Research

An instrument for measuring health-related quality of life in patients with Deep Venous Thrombosis (DVT): development and validation of Deep Venous Thrombosis Quality of Life (DVTQOL) questionnaire

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Abstract

Background: Few studies have evaluated patient-reported outcomes in connection with a primary event of deep venous thrombosis, partly due to a lack of disease-specific measures. The aim here was to develop a disease-specific health-related quality of life (HRQL) measure, the deep venous thrombosis quality of life questionnaire (DVTQOL), for patients with recent exposition and treatment of proximal deep venous thrombosis.

Methods: A total of 121 consecutive outpatients (50 % males; mean age 61.2 ± 14 years) treated with warfarin (Waran®) for symptomatic proximal deep venous thrombosis were included in the study. Patients completed the SF-36, EQ-5D and the pilot version of the DVTQOL.

Results: Items having: high ceiling and floor effect, items with lower factor loadings than 0.50 and items loading in several factors were removed from the pilot version of DVTQOL. In addition, overlapping and redundant items identified by the Rasch analysis were excluded. The final DVTQOL questionnaire consists of 29 items composing six dimensions depicting problems with: emotional distress; symptoms (e.g. pain, swollen ankles, cramp, bruising); limitation in physical activity; hassle with coagulation monitoring; sleep disturbance; and dietary problems. The internal consistency reliability was high (alpha value ranged from 0.79 to 0.93). The relevant domains of the SF-36 and EQ-5D significantly correlated with DVTQOL, thereby confirming its construct validity.

Conclusions: The DVTQOL is a short and user-friendly instrument with good reliability and validity. Its test-retest reliability and responsiveness to change in clinical trials, however, must be explored.

Background

Health-related quality of life is significantly impaired in individuals with vascular disease[1,2]. Besides the risk of acute pulmonary embolism DVT is associated with a variety of symptoms, generally referred to as post-thrombotic syndrome, which restricts patients' daily activities [3-5]. Patients report problems with functioning, low levels of energy, sleep disturbance, pain and limitations in physical mobility that were evaluated by the Nottingham Health Profile (NHP). In a long-term outcomes study of DVT, it was shown that symptoms in the leg, such as pain, swelling, ulceration and discoloration, affected patients' perception of HRQL as measured by the Short Form Health Survey (SF-36) [6,7]. Patients with symptoms reported low levels of physical functioning and severely impaired role functioning. Moreover, there are a number of characteristics of current oral anticoagulation therapies that can potentially induce dissatisfaction and reduce HRQL. Among these are the necessity for frequent doctor visits for regular blood testing, lifestyle limitations, including restrictions on diet and activities, and possible worry about bleedings. Thus, the practical and psychological demand of such therapy has negative effects on patients' perceptions of their HRQL[8,9].

Both general and disease-targeted questionnaires are helpful in increasing the understanding of health-related quality of life outcomes in patients after a deep-vein thrombosis event. General instruments include health profiles and assessments of the overall health state. They can be used to compare the relative burden of illness in the general population and between different diseases. Disease-targeted instruments, on the other hand, may be used to elucidate specific domains of particular importance to the patient.

The general knowledge about the burden of illness in this group of patients is poor and information on disease- and therapy-related HRQL is sparse. In clinical practice, the value of being able to measure HRQL and satisfaction with care that is not adequately captured by traditional measures of morbidity and mortality is self-evident, but most measures are either limited by their narrow focus as they are restricted to patients with varicose veins or leg ulcer [10,11] or they lack evidence of reliability and validity. For routine monitoring of outcomes in chronic venous disorders, the VEINES-QOL questionnaire[12], and Mathias and colleagues' [13] measure for acute ili-ofemoral deep venous thromboses, have been developed. For recent experience of DVT, however, there is no adequate instrument available for use in clinical trials. To meet this need, a new instrument measuring health- and treatment-related quality of life in patients with recent experience of DVT was developed. Data on self-perceived burden of disease and health status are also presented.

Methods

Patients and Methods

Consecutive male and female patients between 18 and 80 years with a verified diagnosis of deep venous thrombosis (ultrasound or phlebography) were recruited from local anticoagulation services at the Sahlgrens' University Hospital, Frölunda, Lundby and Vasa Hospitals in Gothenburg, Sweden, between March 1999 and March 2000. Patients were treated with warfarin (Waran®) between four weeks and six months. Patients were identified in connection with a routine monitoring visit at the hospital laboratory. This was a one-visit open study. Those with other significant medical or surgical diseases such as malignancy, chronic obstructive lung disease, heart failure or any major psychiatric illness or dementia, were excluded. Age, gender, smoking and alcohol habits were recorded. Medical history, concomitant medication and symptom severity (mild, moderate, severe) were noted. Questions were also asked about patient's socio-economic situation. Patients gave their written consent to participate and were free to discontinue their participation in the study at any time. The study was reviewed and approved by the regional Ethics Committee of Gothenburg University. The aim was to recruit 150 patients with verified DVT.

Item generation for the DVTQOL

All discussions and interviews were done in Sweden in a Swedish population. Items for the new DVTQOL questionnaire were identified from individual interviews with DVT patients. Specialists widely experienced in anticoagulation practice (physicians and nurses) were consulted, and a thorough review of the medical literature regarding patient-reported outcomes of venous leg disorders was conducted. We searched in the Medline Database and Swedish Physician Journal for publications written in English between 1991 and 2003. We also searched for information in patient information pages on the Web (e.g. American Venous Forum). Patients were asked to identify issues and problems they had as a result of their illness. For each item, they rated the importance (important/not important). The results were expressed as frequency, i.e. the proportion of patients that experienced a particular item. Items included physical, emotional and sleep issues as well as symptoms and hassle with treatment. Even though several of the items were specific to each individual, there was considerable overlap in the item pool. A total of 65 questions were generated that were carefully formatted for gender, clarity and interpretability. Responses were arranged on a seven-point Likert scale to assess how much or how often the item described the feelings of the patient: degree of distress (not at all, minor, mild, moderate, moderate severe, severe, extremely severe) and frequency of the problem (never, hardly ever, occasionally, sometimes, frequently, most of the time, all of the time). Seven-point scales are supposed

to be easier for the patients to learn and understand and changes are easier to interpret as compared to visual analogue scales[14]. Summary scores for each of the six domains can be calculated (maximum range between 30 and 210). The higher the score, the more discomfort, distress, inconvenience and hassle patients feel. Once this preliminary set of items was developed, we administered the instrument in "face to face interviews" with eight patients. A clinician evaluation of the relevance of the 65 items selected according to the principles described above was also made. All items were written and answered in Swedish.

Patient-Reported Outcomes (PRO) instruments
Patients completed the DVTQOL-65 together with two generic health-related quality of life measures, the Swedish translations of the Short Form Survey, SF-36 (SF-36) and the EuroQol of life (EQ-5D), at their next routine visit, preferable within a week or two.

The SF-36 instrument contains 36 items that measure eight dimensions: Physical Functioning, Role limitation due to Physical health problems, Bodily Pain, General Health perceptions, Vitality, Social Functioning, Role limitations due to Emotional problems and general Mental Health. Item scores for each dimension are coded, summed and transformed to a scale from 0 to 100, with higher scores indicating better self-perceived health. The reliability and validity of the (Swedish) SF-36 is well documented [15,16] in a variety of different patient groups, including patients with vascular diseases[17].

EQ-5D is a measure of health status developed for use in evaluating health outcomes and healthcare[18,19]. It provides a simple descriptive profile and derives a single index value for heath status on which full health is assigned a value of 1 and death a value of 0 (DSI). EQ-5D describes health status in terms of five dimensions: Mobility, Self-care, Usual activity, Pain/Discomfort and Anxiety/Depression. Each dimension has three possible levels: 1-No problem, 2-Some problem and 3-Extreme problem.

Data management
Patients completed the questionnaires, using an Apple Newton hand-held electronic data capture device, prior to the actual laboratory visit in order to avoid potential bias induced by discussions on disease and dosing procedures. For compliance with study regimens, the questionnaires were administrated at the study site under the supervision of the study nurse. Medical information and clinical data were entered into electronic case report forms by the investigator and the study nurse, using a pc laptop computer. Computer-administrated electronic data collections are accepted and desirable for assessments of health-related quality of life in clinical studies since they yield high-quality data and no missing data[20]. It was well accepted among patients, the investigator and the study nurse.

Psychometric evaluation of the DVTQOL
Item reduction
Items with the following characteristics were considered for removal: 1) Semantically identical or very similar items; 2) items with a high ceiling or floor effect, i.e. items where more than 50% endorsed "no discomfort at all" or "extremely severe discomfort", "none of the time" or "all of the time"; 3) items measuring a different construct, i.e. with a low squared multiple correlation (r<0.5) with the other items; 4) items that showed redundancy of measurement by too high a correlation (alpha >0.95). Before items were removed, the clinical importance as judged by the physician and nurse in charge of the study was discussed, i.e. content validity was taken into consideration as well.

Rasch methodology
The most recent application of this methodology was in outcomes research and in instrument development[21,22]. In this study, the Rasch methodology was used to reduce the number of items in the item pool, as this was recommended in previous studies [23,24]. In the Rasch model each item is defined by a difficulty or location parameter. It assumes that the probability of a given respondent to give a "correct" answer to a particular item is a logistic function of the relative distance between the item location parameter and the respondent location parameter [25]. Rasch methodology was utilised to reduce redundant items. Items that were too "easy" or too "difficult" to endorse based on the person-item distribution and items with the same "difficulty" level were also excluded.

Factor analysis
After a first item reduction the data were re-analysed in order to explore how the selected questions were combined into relevant domains. Hence, an exploratory factor analysis was undertaken to identify the underlying concepts or domains. For this purpose a principal components factor analysis with varimax orthogonal rotation was utilised. Items with factor loadings above 0.50 were retained.

Internal consistency reliability
Cronbach's alpha[26] was used to assess the internal consistency reliability. A moderate to high alpha coefficient suggests that the items within a domain measure the same construct, which supports the construct validity as well. Alpha scores between 0.70 and 0.95 are desirable to allow for individual comparisons.

Table 1: Demographic and clinical characteristics (N = 121)

Variables			
Age:	Mean (SD)	61.2 (14.0)	
		n	**%**
Gender:	Male	61	50.4
Smoker:	Yes	24	19.8
Alcohol:	Never	9	7.4
	Occasionally	109	90.1
	Daily	3	2.5
	No symptoms	78	64.5
Clinical signs and symptoms:	Mild	24	19.8
	Moderate	18	14.9
	Severe	1	0.8
Marital status:	Married	77	63.6
Education:	High school	70	57.9
	University	52	43.0
Employment:	Full time	32	26.4
	Part time	8	6.6
	Retired and Unemployed	81	67.0
Sick leave during last 3 months	Yes	23	19.0
	SF-36	**DVT***	**Norm†**
Physical function	PF	67.3	87.9
Role physical	RP	68.0	83.2
Bodily pain	BP	71.6	74.8
General health	GH	62.9	75.8
Vitality	VT	63.7	68.8
Social function	SF	87.6	88.6
Role emotional	RE	73.8	85.7

* Deep Venous Thrombosis † Swedish normative values for the general population (n = 8930)

Construct validity

The SF-36 and EQ-5D were used to compare whether conceptually similar domains had higher correlations than conceptually unrelated domains. This was tested using correlation coefficients.

Statistical methods

Descriptive statistics (i.e. frequencies, means, standard deviations) were used to characterise the demographic data. Pearson's correlation was also used to test the inter-scale correlations of the DVTQOL. On the basis of previous experience, strong correlations were considered to be above 0.40. P-values were adjusted for multiplicity (Bonferroni)[27]; the significance level was p < 0.0005. All statistical analyses were made using SAS 8.1 software[28]. The Winstep software was used for the Rasch analysis [29]. The data quality was excellent in the present study since there were no missing data for any item on the quality of life questionnaires in the study.

Results

From a total of 351 enrolled patients, 121 (50% males; mean age 61.2 ± 14 years) with verified deep venous thrombosis (DVT) were included in the study. Patients' ages ranged from 23–79; 31% were under the age of 65. All patients were treated with warfarin (Waran®) for at least four weeks. About 20% of the enrolled patients refused or were not interested in participating in the study. These individuals, half women, were elderly people (70 ± 12 years). Two individuals discontinued participation in the study, one due to severe asthma and one without giving any specific reason. Clinical signs and symptoms (mild or moderate) were reported by 35 %. Patients were slightly overweight, with a body mass index between 25 and 26.9. Regarding comorbidity, the most common diseases, other than DVT, were hypertension, diabetes, hyperlipemi and cerebral infarction. Patient characteristics and clinical data are summarised in Table 1. Table 1 shows also the mean values of SF-36 by dimension for the DVT and Swedish normative values for the general population. DVT patients reported worse health status in

all dimensions of the SF-36 than the Swedish general population. In all dimensions, except for Social functioning and Bodily Pain, the difference was larger than 5 score units, which is considered to be clinically relevant[30]. When we matched the SF-36 scores for the age groups, elderly patients (>75 years) reported a similar health status as the general age-matched population. Women reported lower scores than men, specifically in the Pain domain.

Psychometric evaluation of the DVTQOL
Factor analysis
Exploratory factor analysis yielded six distinct factors denoting emotional distress: symptoms; limitation in physical activity; hassle with coagulation monitoring; sleep disturbance; and dietary problems. The factors with their respective factor loadings are presented in Table 2. Items with factor loadings above 0.50 were retained. Item nr. 16 had strong loading on both factor one (emotional distress) and three (limitation in physical activity); however, this item was retained because of its clinical importance as judged by clinicians and patients. In conclusion,

Table 2: Exploratory factor analysis of the final DVTQOL

Items	Factors					
	1	2	3	4	5	6
Emotional distress						
1. Feel weak or feeble	**0.66***	0.15	0.15	0.11	0.38	0.02
2. Feel anxious about your health	**0.68***	0.25	0.31	0.22	-0.02	0.35
3. Feel tired	**0.62***	0.14	0.18	0.12	0.34	0.07
4. Unable to live as you'd like	**0.81***	0.15	0.26	0.13	-0.01	0.21
5. Feel anxious about the future	**0.80***	0.08	0.24	0.06	-0.06	0.26
6. Feel irritated	**0.71***	0.26	-0.04	0.05	0.18	-0.12
7. Feel frustrated and impatient	**0.82***	0.12	0.22	0.15	0.18	0.10
Symptoms						
8. Pain in the leg	0.19	**0.64***	0.35	0.04	0.22	0.03
9. Swollen ankles	0.18	**0.65***	0.13	-0.07	0.12	-0.03
10. 'Sense of fatigue' in the leg	0.32	**0.74***	0.23	0.14	0.15	0.07
11. Cramp in the leg	-0.04	**0.62***	0.02	0.04	0.10	-0.03
12. Tension in the muscles	0.21	**0.66***	0.17	-0.04	-0.01	0.12
13. Numbness, crawling or pricking sensation	0.10	**0.72***	0.33	0.09	-0.06	0.13
14. Bruising on the leg	-0.06	**0.54***	-0.23	0.18	0.39	0.04
15. 'Feeling of heaviness' in the leg	0.35	**0.66***	0.22	0.03	0.27	-0.01
Limitation in physical activity						
16. Stumbling, falling or cutting yourself	0.42	0.07	**0.50***	0.04	0.22	0.12
17. Go for long walks	0.23	0.33	**0.79***	0.12	0.15	-0.03
18. Stand still for long periods	0.22	0.26	**0.64***	0.08	0.11	0.13
19. Refrain from physical activities	0.10	0.14	**0.83***	0.14	0.15	0.03
20. Discomfort when walking up stairs	0.39	0.26	**0.64***	-0.02	0.15	-0.08
Hassle with monitoring						
21. Irritation due to monitoring	0.13	0.06	0.09	**0.89***	-0.00	0.09
22. Inconvenience due to monitoring	0.17	0.09	0.10	**0.92***	0.02	0.05
23. Refrain from doing things due to monitoring	0.14	0.00	0.08	**0.94***	-0.04	0.05
Sleep disturbance						
24. Trouble getting to sleep	0.12	0.32	0.18	-0.08	**0.78***	0.03
25. Wake up during the night	0.39	0.22	0.16	-0.06	**0.75***	0.01
26. Not sleeping properly	0.15	0.07	0.23	0.03	**0.78***	0.10
Dietary problems						
27. Awareness of food and drink	0.04	0.05	0.04	0.07	0.12	**0.76***
28. Avoid certain food or drink	0.11	0.06	-0.03	0.12	-0.02	**0.84***
29. Ought to eat and drink	0.21	0.01	0.08	-0.03	0.03	**0.89***
Explained variance	4.85	4.09	3.29	2.79	2.58	2.43
Proportion of explained variance %	16.5	14.0	11.2	9.5	8.8	8.3

the final DVTQOL consists of six domains and 29 items.

Internal consistency reliability was satisfactory (Table 3). Each of the six dimensions had a similarly high Cronbach's alpha value ranging from 0.93 (hassle with monitoring) to 0.79 (dietary problems).

Interscale correlation
Conceptually related domains were significantly related (Table 4). Symptoms significantly correlated to emotional distress, limitation in physical activity and sleep disturbance.

Construct validity
Associations between the DVTQOL and the SF-36 scores (convergent validity) were all in the expected direction (Table 5). All SF-36 domains except for Social Functioning and the Mental Component Summary score significantly correlated to all DVTQOL domains except dietary problems and hassle with monitoring. Correlations between DVTQOL and EQ-5D are shown in Table 6. EQ-5D mobility, anxiety/depression and pain domains significantly correlated with all relevant DVTQOL domains.

Discussion
The present study was conducted to develop a new patient-based measure of health-related quality of life for use in individuals with acute DVT. In contrast to previous measures, the DVTQOL focuses on the early symptoms and problems related to anticoagulation management that patients have after a recent DVT event.

Individual DVTQOL items showed sufficient variation in the item pool that clearly grouped into six factors, reflecting emotional distress, symptoms, limitation in physical activity, hassle with coagulation monitoring, sleep disturbance and dietary problems. In the present study, the mode of therapy was an important issue as 'living with anticoagulation' is a true obstacle, as is the impact of the disease *per se*.

Table 3: Internal consistency reliability (Cronbach's alpha)

	Alpha
Emotional distress	0.91
Symptoms	0.86
Limitation in physical activity	0.86
Hassle with monitoring	0.93
Sleep disturbance	0.83
Dietary problems	0.79

The DVTQOL domains had a high degree of internal consistency, confirming its reliability. DVTQOL correlated with the relevant domains of SF-36 and EQ-5D, which provides evidence on construct validity. Interestingly, the DVTQOL hassle with monitoring domain significantly correlated with the SF-36 general health and mental health, indicating that mandatory visits to the clinic for blood monitoring interact with the perception of general health and emotional distress. Furthermore, patients reported significantly decreased HRQL compared to the general population as measured by the SF-36, regardless of gender and age. This is in agreement with Beyth and colleagues' finding [6] that patients report poorer perception of health, lower levels of physical functioning and more severe role limitations due to DVT.

In conclusion, the DVTQOL is a valid and reliable instrument for measuring HRQL in patients with recent DVT and who are currently on oral anticoagulation treatment. Recognising that instrument development and validation are by no means a one-time event, its test-retest reliability and responsiveness to change in clinical trials must be evaluated.

Table 4: Interscalecorrelations between DVTQOL domains

Domains	Emotional distress	Symptoms	Limitation in physical activity	Hassle with monitoring	Sleep disturbance	Dietary problems
Emotional distress	1.00					
Symptoms	0.49	1.00				
Limitation in physical activity	0.61	0.56	1.00			
Hassle with monitoring	0.32	0.18	0.24	1.00		
Sleep disturbance	0.45	0.50	0.48	0.04	1.00	
Dietary problems	0.33	0.15	0.16	0.16	0.15	1.00

Table 5: Correlations between domains of SF-36 and DVTQOL

SF-36 domains	DVTQOL domains					
	Emotional distress	Symptoms	Limitation in physical activity	Hassle with monitoring	Sleep disturbance	Dietary problems
Physical Functioning	**0.44**	**0.51**	**0.80**	0.09	**0.49**	0.04
Role Physical	**0.49**	**0.33**	**0.59**	0.01	**0.35**	0.19
Bodily Pain	**0.56**	**0.58**	**0.58**	0.08	**0.39**	0.24
General Health	**0.63**	**0.39**	**0.56**	**0.34**	**0.36**	0.19
Vitality	**0.74**	**0.39**	**0.50**	0.26	**0.45**	0.27
Social Functioning	**0.43**	0.30	0.26	**0.31**	0.18	0.15
Role Emotional	**0.51**	**0.35**	**0.36**	0.11	0.23	0.18
Mental Health	**0.74**	**0.39**	**0.44**	**0.33**	**0.35**	0.17
Physical Component Summary	**0.50**	**0.52**	**0.80**	0.07	**0.49**	0.15
Mental Component Summary	**0.61**	0.26	0.18	0.30	0.18	0.20

Note: Bolded coefficients are significant, $p < 0.0005$, after correction for multiplicity (Bonferroni)

Table 6: Correlations between domains of EQ-5D and DVTQOL

EQ-5D	DVTQOL domains					
	Emotional distress	Symptoms	Limitation in physical activity	Hassle with monitoring	Sleep disturbance	Dietary problems
Mobility	**-0.33**	**-0.38**	**-0.73**	-0.05	**-0.34**	-0.05
Self-care	-0.03	0.02	-0.13	-0.11	0.10	0.03
Usual activity	**-0.52**	-0.20	**-0.47**	-0.18	-0.22	-0.15
Pain/Discomfort	**-0.48**	**-0.46**	**-0.50**	-0.18	**-0.31**	-0.24
Anxiety/ Depression	**-0.60**	**-0.31**	**-0.35**	-0.19	**-0.34**	-0.25
TTO	**0.57**	**0.43**	**0.60**	0.20	**0.33**	0.21

Note: Bolded coefficients are significant, $p < 0.0005$, after correction for multiplicity (Bonferroni)

Conclusions

The DVTQOL is a short and user-friendly instrument with good reliability and validity. Its test-retest reliability and responsiveness to change in clinical trials, however, must be explored.

Authors' Contributions

EH (PhD) was responsible for study design, clinical study management, coordination and data management and was involved in the analysis and authoring process.

JC (MSc) was responsible for the statistical analysis.

KRK (PhD) gave input to the analysis and authoring process.

LS (MD) recruited patients iton the study and contributed medical expertise and comments to the manuscript.

AI (PhD) made comments to the manuscript.

IW (Prof) conceived the study.

All authors read and approved the final manuscript. The AstraZeneca internal review group approved the manuscript.

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