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Late consequences of venous thromboembolism: Measuring quality of life after deep vein thrombosis and pulmonary embolism☆

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ABSTRACT

The identification of specific post-thrombotic complications as well as an increased appreciation of the importance of patient-reported outcome measures have triggered an interest in studying health-related quality of life (HRQoL) in patients with a history of venous thromboembolism (VTE).

In order to enable a comprehensive assessment of HRQoL in clinical trials it is recommended that both generic and disease-specific questionnaires be used. SF-36 and EQ-5D are the most widely used generic questionnaires in VTE studies, whereas several disease-specific questionnaires have been developed to evaluate HRQoL following deep vein thrombosis (DVT) and in chronic venous disease (CVD). The most widely used of these is the *VEINES-QOL/Sym*, which was developed for CVD. *VT-QOL* and *DVTQOL* are both questionnaires developed to evaluate HRQoL after DVT, while *PEmb-QoL* is currently the only available disease-specific questionnaire developed specifically for pulmonary embolism (PE).

Although studies show inconsistent results, patients who sustain DVT seem in general to report similar HRQoL compared to the general population. However, patients who develop PTS after DVT report poorer HRQoL using both generic and disease-specific questionnaires. HRQoL appears to be impaired in patients who sustain PE compared to the general population. In these patients, persistent dyspnea after PE has been shown to be a predictor of reduced HRQoL.

Further work is needed to develop practical, patient-derived, valid, reliable and responsive disease-specific HRQoL instruments covering the specific aspects of these diseases.

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1. Introduction

Venous thromboembolism (VTE) which comprises deep vein thrombosis (DVT) of the lower and upper extremities, thrombosis of the caval and splanchnic veins, cerebral venous sinus thrombosis, and pulmonary embolism (PE) is an acute medical emergency resulting from the obstruction the venous vasculature or the pulmonary arteries. Anticoagulation, the mainstay for treatment of VTE, is given to stop thrombus progression and to prevent recurrent venous thrombosis [1]. Long-term outcomes of VTE include bleeding, recurrent venous thrombosis, as well as the chronic sequelae of post-thrombotic

syndrome (PTS), persistent dyspnea after PE and chronic thromboembolic pulmonary hypertension (CTEPH) [2–5].

Studies show that the prevalence and severity of these sequels vary considerably. PTS develops in 40–60% of patients following a proximal DVT of the lower limb and involves variable chronic manifestations including pain, heaviness, swelling, itching, and ulcers [6]. CTEPH is encountered in 3–4% of patients after PE and is characterized by persistent dyspnea and signs of right sided heart failure [7]. It has been shown recently that a larger proportion of patients suffer from persistent dyspnea and reduced exercise capacity, even without having pulmonary hypertension – a condition recently termed post pulmonary embolism syndrome [2]. Naturally, these outcomes can have a substantial impact on the psychological and physical health, well-being, and daily functioning of patients following VTE.

The increasing awareness of these chronic sequelae, together with the increased focus on patient reported outcome measures (PROMs) during the last two decades, has highlighted the utility of studying

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health-related quality of life (HRQoL) in patients with a history of DVT and PE.

The aim of this review is to present the current state of knowledge on this subject including a description of available instruments for HRQoL assessment, as well as results from clinical studies on HRQoL after DVT and PE.

2. Methods

A non-systematic review of the literature was carried out for English language publications using PubMed and Academic Search Premier up to March 2017 in order to identify available instruments for HRQoL in DVT and PE and related studies. We used the search term *quality of life* in combination with the terms *venous thrombosis, chronic venous disease, deep vein thrombosis, post-thrombotic syndrome, and pulmonary embolism*. In addition, we manually searched references from the relevant articles we identified.

3. HRQoL; definitions and development of measurement tools

Several definitions for quality of life (QoL) exist. One of the most widely recognized is the World Health Organization's definition which states that QoL can be regarded as "...an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives, and in relation to his/her goals, expectations, standards and concerns. It is a broad-ranging concept, incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment" [8].

To distinguish between QoL in general and aspects of importance for clinical medicine, the term health-related quality of life (HRQoL) is used. HRQoL refers specifically to the impact that health conditions and their treatments have on an individual's or a group's perceived health.

Traditional measures of morbidity and mortality are limited in their ability to describe and quantify the overall and multidimensional impact of illness, particularly chronic illness. Consequently, various generic and disease-specific instruments have been constructed to assess patients' physical and psychological health and well-being, social role, and daily functioning [9–11]. The generic instruments may be used irrespective of illness or condition. They provide the possibility of comparison with normative data, such as general population data as well as between different patient groups. However, generic instruments may lack the sensitivity to capture disease specific aspects and to detect clinically-relevant changes over time. Mainly for this reason, disease-specific instruments have been developed. In order to allow for comparison between groups and to relate to healthy persons, as well as to ensure sensitivity in the population at hand, a combination of generic and disease-specific HRQoL measures is recommended in clinical trials [12–14].

HRQoL measurements may be useful to identify risk factors of reduced HRQoL and to recognize important subgroups, e.g., patients with poorer outcomes. Such information may help to guide interventions and follow-up. In interventional clinical trials, measurement of HRQoL can be a primary or a secondary outcome measure and can contribute to the evaluation of the overall treatment effect [14]. Finally, HRQoL measurements can evaluate symptom relief, facilitate patient-physician communication and improve person-centeredness in clinical research.

Developing a HRQoL instrument is an extensive procedure that entails a thorough review of the literature, interviews of patients and healthcare personnel, the construction of a score, and finally the field-testing of that score. There has been increased focus on patients' involvement in each of these steps to increase the validity of HRQoL results. For instance, the American Food and Drug Agency (FDA) has emphasized that the content validity of a patient reported outcome instrument is likely to be questioned without adequate documentation of

patient input [15]. Notably, several studies have highlighted that the agreement between patients and physicians on HRQoL is poor [16]. The European Organization for Research and Treatment of Cancer (EORTC) has also emphasized that strict eligibility criteria should be adopted to ensure that patients recruited in item development of questionnaires adequately represent the target population for which the questionnaire is being developed, e.g., different disease stages and treatment strategies [17].

To address methodological quality regarding development, testing of measurement tools, and scientific reporting, several efforts have been made to address and establish quality standards, including the CONSORT PRO extension and the Cosmin checklist [18,19]. In general, it is required that the instruments have well-documented validity, reliability and responsiveness (see Table 1 for definitions).

4. Quality-adjusted life years (QALYs)

To assess the value for money and cost-effectiveness of medical interventions, economic evaluations in health care often measure so called quality-adjusted life years (QALYs). QALYs combine the quality and quantity of life into one outcome in order to measure disease burden. One QALY equates to one year in perfect health. Some HRQoL instruments have been specifically designed to measure preference or utilities (e.g., valuations for different levels of a predefined set of domains, such as pain and mobility), such as the generic EQ-5D. At the same time, these measures have been criticized for not capturing the multi-dimensional nature of HRQoL, by focusing mainly on physical functioning and not that much on people's mental and social well-being [14,20].

5. Questionnaires used to measure HRQoL after VTE

Several HRQoL questionnaires have been used for studying HRQoL in patients with a history of DVT and PE. Following is a basic description of the most commonly used generic and disease-specific questionnaires, please, see Table 2.

6. Generic questionnaires

6.1. EuroQoL-5D (EQ-5D)

The EQ-5D comprises five dimensions (mobility, self-care, pain, usual activities, and psychological status) complemented by a visual analogue scale (VAS) for the evaluation of own health [21]. Each of these dimensions was originally scored according to three levels of severity (EQ-5D-3L). A new version was developed with five response levels (EQ-5D-5L) to improve sensitivity and responsiveness by grading severity into no problems/some problems/moderate problems/severe problems/extreme problems.

Table 1
Definitions of psychometric properties of HRQoL questionnaires.

Validity	The QoL questionnaire measures what it is intended to measure and that it is useful for its intended purpose - Internal: the results are correct for the particular group of people being studied - External: generalizability
Reliability	The ability to yield the same score each time a measure is administered
Sensitivity	The ability to detect differences between patients or groups of patients
Responsiveness	The ability of a measure to reflect underlying change when a patient improves or deteriorates
Content validity	The extent to which a scale or questionnaire represents the most relevant and important aspects of a concept in the context of a given measurement application

Table 2
Summary of HRQoL questionnaires used in VTE research.

Questionnaire	Specifically developed for VTE	Patient involvement	Validity	Reliability	Responsive-ness	No. of items (components)	Recall period
Generic							
EQ-5D	N/A	Yes	Yes	Yes	Yes	5 + VAS scale	None
SF-36	N/A	Yes	Yes	Yes	Yes	36 (8)	4 weeks
SF-12	N/A	Yes	Yes	Yes	Yes	12	4 weeks
Disease specific for DVT							
CIVIQ	No	Yes	Yes ^a	Yes ^a	Yes ^a	20 (4)	4 weeks
DVTQOL	Yes	Yes	Yes	Yes	Not investigated	29 (6)	Not specified
Mathias	Yes	No				80	4 weeks
VEINES-QoL/Sym	No	No	Yes	Yes	Yes	26 (2)	4 weeks
VT-QOL	Yes	Yes	Yes	Yes	Not investigated	25 (4)	4 weeks
Disease specific for PE							
PEmb-QoL	Yes	Yes	Yes	Yes	No	40 (5)	30 days

CIVIQ; Chronic Venous Insufficiency quality of life Questionnaire, DVTQOL; Deep Venous Thrombosis Quality Of Life questionnaire, EQ-5D; EuroQoL 5D, PEmb-QoL; Pulmonary Embolism Quality of Life questionnaire, SF-36; Short Form 36, VEINES-QoL/Sym; Venous Insufficiency Epidemiologic Study-Quality of life/Symptoms questionnaire, VT-QOL; Venous Thrombosis Quality Of Life questionnaire.

^a Only in patients with chronic venous disease, not in DVT patients.

Using the EQ-5D descriptive system, results can be summarized as a weighted mean of the five dimensions [22]. Index-based values (utilities) are a major feature of the EQ-5D instrument, facilitating the calculation of QALYs commonly required in economic evaluations. Higher values on EQ Index and VAS indicate better HRQoL.

EQ-5D is owned by the EuroQol Group and is available in >130 languages [23]. A prior written consent of the EuroQol is required for use of this instrument. Licensing fees are determined by the EuroQol Research Foundation on the basis of the user information provided in the registration form [23]. The paper version of EQ-5D is usually provided free of charge for non-commercial use (i.e. academic research).

The strengths of the EQ-5D include its simplicity and its experienced applicability in a wide range of health conditions and treatments. It provides an overall numeric estimate of HRQoL which can be used for both clinical and economic evaluations of health care. Population norms are available in many countries. However, the questionnaire has been found to be culture-specific, with concepts more common to western culture [24].

6.2. Short-forms: (SF-36 and SF-12) health survey questionnaire

The SF-36 is the most widely used generic HRQoL instrument [24] involving functional, psychological, and social status domains. It consists of 36 items, some with 5 or 6 points and others with 2 or 3 [25]. Each of the 36 items corresponds to one of eight subscales. Raw scores are transformed into a 0–100 scale score, where higher scores indicate better HRQoL. In addition to the eight subscales, two summary scores can be calculated and are often reported: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The first version of SF-36 was revised regarding item wording and response choices and SF-36v2 was made available for use in 1996.

The shortened questionnaire, SF-12 (current version SF-12v2) requires only one third of the time for completion compared to the SF-36 [26]. Comparisons between SF-36 and SF-12 in the general population have indicated very good correlation and agreement, also in specific subpopulations [27,28].

Both instruments are owned by OPTUM and are available in >170 languages. A prior consent is required for use. Licensing fees are determined by OPTUM Office on the basis of the user information provided in the registration form [29].

A major advantage of the SF-36 is its extensive application in several conditions, background populations, and its well proved psychometric characteristics. Population norms are available in many countries. A

possible limitation is that the social functioning scale is too narrow in scope to cover social well-being [24].

7. Disease specific questionnaires for DVT

7.1. The Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) [30]

The CIVIQ was developed to assess HRQoL in patients with chronic venous diseases (CVD) [31]. During its development, patients with CVD were interviewed to identify important features of HRQoL in CVD and the interview guide was drawn from a review of the literature and from interviews with four medical specialists and three general practitioners. The questionnaire consists of 20 items across 4 dimensions; physical, psychological, social, and pain. The scores for each dimension is the sum of the constituent items and the total score is the sum of the 20 items. Absolute scores are converted to an index, corresponding to the SF-36 index used. Three scores can be calculated: a score per item (value 1–5), a score per dimension (value 0–100), and a global score (value 0–100); higher scores represent better HRQoL. The CIVIQ has been found to be reliable, valid, and responsive to change in CVD [31]. The questionnaire has been used in clinical studies studying HRQoL after DVT [32,33], but has not been validated in this population. Having neither been specifically developed, nor validated for DVT may be considered a limitation of the questionnaire for use in this population. A short version with only 14 items (CIVIQ-14) has also been developed [34].

7.2. The deep venous thrombosis quality of life (DVTQOL)

This questionnaire was developed to assess HRQoL in patients with acute DVT who receive oral anticoagulation with vitamin K antagonist [35]. Items for the DVTQOL questionnaire were identified from interviews with DVT patients. In addition, specialists experienced in anticoagulation practice (physicians and nurses) were consulted, and a review of the literature on patient-reported outcomes of venous disorders was conducted. The questionnaire consists of 29 items across 6 dimensions; emotional distress, symptoms, limitations in physical activity, burden of anticoagulation monitoring, sleep disturbance, and dietary problems. The dimensions significantly correlated with relevant dimensions of both SF-36 and EQ-5D. The DVTQOL is valid and reliable, but test-retest and responsiveness to change have not been examined (21). We are not aware of other studies that have used the DVTQOL questionnaire. This tool does not seem appropriate for use in patients being treated with new direct oral anticoagulants, as six of the questions cover items related to “Hassle with monitoring” or “Dietary problems.”

7.3. HRQoL questionnaire by Mathias et al.

This 80 item questionnaire was developed as a comprehensive questionnaire for patients with acute ilio-femoral DVT using elements from both generic HRQoL questionnaires (Health Utilities Index, SF-12, and the Medical Outcome Study) and additional DVT specific items [36]. Four patients were involved in a pretest of the questionnaire before implementation, which did not lead to any change in the questionnaire. The baseline part of the questionnaire has two sections; baseline assessment and pre-DVT assessment. The follow-up questions are for use six months after baseline. Besides the limited patient involvement during development, the questionnaire is extensive, with a total of 80 items. The instrument has been found to be valid, reliable, reproducible, and responsive to change, but to our knowledge it has not been used in clinical trials after the validation study.

7.4. Venous Insufficiency Epidemiological and Economic Study (VEINES-QOL/Sym)

The VEINES-QOL/Sym is most commonly used for the measurement of HRQoL following DVT [37]. Items in the VEINES-QOL/Sym questionnaire were developed for CVD based on findings from the literature, review of existing measures, and expert opinion. The questionnaire consists of 26-items and was modeled after the construct of SF-36, i.e. with similar format and response scales. The items were modified to relate to leg problems instead of general health, and cover CVD-related symptoms (10 items), limitations in daily activities (9 items), psychological impact (5 items), the amount of change in the respondent's leg problem over the past year (1 item), and the time of day that the leg problem is most intense (1 item). Out of the 26 items, 25 are summed to create an overall VEINES-QOL summary score. A subset of 10 items is summed to create a separate symptom severity score, the VEINES-Sym score. The VEINES-QOL/Sym questionnaire has been validated in DVT patients.

Besides lacking patient involvement during development of this instrument, this tool was not developed for patients with previous DVT and therefore does not necessarily capture all relevant aspects related to DVT, e.g. anxiety for bleeding complications while on anticoagulation or fear of recurrence. However, the instrument seems appropriate for use in the evaluation of long-term HRQoL after DVT since it captures aspects related to CVD and it is available in many languages.

7.5. Venous Thrombosis-QOL (VT-QOL)

This questionnaire was developed based on interviews with DVT patients and consists of 25 items across 4 dimensions; physical functioning, social functioning, general mental health, and thrombosis repercussions [38]. It is possible to calculate sub-scores on all subscales with a range of 0–100 similar to SF-36. In the validation study, a strong correlation between the VT-QOL and SF-36 scores was found. In addition, pain and restriction in daily activity were significantly correlated with most subscales of VT-QOL. The VT-QOL was found reliable and valid, but test-retest and responsiveness to change were not evaluated. We are not aware of other studies using VT-QOL in the assessment of HRQoL in DVT. Although, detailed assessment of this tool is difficult since the complete version of the questionnaire was not published in the original manuscript, the questionnaire covers a number of items that can be relevant following acute DVT.

8. Disease specific questionnaires for PE

8.1. Pulmonary Embolism Quality of Life (PEmb-QoL)

PEmb-QOL is the only validated disease-specific questionnaire for PE [39,40]. The development of the PEmb-QoL was based on qualitative, semi-structured interviews with 10 patients (4 males/6 females) who

were selected because of severe chronic complaints following PE [40]. The instrument outline was modeled on the VEINES-QOL/Sym questionnaire and contains 40 items across six dimensions: frequency of complaints (8 items), activities of daily living limitation (13 items), work-related problems (4 items), social limitations (1 item), intensity of complaints (2 items), and emotional complaints (10 items). The two questions concerning which time of day lung symptoms are most intense and change over the last year, are descriptive and not included in the score. A summary score was not presented in the original validation study, but this has been suggested in subsequent validation studies. The PEmb-QoL is available in several languages [41,42].

9. HRQoL after DVT

Studies comparing HRQoL in patients after DVT to population norms or matched controls with no history of DVT have shown conflicting results. In a study of patients who had sustained iliofemoral DVT 60 months previously and then developed venous claudication, significant lower scores were found in five of eight SF-36 dimensions (physical functioning role physical, general health, social functioning, and mental health) compared to age- and gender matched U.S. population norms [43]. In line with this study, Van Korlaar et al. found that HRQoL of patients with previous (>24 months) DVT was impaired in all SF-36 domains compared to a general U. S. population sample [38].

Kahn et al. followed 395 patients with DVT for four months. The findings within this time frame indicated a reduced HRQoL that was comparable to patients suffering from chronic diseases of the heart, lung, or joints. Mean SF-36 physical component scores at 0, 1 and 3 months were substantially lower than Canadian adult norms. Scores at one month were also lower than in patients with arthritis or chronic lung disease, and were similar to patients with angina pectoris, and at four months were similar to patients with arthritis or chronic lung disease. Mean mental component score at baseline and at one month were lower than Canadian adult norms and were similar to patients with chronic lung disease, but were similar to Canadian adult norms after four months [44].

Using EQ-5D-3L, Utne et al. showed that HRQoL after a mean follow-up time of 5 years in 254 patients with previous DVT was lower than age- and sex-matched buddy controls. HRQoL was also significantly lower than age- and sex-adjusted population norms. The difference was significant in all five items [45].

However, a recent meta-analysis of patients with a history of DVT that included 14 studies up to March 2016, showed that measures of physical health, mental health, and disease-specific QoL were similar to population norms after at ≥ 1 year. Of all studies, nine were eligible for pooled-effects analyses of the SF-12 and SF-36 physical and mental component scores, and eight studies were eligible for a pooled-effects analysis of the VEINES-QOL. The meta-analysis showed that one year after an episode of DVT both generic and disease-specific HRQoL scores were comparable to population norms [46]. We are, however, unaware of any study comparing HRQoL after DVT in patients with different ethnicity with population norms.

HRQoL following DVT has in longitudinal studies been shown to improve over time [47]. Kahn et al. found that mean SF-36 physical and mental component scores as well as VEINES-QOL and VEINES-Sym scores improved from baseline to 24 months. However, the magnitude of improvement in physical component scores, VEINES-QOL and VEINES-Sym scores during follow-up were significantly reduced among patients who developed PTS compared to patients without PTS [47].

Compared to other patients with CVD, DVT patients seem to have poorer HRQoL. In an international prospective cohort study with 1531 patients with CVD of whom 151 had a prior DVT, HRQoL was poorer in patients with prior DVT compared with patients with other forms of CVD [48]. HRQoL was assessed both with SF-36 and with VEINES-

QOL/Sym. This was confirmed in another study by Sanchez et al. using SF-12 and CIVIQ-20 [32].

10. What determines HRQoL after DVT?

Many studies have shown that PTS is the main predictor of a persistent reduction in HRQoL following acute DVT [38,45,47,49]. This has been consistent both when using the generic HRQoL questionnaires SF-36 and EQ-5D and the disease-specific VEINES-QoL/Sym.

Other factors that have been found to be associated with impaired HRQoL after DVT are age, obesity, comorbidity, location and extent of the thrombus, and socioeconomic status. However, these factors have been evaluated to a lesser extent and their association with impaired HRQoL has been inconsistent across studies [45,47,50].

Data on the effect of therapy on HRQoL are limited. In the CaVenT trial which compared catheter-directed thrombolysis (CDT) to conventional anticoagulation alone in patients with ilio-femoral DVT, HRQoL assessed by EQ-5D and VEINES-QoL/Sym was not better in the CDT group despite a reduction in PTS at 2 and 5 years after treatment [49, 51]. However, PTS was associated with poorer HRQoL independent of treatment group, supporting previous findings that PTS carries a major negative impact on patients' lives. A few reports on patients with severe PTS treated with endovascular stenting for chronic vein obstructions have indicated improvement in terms of symptom relief, but we are not aware of any HRQoL studies following such treatment.

The transition from warfarin to DOACs for the treatment of acute DVT has its basis in results from large RCTs showing similar or better efficacy and/or safety of DOACs as compared to warfarin, in addition to the added advantage of not needing to monitor anticoagulation levels with DOACs. However, none of these RCTs included an evaluation of HRQoL. Emerging data from a Norwegian cross-sectional study comparing rivaroxaban- to warfarin-treated patients indicate reduced prevalence of PTS and improved HRQoL measured by EQ-5D-3L and VEINES-QoL/Sym in the rivaroxaban group two years after first-time DVT (submitted for publication and accepted for oral presentation on the upcoming ISTH 2017 meeting) [52].

11. HRQoL after pulmonary embolism

Although classified as the same disease entity, long-term outcomes, including HRQoL, have been less extensively studied in PE than in DVT. The identification of post PE syndrome that develops in 30–50% of patients has, however, triggered an increased interest in studying HRQoL after PE [2,53,54].

In the first study using SF-36 to evaluate HRQoL in PE patients, Klok et al. reported that PE patients had significantly lower scores in all SF-36 subscales compared to the Dutch general population norms. The largest difference was observed in the subscales physical role limitation and physical functioning. Of note, however, 50% of patients had other cardiopulmonary comorbidities which may have contributed to their findings [53].

In a similarly designed study, using the EQ-5D-3L, Tavoly et al., reported that patients with PE had significantly lower EQ-5D index values and EQ-VAS scores when compared to the population norms [42]. To adjust for possible incidental events of VTE, which cannot be adjusted for in the general population norms, the PE cohort was also compared to a sex- and age-matched control group revealing similar findings [42]. In this cohort only 9% of PE patients had cardiopulmonary comorbidities (29).

van Es et al. evaluated possible differences in HRQoL between patients after PE and other cardiopulmonary diseases including chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF) and first year after acute myocardial infarction (AMI). Patients in the PE cohort with these comorbidities within the preceding year were excluded. Compared to the general population, once again PE patients scored significantly lower in all the SF-36 subscales except physical

functioning, mental health, and pain [55]. However, compared to patients with COPD and CHF, PE patients had significantly higher scores in all subscales [55].

In a recent prospective study 100 PE patients were followed for 1 year. After one month, the patients had significantly lower SF-36 scores compared to the general population norms, but this finding was not sustained at the 12 months [56,57]. Although the study was not designed for specifically evaluating this outcome, it contradicts previous findings of worse HRQoL compared to the general population [42, 53,55].

The metaanalysis reported by Lubberts et al. included two studies (with a total of 192 patients) with previous PE. Pooled analysis showed that physical component score was lower compared to population norms. The mental component score was on the other hand comparable to the population norms [46]. In another metaanalysis that focused on PE studies only, Sista et al., reported pooled SF-36 physical component score after a median follow-up of 25 months corresponding to the 40th percentile compared to population norms [58]. However, significant heterogeneity was identified among studies.

12. What determines QoL after PE?

CTEPH is a rare, but serious sequel of PE which has been shown to have a severe impact on HRQoL [59], affecting physical, psychological and social aspects of the patients' daily lives [60]. As such, CTEPH should be regarded as a separate disease entity and not only a determinant of HRQoL in PE populations.

Although no study has formally excluded CTEPH, in general, persistent dyspnea and reduced exercise capacity, i.e. post PE syndrome, have been shown to be associated with impaired HRQoL after PE [42, 57]. A recent study indicated that pulmonary artery systolic pressure and main pulmonary artery diameter at baseline to be associated with poorer HRQoL [57]. As with DVT, the association between other factors and HRQoL has been conflicting [53,57].

In the only randomized controlled trial evaluating HRQoL after systemic thrombolysis for PE (TOPCOAT study), Kline et al. found that patients receiving thrombolysis reported better physical component score, but not mental component score of SF-36 at 90 days follow-up [61]. However, a following sub-study that focused on HRQoL failed to show that thrombolysis was a significant determinant of better physical component score [62].

13. Discussion

Chronic sequelae following acute VTE can have a profound impact on HRQoL. The immediate period after acute VTE is usually dominated by the clinical manifestations and psychological effects of the acute disease. While symptoms may take weeks to months to subside the next phase may be dominated by worries and fears related to bleeding from anticoagulation and consequent restriction of daily activities. In some patients, symptoms may resolve completely whereas in others, manifestations of the chronic complications PTS, CTPEH, and Post PE Syndrome may gradually appear. While cessation of anticoagulation may cause relief from the fear of bleeding, there may be an increased worry about sustaining a recurrent VTE.

Accordingly, short-term assessment may include patients' experiences with the acute manifestations of VTE, the burden of anticoagulation therapy including possible repeated INR monitoring and dose-adjustment for warfarin-users and how to live with the risk of bleeding complications versus the risk of recurrence. Long-term HRQoL assessments, on the other hand, are likely to be related to the chronic sequelae of VTE.

Currently, there are no HRQoL questionnaires that seem to cover all disease phases. The most commonly used disease specific questionnaires the VEINES-QoL/Sym and PEmb-QoL address long-term impact of DVT and PE, respectively. Only PEmb-QoL, however, asks about

worries related to anticoagulation and recurrence. Although specifically developed for VTE, reports on VT-QOL and DVTQOL are very limited.

The importance of patients' involvement in research has been increasingly emphasized by clinical researchers and funding bodies. Such involvement during questionnaire-development is crucial, since only patients can determine which health outcomes are relevant to them. To our knowledge, none of the disease-specific HRQoL questionnaires for DVT and PE have involved patients during questionnaire development, and some, namely, the VEINES-QOL/Sym, did not involve patients at all [37]. As a result, the underlying development methodology does not meet the standard of current guidelines – an obvious limitation of today's instruments.

Although studies on DVT show inconsistent results, HRQoL after DVT, however, seems in general to be comparable to the general population. PE patients, on the other hand, seem to suffer impaired long-term physical health. PTS and Post PE Syndrome are robust predictors of impaired HRQoL as determined by both generic and disease-specific questionnaires.

In order to study clinical importance of HRQoL measures, the concept of minimal clinically important difference, the smallest change in an outcome that a patient may deem important was introduced [63]. More recently, the term minimally important difference (MID) has been recommended. Four methods are commonly employed to estimate MIDs: patient rating of change (global transition items), clinical anchors, standard error of measurement, and effect size [64]. For few of the disease-specific HRQoL questionnaires used in VTE studies, has the MID been clearly established or reported [65]. Thus, there is currently no consensus on MID. Furthermore, a calculation of the MID depends on the population at hand, baseline risk, improvement, and deterioration during follow-up.

Currently HRQoL questionnaires are primarily used for research purposes. However, in addition to their value in clinical research, HRQoL questionnaires can be used as a supplement to traditional clinical examination and diagnostic tests to aid in selecting patients who require certain interventions and in determining the intensity of follow-up.

An important challenge with the available instruments, is the fact that most of the HRQoL questionnaires are quite comprehensive, e.g., the SF-36 contains 36 questions, the PEmb-QoL 40 questions and the VEINES-QOL/Sym 26 questions. This may limit their acceptability and use in daily clinical practice.

In conclusion, identification of the various chronic sequelae after VTE and increased appreciation of PROMs have triggered an interest in developing disease-specific questionnaires for studying HRQoL after DVT and PE. In general, patients who sustain DVT seem to report similar HRQoL compared to the general population while HRQoL appears to be impaired in patients who sustain PE compared to the general population. However, none of these disease-specific questionnaires meets current methodology standards for the development of HRQoL questionnaires. Therefore, there is an urgent need today for practical, patient-derived, valid, reliable and responsive disease-specific HRQoL instruments covering specific aspects of VTE.

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