunities since the diagnosis of VTE?"

Abbreviations ICHOM: International Consortium for Health Outcomes Measurement, VTE: venous thromboembolism, PROMIS: Patient-Reported Outcomes Measurement Information System, PEmb-QoL: Pulmonary Embolism Quality of Life, VEINES-QOL: Venous Insufficiency Epidemiological and Economic Study–Quality of Life.

The development of the ICHOM set is a crucial step toward value-based health care. In the meantime, the set is expected to change the landscape of VTE trials by shifting the focus of primary and secondary study outcomes. Capturing the patient perspective and integrating patients' values in daily clinical practice by routinely using patient-reported outcome measures (PROMs) will improve health-care professionals' understanding of the full impact of VTE on individual patients. In addition, the use of PROMs empowers patients to be actively involved in their care. Widespread implementation of the ICHOM set, therefore, not only will allow for the comparison of the quality of health-care systems or patient pathways, but also is believed to facilitate an increase in quality of care by itself.[72]

Furthermore, measuring outcomes that are important to patients will contribute to the identification of patients' specific needs and preferences and help provide targeted treatment. Managing the broad spectrum of consequences after VTE reaches far beyond anticoagulant therapy. A holistic approach for the treatment of VTE includes the targeted management of risk factors, identification of the optimal anticoagulant treatment, use of thromboprophylaxis in high-risk situations and counselling on maintaining a healthy lifestyle, and also involves targeted interventions such as cardiopulmonary rehabilitation and interventions to enhance psychological well-being.[20,76]

VTE-COS

The core set of outcome measures for VTE patients developed for use in daily practice may not be the most optimal set for use in clinical trials. The ongoing venous thromboembolism core outcome set (VTE-COS) project focuses on the development of a standardized core set of outcomes to be measured and reported in VTE trials.[26,77] As part of VTE-COS, large themes important in describing the consequences of VTE from patients' perspectives relevant for clinical trials were recently evaluated, independent from the ICHOM project. Acute impacts, psychological distress, change of life, coping and control, challenges of treatment, and negative experiences were identified as the most important themes.[77] These themes show -not surprisingly- a large overlap with the core outcomes as determined in the ICHOM set, which underlines the relevance of capturing these to guide management decisions and design trials. VTE-COS is expected to present its main findings in the next two years.[78]

Conclusion

The complete picture of outcomes of VTE care consists of conventional clinical outcomes, patient-centered outcomes, and society-level outcomes. The combination of these allows for a holistic, modern view on caring for VTE patients and the introduction of outcome-driven patient-centered health care. Implementing this transformation is complex, requires buy-in from all key stakeholders, and will take time. It is not a single step but rather an overarching strategy that requires restructuring how VTE studies are designed and VTE care is organized, delivered, and measured. Even so, to keep delivering sustainable care, health-care systems and organizations are starting to adapt to this new concept. Conventional outcomes do not need to be abandoned but rather routinely complemented with patient-reported and economic outcomes. We have to acknowledge that the current VTE care is yet far from perfect. Targeting and improving the full spectrum of VTE-associated complications goes far beyond treatment with anticoagulants and also involves targeted interventions such as rehabilitation and psychosocial support. This review is a call to action to shift the focus to outcomes that matter, both in clinical practice and in research - an opportunity to change and make a difference in the lives of patients. After all, the adage “one cannot improve what is not measured” is undeniably true.

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