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Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis; from the CaVenT study (an open RCT)

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Summary:

Objectives: To investigate whether additional catheter-directed thrombolysis (CDT) improves long-term patient reported quality of life (QOL) compared to standard treatment with anticoagulation and compression stockings alone in patients with proximal deep vein thrombosis (DVT).

Design: Open-label randomised controlled trial.

Setting: 19 hospitals in the Norwegian southeastern health region.

Participants: Patients (18-75 years) with a high proximal DVT, symptoms <21 days, and no increased risk of bleeding were eligible. 189 of 209 recruited patients completed 24 months follow-up.

Interventions: Participants were randomized to additional CDT with alteplase for 1-4 days or to standard treatment only with 6 months anticoagulation and 24 months of compression stockings.

Primary and secondary outcome measures: Planned secondary outcome measures included QOL as assessed with the generic instrument EQ-5D and the disease specific instrument VEINES-QOL/Sym. Primary outcome measure was post-thrombotic syndrome (PTS) after 24 months.

Results: After 24 months there were no differences in QOL between the additional CDT and standard treatment arms; EQ-5D index was 0.80 (95% CI 0.746-0.849) and 0.84 (95% CI 0.807-0.875), VEINES-QOL score was 50.1 (95% CI 47.9-52.3) and 49.9 (95% CI 48.0-51.8), and VEINES-Sym score was 50.3 (95% CI 48.0-52.5) and 49.8 (95% CI 47.9-51.6), respectively (p-values >0.37). Independent of treatment arms, patients with PTS had poorer outcomes than patient without PTS; EQ-5D index was 0.77 (95% CI 0.730-0.819) vs. 0.86 (95% CI 0.823-0.903), VEINES-QOL score was 45.6 (95% CI 43.4-47.9) vs. 54.2 (95% CI 52.8-55.6), and VEINES-Sym score was 45.0 (95% CI 42.7-47.2) vs. 54.8 (95% CI 53.5-56.0), respectively (p-values <0.001).

Conclusions: QOL did not differ between patients treated with additional CDT compared to standard treatment alone. Patients who developed PTS reported poorer QOL and more symptoms than patients without PTS. QOL should be included as an outcome measure in clinical studies on patients at risk of PTS.

Trial registration: NCT00251771

Article summary

Article Focus

- Assessment of patient reported quality of life may provide meaningful information not captured by clinical scores and other traditional health outcome measures.
- Additional catheter-directed thrombolysis for proximal deep vein thrombosis improves long-term clinical outcome by reducing post-thrombotic syndrome and is likely to be a cost-effective alternative to standard treatment alone.
- Our objective was to investigate whether additional thrombolysis also improves long-term quality of life compared to standard treatment alone.

Key Messages

- Quality of life did not differ between patients allocated thrombolytic therapy compared to control patients who receive standard anticoagulation and compression stockings only.
- Patients who developed post-thrombotic syndrome had poorer generic and disease specific quality of life scores compared to patients without post-thrombotic syndrome.
- Quality of life assessment should be among the long-term outcome measures in clinical research on patients who are at risk of developing post-thrombotic syndrome.

Strengths and Limitations

- A robust study design where patient reported quality of life was assessed using validated generic and disease-specific instruments within the setting of a multicenter open-label randomized controlled trial.
- The study was designed to detect a difference in the frequency of post-thrombotic syndrome between the two treatment arms and may have been underpowered to detect a clinically meaningful difference in quality of life.
- More longitudinal assessments of quality of life would have allowed for better explanatory analyses, and may have added to the interpretation of clinically meaningful differences in the disease specific quality of life scores.

Introduction

Following standard treatment including anticoagulation and compression stockings, still at least 1 in 4 are at risk of developing a post-thrombotic syndrome (PTS) after suffering a proximal deep vein thrombosis (DVT) [1-3]. PTS is characterized by persistent pain, heaviness, swelling, and deterioration of the skin. Previously in the CaVenT Study we have shown that additional catheter-directed thrombolysis (CDT) in patients with high proximal DVT and low risk of bleeding, reduced the frequency of PTS from 56% to 41% (p=0.047) after 2 years and that CDT is likely to be a cost-effective alternative to standard treatment only [4,5]. However, as PTS is a chronic condition associated with substantial morbidity and with no healing treatment options, patient reported assessment of both generic and disease-specific health-related quality of life (QOL) including the impact on health and daily functioning may provide meaningful information not captured by clinical scores and other traditional health outcome measures. Development of PTS has been shown to be a principal determinant of QOL following DVT of the lower limb; however, there is currently no gold standard for the PTS diagnosis [6]. We aimed at investigating whether additional CDT for a high proximal DVT improved long-term QOL compared to standard treatment alone.

Materials and methods

Study population

Patients were recruited as part of the CaVenT study, an open randomized controlled trial (RCT), from 19 hospitals within the South-Eastern Norway Regional Health Authority, which serves a population of 2.6 million people. Patients aged 18–75 years with a first-time objectively verified acute high proximal DVT, defined as thrombus in mid-thigh level or higher, and with a low risk of bleeding, were eligible for inclusion if symptoms had lasted <21 days. Complete eligibility criteria and trial profile have been

reported previously [5,7]. Patients were randomly assigned, using sealed numbered envelopes, to standard treatment with at least 6 months of anticoagulation and compression stockings for 24 months or to CDT with alteplase for 1-4 days in addition to standard treatment; the treatment strategies have previously been reported in detail [5,8]. Prior to treatment allocation, written informed consent was obtained by the local trial site investigator. The study protocol was approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Medicines Agency, and was registered at www.clinicaltrials.gov with the unique trial identifier NCT00251771.

Variables and instruments

Long-term quality of life

After 6 and 24 months follow-up the patients completed a self-reporting questionnaire including the validated Norwegian versions of the generic instrument EQ-5D (www.euroqol.org) and the disease-specific QOL instrument VEINES-QOL/Sym [9,10]. The VEINES-QOL/Sym comprises 26 items regarding problems of the lower limbs [4]. The instrument measures symptoms, limitations in daily activity and psychological impact during the previous 4 weeks, and change over the past year. Responses are rated on 2- to 7-point descriptive scales, and two summary scores are computed. The VEINES-QOL summary score assesses QOL, and the VEINES-Sym score is a subscale that measures symptom severity only. Higher scores represent better QOL and/or fewer symptoms, and a difference or change of ≥4 points has been suggested to represent a clinically meaningful difference [10].

The EQ-5D is a preference-based generic instrument for describing and valuing QOL, and is a widely used health measure outcome in clinical trials and cost-effectiveness and cost-utility analyses. This descriptive classification system comprises the five items mobility, self-care, activity, pain, and anxiety; each with the three levels reflecting the patient's status that particular day. The scoring gives a single

number/health status index ranging from 0 (dead) to 1 (best possible health). A difference or change in this index of ≥0.08 is likely to represent a clinically meaningful difference [11,12].

Assessment of post-thrombotic syndrome

In the absence of a gold standard for a PTS diagnosis, the Villalta score has been recommended for PTS assessment in clinical trials [13]. This score includes the five patient-rated symptoms pain, cramps, heaviness, paresthesia, pruritus, and the six clinician-rated signs edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, and redness. Each sign or symptom is rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and summed to produce a total score, where less than 5 indicates no PTS, 5–14 indicates mild or moderate PTS, and 15 or more (or presence of venous ulcer) indicates severe PTS.

Statistical analysis and sample size

Health related QOL was among the pre-specified secondary outcomes of the CaVenT Study, while the primary outcome of PTS after 2 years was the basis for the sample size calculation [7]. For all patients a EQ-5D summary index was calculated based on values from a Danish population as no Norwegian algorithm exists [14]. Scores for VEINES-QOL and VEINES-Sym were computed using standard scoring algorithms obtained from the authors [10]. Statistical analyses were by intention to treat. When comparing dichotomous variables between groups, a two-sided chi-square test was used. Normal distribution was tested visually using plots, followed by comparing non-normally distributed continuous variables between independent groups with a two-sided Mann-Whitney U test. Findings with p-values less than 0.05 were deemed statistically significant. The statistical analyses were performed using the statistical package SPSS, version 18.0 (SPSS Inc, Chicago, IL, USA).

Results

209 patients with a high proximal DVT were recruited and randomized to additional CDT or to standard treatment alone during 2006-2009. Table 1 shows the demographic and clinical characteristics of the 189 patients with complete 2 years follow-up included in the present analysis; 90 in the CDT group and 99 controls. Mean age was 51.5 years (SD 15.8) and 70 (37%) participants were female. Mean duration of symptoms before diagnosis and start of treatment was 6.6 days (SD 4.6). Most baseline demographic and clinical characteristics, including VEINES-QOL/Sym and EQ-5D scores, were fairly equally distributed between the two treatment groups. Details on the study participants including the complete trial profile have been reported elsewhere [5].

Table 1 Demographic and clinical characteristics

	Adjunctive catheter-directed thrombolysis (n=90)		Standard treatment only (n=99)	
Baseline				
Age (years)	53.3	(15.7)	50.0	(15.8)
Women	32	(35.6)	38	(38.4)
Duration of symptoms of acute DVT (days)	6.4	(4.4)	6.8	(4.8)
EQ-5D index	0.46 (0.372-0.548)		0.63 (0.422-0.844)	
VEINES-QOL score	50.2 (48.2-52.3)		50.1 (47.8-52.4)	
VEINES-Sym score	50.4 (48.4-52.5)		49.5 (47.2-51.8)	
No risk factor for venous thrombosis	31	(34.4)	26	(26.3)
Transient risk factors for venous thrombosis				
Surgery previous 3 months	15	(16.7)	13	(13.1)
Trauma previous 3 months	10	(11.1)	15	(15.2)
Short term immobility	20	(22.2)	19	(19.2)
Infection previous 6 weeks	6	(6.7)	9	(9.1)
Pregnancy previous 3 months	5	(5.6)	3	(3.0)
Hormonal replacement therapy	4	(4.4)	6	(6.1)
Oral contraceptive pill	3	(3.3)	11	(11.1)
Permanent risk factors for venous thrombosis				
Previous venous thrombosis	9	(10.0)	9	(9.1)
Cancer	3	(3.3)	1	(1.0)
Obesity	9	(10.0)	11	(11.1)
Inflammatory bowel disease	0	(0.0)	3	(3.0)
1st degree relative with venous thrombosis	9	(10.0)	13	(13.1)
Two risk factors for venous thrombosis	26	(28.9)	18	(18·2)
Three risk factors for venous thrombosis	10	(11.1)	14	(14.1)
Thrombophilia				
Heterozygous F5 6025 polymorphism	23	(25.6)	22	(22.2)
Homozygous F5 6025 polymorphism	1	(1.1)	4	(4.0)
Other thrombophilic factor(s)	15	(16.7)	13	(13.1)
At 24 months follow-up				
Daily wear of compression stockings class II	57	(63.3)	51	(51.5)
Recurrent venous thromboembolism	10	(11.1)	18	(18.2)
Diagnosed with cancer	4	(4.4)	7	(7.1)

DVT=deep vein thrombosis. Data are mean (SD) for time, mean (95% CI) for scores, or n (%)

There were no differences between the two treatments groups in mean generic QOL scores, disease-specific QOL scores, or symptom severity score after 24 months follow-up (Table 2). Both VEINES-QOL and VEINES-Sym scores obtained at 6 months follow-up were higher in the CDT arm compared to control patients (p=0.048 and p=0.016, respectively), however, the differences of 3.2 and 2.4 points, respectively, were below the ≥4 points cut-off for a clinically meaningful difference. The 6 months' EQ-5D score did not differ between the treatment groups.

Table 2 Generic and disease-specific quality of life and symptom severity according to treatment allocation

		Additional catheter-directed thrombolysis (n=90)	Standard treatment only (n=99)	P-value*
24 months				
Generic QOL	EQ-5D	0.80 (0.746-0.849)	0.84 (0.807-0.875)	0.705
Disease-specific QOL	VEINES-QOL	50.1 (47.9-52.3)	49.9 (48.0-51.8)	0.595
	VEINES-Sym	50.3 (48.0-52.5)	49.8 (47.9-51.6)	0.368
6 months				
Generic QOL	EQ-5D	0.82 (0.780-0.856)	0.81 (0.777-0.852)	0.893
Disease-specific QOL	VEINES-QOL	51.3 (49.2-53.4)	48.9 (46.8-50.9)	0.048
	VEINES-Sym	51.7 (49.8-53.7)	48.5 (46.4-50.6)	0.016

Data are mean scores (95% CI). *Mann Whitney U test

Independent of treatment allocation, the mean VEINES-QOL and VEINES–Sym scores were lower in patients who developed PTS compared to patients without PTS at both 6 and 24 months follow-up (p-values <0.001) (Table 3). The differences were 6.0 points after 6 month, and increased to 8.6 and 9.8 points, respectively, after 24 months. The mean EQ-5D index was 0.09 points lower in PTS patients at 24 months follow-up (p<0.001); however, there was no difference after 6 months. When looking at the PTS cases only at 24 months follow-up the three scores did not differ between the two treatment groups (p>0.8, data not shown).

Table 3 Generic and disease-specific quality of life and symptom severity according to PTS development

		PTS (n=92)	No PTS (n=97)	P-value*
24 months				
Generic QOL	EQ-5D	0.77 (0.730-0.819)	0.86 (0.823-0.903)	<0.001
Disease-specific QOL	VEINES-QOL	45.6 (43.4-47.9)	54.2 (52.8-55.6)	<0.001
	VEINES-Sym	45.0 (42.7-47.2)	54.8 (53.5-56.0)	<0.001
6 months				
Generic QOL	EQ-5D	0.80 (0.770-0.837)	0.82 (0.788-0.869)	0.062
Disease-specific QOL	VEINES-QOL	46.8 (44.6-49.0)	53.0 (51.3-54.7)	<0.001
	VEINES-Sym	46.9 (44.6-49.1)	53.0 (51.4-54.6)	<0.001

Data are mean scores (95% CI). * Mann Whitney U test

Looking at individual items concerning problems with mobility (EQ-5D) and limitations in daily activities at home, work or during leisure time (VEINES-QOL) there was no differences between the two treatment groups; however patients with PTS reported more problems and limitations than patients without PTS (data not shown).

The proportions of patients that reported clinically meaningful changes over time during the 6 to 24 months follow-up did not differ between the two treatment groups with regards to the two QOL scores, and the majority of patients reported no QOL change (table 4). In both groups 1 in 5 patients reported worsening of the Sym score, and 32% of control patients reported improved symptom severity compared to 16% treated with CDT (p=0.029).

Table 4 Changes in generic and disease-specific quality of life and symptom severity during 6 to 24 months follow-up*

		Additional catheter-directed thrombolysis (n=90)		Standard treatment only (n=99)		P-value**
		n	% (95% CI)	n	% (95% CI)	
Generic QOL	EQ-5D improved	15	16.7 (10.0-24.4)	24	24.5 (16.6-33.4)	0.233
	EQ-5D worsened	22	24.4 (16.4-34.1)	16	16.3 (9.9-24.4)	
Disease-specific QOL	VEINES-QOL improved	17	19.5 (11.8-28.0)	27	27.3 (19.2-36.7)	0.462
	VEINES-QOL worsened	19	21.8 (13.6-30.4)	19	19.2 (12.3-27.8)	
	VEINES-Sym improved	14	15.9 (9.1-24.2)	32	32.3 (23.7-42.0)	0.029
	VEINES-Sym worsened	20	22.7 (14.5-31.7)	21	21.2 (14.0-30.1)	
		PTS (n=92)		No PTS (n=97)		P-value*
		n	% (95% CI)	n	% (95% CI)	
Generic QOL	EQ-5D improved	15	16.5 (9.8-24.9)	24	24.7 (16.9-34.0)	0.041
	EQ-5D worsened	25	27.5 (18.8-36.9)	13	13.4 (7.7-21.3)	
Disease-specific QOL	VEINES-QOL improved	21	23.3 (15.1-32.2)	23	24.0 (16.1-32.9)	0.017
	VEINES-QOL worsened	26	28.9 (19.8-38.1)	12	12.5 (6.9-20.1)	
	VEINES-Sym improved	20	22.0 (14.2-31.0)	26	27.1 (18.7-36.3)	0.017
	VEINES-Sym worsened	28	30.8 (21.7-40.4)	12	13.5 (7.7-21.3)	

*A meaningful change was defined as ≥4 points for VEINES-QOL/Sym scores and ≥0.08 for the EQ-5D index; improvement or worsening below this was registered as no change. **chi-square test

Correspondingly, when comparing proportions with meaningful changes in the three different scores during follow-up in patients with and without development of PTS independent of treatment allocation, the EQ-5D and VEINES-QOL scores worsened in nearly 30% of patients with PTS compared to 13% of patients who did not develop PTS (p=0.041 and p=0.017, respectively)(table 4). Finally, 31% patients with PTS reported worsening of the Sym score compared to 14% of patients without PTS (p=0.017).

Discussion

We have previously shown that after a high proximal DVT additional CDT reduces the frequency of PTS [5]. Nevertheless, in the present report we found no differences in long-term QOL between patients

treated with additional CDT compared to patients who received standard treatment with anticoagulation and compression stockings alone. However, patients who developed PTS after 24 months reported poorer QOL with both EQ-5D and VEINES-QOL, and more symptoms on Sym score compared to patients without PTS. This finding is in line with other reports, and the VEINES-QOL/Sym scores were in similar ranges as previously reported in DVT populations [6,15-17].

To our knowledge we are the first to investigate QOL after CDT in a well-designed study using validated QOL instruments and PTS assessment. We have recently in a retrospective study of 71 patients previously treated with CDT shown that VEINES-QOL/Sym scores were poorer in patients with established PTS compared to no PTS (median) 6 years after the index DVT, and poorer in patients compared to a control group without previous DVT [17]. Another retrospective study of corresponding size found improved QOL and less post-thrombotic symptoms in patients treated with CDT compared to similar patients treated with anticoagulation only; however, this study did not use a disease-specific QOL instrument or a validated assessment of PTS [18]. This finding was not supported in our RCT, and long-term QOL may not represent a significant secondary efficacy outcome after CDT.

The baseline scores were obtained within 1-2 days following the verification of the acute DVT, and the low EQ-5D scores are likely to reflect the patients' medical emergency situation at that time point. The items of the VEINES instrument are concerned with "the last 4 weeks" and mean symptom duration among study participants was only 6-7 days and, as indicated by the relatively better scores, the VEINES-QOL/Sym baseline results are likely to reflect a longer period including time before symptom onset. Finally, QOL is a more appropriate outcome for chronic conditions, and together with our lack of longitudinal assessments, we did not include baseline scores in our analyses.

The finding that more control patients reported a meaningful improvement in the Sym score during follow-up than patients treated with CDT, should be interpreted with caution as the 6 months Sym score

was higher in the CDT arm, though this difference did not reach a meaningful difference of at least 4 points.

We regard our study population to be representative and the CDT procedure to be applicable in a clinical setting [5]. However, due to the open label design, bias in patient reported outcomes like QOL cannot be excluded, and it is uncertain in what direction such bias would impact the results. Finally, two ongoing RCTs; the American ATTRACT study and the DUTCH CAVA trial, will provide additional data to the field of QOL after CDT treatment (www.clinicaltrials.gov; NCT 00790335 and NCT 00970619).

The Villalta scale has been validated and recommended for assessment of PTS [13,19], however, as no gold standard exists and a relatively high frequency of PTS was found in both treatment arms, concerns have been raised about the clinical benefit of CDT as shown in the CaVenT study [5,20]. The present findings of poorer QOL in those who developed PTS, as obtained within an appropriately designed RCT, underpin our perception that the 15% absolute reduction in PTS as assessed with the Villalta scale and shown in CavenT, does represent a clinically meaningful effect of additional CDT [5].

It has been recommended to include QOL as part of the long-term follow-up assessment of patients at risk of PTS [6], and a recent review "recommend(s) that the Villalta score combined with a venous disease-specific quality-of-life questionnaire be considered as the "gold standard" for the diagnosis and classification of PTS" [21]. The VEINES questionnaire would be a candidate, but such a combination must be validated in properly designed studies and take into account the apparent overlap between the Villalta score and the VEINES-scores; all items in the Sym score are covered in the QOL score, 2/3 of Sym items are covered in Villalta, and 1/4 of the QOL items are covered in Villalta. Finally, 5 of 11 items in Villalta score, i.e., the symptom rating, are in fact patient reported outcomes (PRO), and combining with another patient PRO instrument should seek to avoid assessing the same thing twice over.

The generic instrument EQ-5D showed a clinically meaningful and statistically significant poorer QOL measure in patients who developed PTS, indicating that this preference based questionnaire can be included in studies on PTS and thereby allowing analyses on utilities and cost-effectiveness for decision making [22]. However, the sample size was powered to detect a 15% reduction in PTS after additional CDT, not improvement in QOL, which was among the secondary outcome measures. Accordingly, the negative finding in terms of no difference in QOL between the treatment arms, may relate to the sensitivity of the instruments, the prevalence of PTS, and the lack of power to detect a statistically significant difference. Finally, the VEINES scores differed significantly between patients with PTS vs. no PTS, and the magnitude of the mean difference was 6 points or higher. This has been reported to represent meaningful differences, but a well-established definition or cut-off for a clinically meaningful difference in VEINES scores is lacking, and also this limitation must be taken into account when interpreting the results [10].

In conclusion, there was no difference in long-term QOL between patients with a high proximal DVT treated with additional CDT compared to those treated with anticoagulation and compression therapy alone. Patients who developed PTS reported poorer QOL and more symptoms than patients without PTS. This is in line with previous reports, and supports the use of QOL as an outcome measure in clinical research on patients who are at risk of PTS.

Addendum: role of each author

T Enden: Design of study, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript, obtaining funding

H S Wik: Acquisition of data, interpretation of data, critical revision of manuscript

A K Kvam: Interpretation of data, and critical revision of manuscript

Y Haig: Acquisition of data and critical revision of manuscript

N E Kløw: Design of study, acquisition of data, critical revision of manuscript, obtaining funding

P M Sandset: Design of study, acquisition of data, critical revision of manuscript, obtaining funding

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Disclosure of Conflicts of Interests

The authors state that they have no conflict of interest.

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Data sharing

Unpublished data from the CaVenT study are available to T Enden, Y Haig, NE Kløw and PM Sandset through authorized access to the research server at Oslo University Hospital, Ullevål

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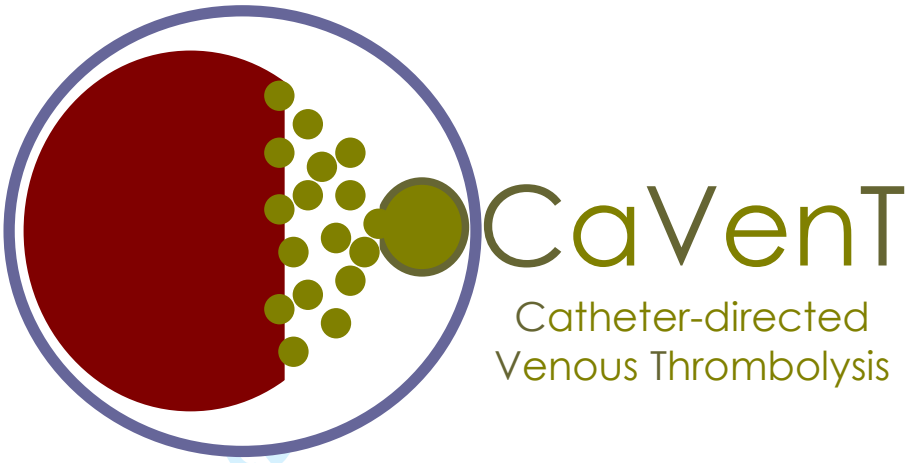
CONSORT Statement 2001 - Checklist

Items to include when reporting a randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	2
INTRODUCTION Background	2	Scientific background and explanation of rationale.	3
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	3
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	4
Objectives	5	Specific objectives and hypotheses.	3
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	5
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	5
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	3,4
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	3
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	4
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	3
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	5
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	6
Recruitment	14	Dates defining the periods of recruitment and follow-up.	5
Baseline data	15	Baseline demographic and clinical characteristics of each group.	6 + table 1
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	5 + table 2
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	8 + tables 2,3,4
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	3
Adverse events	19	All important adverse events or side effects in each intervention group.	Previous publication(s)
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	11-13
Generalizability	21	Generalizability (external validity) of the trial findings.	12
Overall evidence	22	General interpretation of the results in the context of current evidence.	11-13

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; **357**:1191-1194.



Protocol

Catheter-directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis - an open Randomized, Controlled, Clinical Trial

The CaVenT Study Group

Working Protocol - Amendment 04 – August 2007

CONTENTS

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1 SYNOPSIS

Deep vein thrombosis (DVT) is a severe disease which may cause severe disability and which is sometimes fatal. Conventional treatment with low molecular weight heparin (LMWH) and oral antiocoagulants is associated with some degree of long-term sequalae, i.e., post-thrombotic syndrome (PTS), in more than 60-80% of the patients. Systemic thrombolytic therapy reduces the risk of PTS, but is associated with an unacceptably high risk of bleeding complications, many being disabling or fatal. Catheter-directed thrombolytic (CDT) therapy is a novel treatment modality which has been introduced in many hospitals worldwide. Low dose fibrinolytic agents are delivered continuously and directly into the thrombus through a catheter until thrombus has dissolved. Although many, mostly small series, have suggested a beneficial effect of this costly treatment in terms of increased patency of the veins and improved short term functional outcome, there are no randomized clinical trials documenting its short and long-term efficacy and safety.

The present study is a randomized, open-label, multi-center clinical trial among hospitals in the Eastern and Southern Norway Health Authorities (Helse Øst and Sør). Patients with acute iliofemoral vein thrombosis will be randomized to either conventional treatment or CDT in addition to conventional treatment. Main outcome parameters are patency rates at 6 months and prevalence of PTS at 24 months. A number of secondary outcomes include bleeding complications, recurrent thrombosis, quality of life (QoL), markers of importance for successful lysis and recurrent thrombosis, and whether PTS is related to patency at the end of treatment.

Our main short-term hypothesis is that CDT of first-time acute DVT will increase patency of the affected iliofemoral vein segments after 6 months from <50% on conventional therapy to >80% after CDT. Our main long-term hypothesis is that CDT will improve long-term functional outcome, i.e., risk of PTS, assessed after 2 years, from >25% on conventional treatment to <10% after CDT. The estimated sample size is at least 100 evaluable patients in each group using a statistical significance (α) = 5% and a statistical power (1-β) = 80%.

2 BACKGROUND

Deep vein thrombosis (DVT) of the lower extremities is a common disease, which is associated with significant morbidity. The incidence of DVT is estimated as 1 event per 1,000 per year, which ranks it as one of the more common cardiovascular disorders [1]. Furthermore, DVT is associated with several important short- and long-term outcomes [2]. Short-term there are symptoms of pain and swelling due to inflammation and obstruction. In a small minority of cases, the condition leads to phlegmasia cerulea dolens in which extensive venous obstruction leads to ischemia or infarction of the extremity. Lastly, DVT can also lead to pulmonary embolism (PE), which can be fatal. Long-term sequelae of DVT include recurrent venous thromboembolism (VTE), post-thrombotic syndrome (PTS), and chronic thromboembolic pulmonary hypertension.

Anticoagulation therapy is the basic treatment of DVT[3], which purpose is to inhibit the thrombotic process and the inflammatory response so that the thrombus can be cleared by endogenous fibrinolysis. Anticoagulation therapy thereby alleviates acute symptoms, prevents PE, and recurrent events. In most cases, anticoagulation is achieved acutely with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) therapy, followed by long term anticoagulation with oral vitamin K antagonists (eg warfarin).

Anticoagulation therapy is highly efficacious for the prevention of recurrent VTE, PE, and death[3;4], but the ability to prevent PTS as an outcome is less clear[5]. PTS is thought to be a result of residual venous stenosis and damage to the venous valves which together cause venous hypertension. Venous hypertension leads to chronic edema and fibrin deposition in the interstitial tissues, which in turn bring about poor oxygen exchange. Insufficient oxygenation induces skin changes, pain and, in severe cases, chronic ulceration.

Several studies have addressed the epidemiology of PTS[5;6], i.e., the incidence of PTS over time, its risk factors, the relationship between vein patency and development of PTS, and the usefulness of compression stockings to prevent PTS following a first episode of acute DVT treated with anticoagulation alone[5;7-10]. The incidence of moderate or severe PTS varied across these studies, but in general increased over time. Moderate to severe PTS developed in 2% to 11% of patients with DVT provided that compression stockings were worn at some early point after the acute DVT. Elastic compression stockings may reduce the risk of PTS by approximately 50%[11;12]. Risk factors for severe PTS identified by some, but not all of these studies, were recurrent ipsilateral DVT, extent of initial thrombus, and obesity. Although the role of return of vein patency has not been established, it may still be an appropriate surrogate for long-term outcomes.

Thrombolytic agents, such as streptokinase (SK), urokinase (UK), and recombinant tissue plasminogen activator (rt-PA) are, theoretically, ideal adjuvants to standard anticoagulation therapy because they potentially dissolve thrombi, promote early vein recanalization, and thereby, minimize vein stenosis and valve dysfunction[13;14]. Therefore, treatment strategies incorporating these agents with anticoagulation may be more effective than those using anticoagulation alone for the prevention of PTS. In addition, in the minority of cases with phlegmasia cerulea dolens, thrombolytic therapies may prove limb saving. However, despite the theoretical advantages and a history of more than 30 years of use, thrombolytic therapy has not been widely embraced for DVT treatment due to poor

Table 1 Summary results for the trials comparing streptokinase (SK) to intravenous unfractionated heparin (UFH); Values in parentheses are percent of cases.

Study	**SK**		**UFH**		**Odds Ratio (95% CI)**	
	Events/N	**(%)**	**Events/N**	**(%)**		
	Efficacy = significant lysis					
Robertson 1[15]	5/8	(63)	1/8	(13)	9.4	(0.9, 98.1)
Kakkar[16]	7/10	(70)	2/20	(20)	8.2	(1.1, 58.7)
Robertson 2[17]	5/9	(56)	1/7	(14)	6.2	(0.6, 62.1)
Tsapogas[18]	10/19	(53)	1/15	(7)	12.6	(1.7, 96.5)
Porter[19]	13/24	(54)	8/26	(31)	2.6	(0.8, 8.2)
Elliot[20]	17/26	(65)	0/25	(0)	188.4	(3.4, 10494)
Arnesen[21]	15/21	(71)	5/21	(24)	7.6	(1.9, 29.3)
Total	**72/117**	**(62)**	**18/112**	**(16)**	**8.5**	**(4.4, 16.3)**
	Major Hemorrhage					
Robertson	2/8	(25)	0/8	(0)	11.9	(0.2, 843)
Kakkar	3/30	(39)	2/10	(20)	1.6	(0.2, 11.8)
Tsapogas	4/19	(21)	0/15	(0)	17.0	(0.3, 1022)
Porter	4/24	(17)	1/26	(4)	4.2	(0.5, 34)
Elliot	2/26	(8)	0/25	(0)	9.4	(0.1, 607)
Schulman[22]	3/17	(18)	1/19	(5)	3.3	(0.4, 29.4)
Arnesen	2/21	(10)	2/21	(10)	1.0	(0.1, 7.1)
Total	**20/115**	**(16)**	**6/124**	**(5)**	**3.9**	**(1.5, 10.3)**

Table 2 Summary results for the trials comparing urokinase (UK) to intravenous unfractionated heparin (UFH); Values in parentheses are percent of cases.

Study	UK Events/N	(%)	UFH Events/N	(%)	Odds Ratio (95% CI)	
	Efficacy = significant lysis					
Goldhaber[23]	1/8	(13)	1/9	(11)	1.1	(0.1, 2.9)
Kiil[24]	1/11	(9)	1/9	(11)	0.8	(0, 14.9)
Total	**2/19**	**(11)**	**2/18**	**(11)**	**1.0**	**(0.1, 7.2)**
	Major Hemorrhage					
Goldhaber	0/8	(0)	1/9	(11)	0.2	(0, 16.3)
Kiil	0/11	(0)	3/9	(33)	0.8	(0, 2.8)
Total	**0/19**	**(0)**	**4/18**	**(22)**		

Table 3 Summary results for the trials comparing recombinant tissue plasminogen activator (rt-PA) to intravenous unfractionated heparin (UFH); Values in parentheses are percent of cases.

Study	rt-PA Events/N	(%)	UFH Events/N	(%)	Odds Ratio (95% CI)	
	Efficacy = significant lysis					
Goldhaber[23]	15/53	(28)	0/12	(0)	10.1	(0.8, 999)
Turpie 2[25]	6/29	(21)	2/30	(7)	3.7	(0.6, 29)
Turpie 1[25]	7/12	(58)	0/12	(0)	34.1	(2.0, 999)
Total	**28/94**	**(30)**	**2/54**	**(4)**	**11.7**	**(2.6, 53)**
	Major Hemorrhage					
Goldhaber	1/53	(2)	0/12	(0)	0.7	(0.01, 999)
Turpie 2	0/29	(0)	0/30	(0)	0.3	(0, 22000)
Turpie 1	1/12	(0)	0/12	(0)	1.0	(0.02, 43)
Verahaeghe[26]	0/11	(0)	3/9	(33)	7.3	(0, 2.8)
Total	**0/105**	**(2)**	**3/63**	**(48)**	**0.4**	

documentation of its efficacy and high short-term risk of bleeding[27]. Overall only a few hundred patients have been evaluated in randomized clinical trials. The effects of SK treatment versus heparin are summarized in Table I, the effects of urokinase versus heparin in Table II, and that of rt-PA versus heparin in Table III. The overall clinical effects are shown in Table IV.

Table 4 Summary results of all trials of thrombolytic therapy for acute DVT (after[13]).

Treatment	Success rate (% with significant lysis)	Major hemorrhage (%)
Unfractionated heparin	12	6
SK	62	16
SK high dose	Uninterpretable	Uninterpretable
SK low dose	27	15
UK	11	0
rt-PA	30	8
rt-PA high dose	6	29
rt-PA local administration	27	10
Catheter directed (UK and rt-PA) (no randomized clinical trials)	83	11

Several published studies using ultrasound imaging have demonstrated considerable endogenous ability to lyse thrombi after conventional anticoagulation therapy[2]. One year after acute DVT, somewhere between 30% and 73% of patients will normalize their ultrasound findings. Earlier in the disease course, patency rates are lower, demonstrating that over time there is continued recanalization of the vein. The studies do not describe PTS incidence and whether or not development of the condition correlates with recanalization status. Without this information, it is difficult to answer the important question of whether or not early recanalization protects against development of PTS.

Catheter-directed thrombolytic therapy (CDT) is a relatively new technique for treatment of DVT[13;28] and its efficacy has recently been reviewed[29]. It involves application of the thrombolytic agent directly into the thrombus using a catheter with multiple side holes. The catheter is passed into the clot under radiographic guidance. The venous puncture may be central or peripheral to the thrombosed vein. For thrombolysis of the pelvic and the femoral veins, the access was in the early studies of the internal jugular, or the contralateral or ipsilateral femoral veins. Subsequent investigators have used the ipsilateral popliteal vein with success and this appears to be the site of choice. The thrombolytic agent is administered over 1-4 days until dissolution of the clot is apparent. Both UK, alteplase (Actilyse®), reteplase (Rapilysin®) and tenecteplase (Metalyse®) has been used, but UK is no longer available in the market, and only alteplase may be given as a continuous iv infusion, preferably at 0.001-0.02 mg/kg/hour[30;31]. Heparin therapy should be given concomitantly intravenously probably at subtherapeutic doses[29;30;32;33], corresponding to a 1.2-1.7 times prolongation of aPTT.

The decision to discontinue the drug is based on daily venographic examinations through the indwelling catheter. Depending on the findings the catheter may be pulled out, the infusion continued, or the catheter repositioned. To obtain flow in the veins balloon inflation may be performed at the follow-up. Thrombolytic agents are given until there is no more evidence of thrombosis or until there is little improvement in venographic appearance. After 72-96 hours thrombolysis is discontinued. Adjuvant therapies include angioplasty, angioplasty with stents, thrombectomy, and surgically created arterio-venous fistulas.

So far, there are no randomized clinical trials with long-term follow-up on the efficacy of CDT therapy, but at least 15 case series have been reported[29;34-37]. Combining the studies, 263 patients received this type of therapy for thrombosis of the iliofemoral veins or inferior vena cava. 221 (84%) patients were considered to have successful short-term outcomes based on venographic appearance and 13 (4.9%) patients had bleeding severe enough to warrant transfusion. Long term outcomes were not reported, and the authors did not describe the proportion of patients requiring adjuvant therapy.

A National DVT Registry was established in North-America to analyze results in a large number of patients treated with CDT[38]. This registry included 473 patients with documented lower extremity DVT treated with CDT, but follow-up data included only 287 patients who received 312 treatments. Thrombi subjected to lysis included either ilio-femoral vein thrombosis in 71% of cases and femoro-popliteal vein thrombosis in 25% of cases. The mean age of patients was 47.5 years and the mean duration of infusion was 53 h. All patients had six months of therapy with oral anticoagulants following CDT and many had heparin as well. Complete lysis was obtained in 31% of patients, 50-99% lysis in 52% and <50% lysis in 17%. Successful lysis was not related to location of the thrombus. The overall primary patency rate was 80% at 12 months, with better patency for ilio-femoral segments than the femoro-popliteal segments. Major bleeding complications occurred in 11% of patients; 39% of these at the venous insertion site, 13% were retroperitoneal hematoma. Minor bleeding events occurred in 16% of patients, again most often at the venous entry site. There was one fatal intracranial hemorrhage, one subdural hematoma, and 6 pulmonary emboli of which one was fatal. Thus, the overall mortality rate from lysis was 0.4%. There was no data on PTS.

If the PTS differs between standard therapy and thrombolytic therapy then the quality of life may differ between patients also. Comerota assessed health-related quality of life in patients after CDT therapy compared to a group of patients treated with standard anticoagulation therapy[39]. The delayed functional outcome and wellbeing scores were significantly better in the thrombolytic therapy group. Although this study had some methodological shortcomings[13], the findings are still suggestive that thrombolytic therapy may offer improved quality of life in patients who achieve successful thrombolysis.

Compared to historical data of anticoagulation and intravenous thrombolysis, CDT probably has higher recanalization rates. The studies so far, indcluding one RCT with 6 months follow-up and 35 patients[40], have been promising, but unfortunately no high-quality randomized studies with long-term follow-up have been performed. Experimental data indicate that valves of the femoral veins may be preserved[41;42]. It is therefore possible that PTS may be reduced. However, long term studies have not been performed. In the absence of well-designed randomized clinical studies both for early findings, the implications of early patency for long-term clinical results, the complications, and the costs related to treatment, CDT therapy for DVT should at present be considered experimental treatment. Still, some Norwegian hospitals including Aker and Ullevål University Hospitals, Rikshospitalet, and the Østfold Hospital Trust Fredrikstad, do provide this high-intensive treatment to selected patients. A case-series with careful follow-up at Aker University Hospital has recently been published[31].

In the present study, we aim to investigate the role of CDT therapy for treatment of acute DVT as compared with established treatment with low molecular weight heparin. The study will be an open-label, randomized study of patients with first-time acute DVT of the affected limb, and our major outcome parameter will be the frequency of PTS as related to early venographic patency. The results of this study have the potential to properly define the role of this costly treatment in the future.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVES

To investigate whether catheter-directed thrombolytic therapy for first-time acute DVT of the iliofemoral veins may:

3.1.1 increase patency rate at 6 months.

3.1.2 reduce the risk of PTS at 2 years.

3.2 SECONDARY OBJECTIVES

3.2.1 To investigate frequency of clinically relevant bleeding related to the procedure.

3.2.2 To investigate effects on quality of life (QoL).

3.2.3 To investigate cost-effectiveness of treatment.

3.2.4 To investigate the procedural success of CDT.

3.2.5 To identify markers of importance for successful thrombolysis.

3.2.6 To investigate patency at 2 years.

3.2.7 To investigate PTS at 6 and 60 months.

3.2.8 To investigate whether presence or absence of PTS at any time point is related to patency at end of treatment.

3.2.9 To investigate prevalence of vein anomalies (and need for angioplasty or stents).

3.2.10 To investigate prevalence of underlying thrombophilia.

3.2.11 To investigate frequency of recurrent VTE during follow-up.

3.2.12 To identify markers of importance for recurrent thrombosis.

4 HYPOTHESES

Our main short-term hypothesis is that CDT of first-time acute DVT will increase patency of the affected iliofemoral vein segments after 6 months from <50% on conventional therapy to >80% after CDT. Our main long-term hypothesis is that CDT will improve long-term functional outcome, i.e., risk of PTS, assessed after 2 years, from >25% on conventional treatment to <10% after CDT.

5 PATIENT POPULATION

5.1 INCLUSION CRITERIA

5.1.1 Age 18-75 years.

5.1.2 Onset of symptoms <21 days.

5.1.3 Objectively verified DVT (ultrasonography, venography, computed tomography, or magnetic resonance imaging) localized in the upper half of the thigh, the common iliac vein or the combined iliofemoral segment.

5.1.4 Informed consent (Appendix 1).

5.2 EXCLUSION CRITERIA

5.2.1 Anticoagulant therapy prior to trial entry for >7 days.

5.2.2 Contraindications to thrombolytic therapy, including bleeding diathesis.

5.2.3 Indications for thrombolytic therapy, e.g., phlegmacia coerolia dolens or isolated vena cava thrombosis.

5.2.4 Severe anemia (hemoglobin <8 g/dL).

5.2.5 Thrombocytopenia (platelets $<80 \cdot 10^9$/L).

5.2.6 Severe renal failure – creatinine clearance <30 ml/min. Creatinine clearance will be calculated according to the following formula:

$$\text{Creatinine clearance (ml/min)} = \frac{b \times (140 - \text{age (yrs)}) \times \text{body weight (kg)}}{\text{serum creatinine (µmol/L}}$$

b=1.23 (females); 1.04 (males)

5.2.7 Severe hypertension, i.e. persistent systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg.

5.2.8 Pregnancy and thrombosis ≤7 days post-partum (may be included after 7 days post-partum).

5.2.9 Less than 14 days post-surgery or post-trauma (may be included after 14 days).

5.2.10 History of subarachnoidal or intracerebral bleeding.

5.2.11 Disease with life expectancy <24 months.

5.2.12 Drug abuse or mental disease that may interfere with treatment and follow-up.

5.2.13 Former ipsilateral proximal DVT.

5.2.14 Malignant disease requiring chemotherapy.

5.2.15 Any thrombolytic therapy within 7 days prior to trial inclusion.

6 METHODS

6.1 DESIGN

Multi-center, open-label, randomized clinical study on the effect and safety of CDT therapy as compared with conventional therapy for the treatment of acute, first-time ilio-femoral DVT. The study will be a collaborative study of hospitals belonging to the Eastern and Southern Norway Health Authorities (Helse Øst and Sør).

6.2 PATIENT RECRUITMENT

Eligible patients (section 5) will be invited to participate in the study. Informed consent (Appendix 1) in accordance with the revised Helsinki Declaration must be obtained from the patient before randomization.

6.3 RANDOMIZATION

Patients will be randomized by sealed numbered envelopes using block randomization. Each envelope will contain information on treatment allocation. A new patient will be allocated the lowest numbered envelope. Treatment will be open-label, but stratified for extension of DVT, i.e., only femoral or iliofemoral DVT.

6.4 TREATMENT

6.4.1 Acute treatment

Patients will be randomized to one of the following treatment groups:

Group I	Catheter-directed thrombolytic therapy with rt-PA in addition to conventional treatment with low molecular weight heparin (for details – see 6.4.2)
Group II	Conventional treatment with low molecular weight heparin (see 6.4.3)

Drugs will be ordered from the hospital's pharmacy according to local routines.

- Group I will be given rt-PA (Actilyse®) combined with unfractionated heparin and followed by low molecular weight heparin (LMWH) and warfarin.
- Group II, the conventional treatment arm, will be given LMWH, either sc dalteparin (Fragmin®), 200 IU/kg od, or enoxaparin (Klexane®), 1.5 mg/kg od, according to local routines, and warfarin.

6.4.2 Group I - Catheter-Directed Thrombolytic (CDT) therapy – procedures

- ***Anticoagulant and fibrinolytic therapy***
  - Discontinue oral anticoagulants - INR should be <1.5 before the procedure.
  - In case of prior sc LMWH therapy treatment should be discontinued at least 8 h before the procedure, and in case of prior UFH treatment APTT (Cephotest®) should be adjusted to 40-60 sec during the procedure (see below).
  - An iv bolus dose of UFH, 5000 U, should be given followed by continuous iv UFH[1] infusion at 15 U/kg/h. Adjust dose to keep APTT (Cephotest®) at 40-60 sec, first adjustment 6-12 h after start of treatment.
  - During the thrombolytic treatment keep APTT (Cephotest®) at 40-60 sec.
  - At the completion of thrombolytic treatment:
    - ✓ discontinue UFH
    - ✓ give sc LMWH after 1 h, (either dalteparin, Fragmin®, 200 U/kg bid, or enoxaparin, Klexane®, 1,5 mg/kg bid).
    - ✓ Oral warfarin (Marevan®) will be initiated according to local routines.
    - ✓ LMWH will be discontinued when INR has been in therapeutic range (2.0-3.0) for at least 24 hours, but should not be given for less than total 4-5 days.

- ***Interventional procedures.*** In an interventional radiology unit, an introducer will be inserted into an appropriate vein, preferentially the popliteal vein, guided by ultrasound to prevent puncture of the artery or laceration of the vein wall and to secure only a single puncture. If possible, the wire and catheter should be introduced above the proximal part of the thrombus (use fitting-sized perfusion catheters, e.g., 10, 20, 30, or 50 cm). A venography should then be performed to disclose the topography of the thrombus. CDT may be discontinued if introduction of the catheter through the occluded segment is not successful. Catheters should be properly fixed to the skin.

  The perfusion catheter (and the perfusion wire) should cover the central to peripheral part of the thrombus. Rt-PA (Actilyse®), 20 mg diluted in 500 ml 0.9% NaCl, will be infused at 0.01 mg/kg/h. Maximal dose infused will be 20 mg/24 h. The rt-PA dosage may be split into two catheters using lower consentration, keeping flow the same.

[1] A suitable working solution should be made to contain UFH 40 U/ml in 0.9% NaCl, e.g., mix 20000 U of UFH in 500 ml 0.9% NaCl or 40000 U in 1000 ml 0.9% NaCl. The infusion rate (ml/h) then reflects total units of UFH per 24 hrs in thousands, e.g., 25 ml/h corresponds to 25000 U/24 h, 30 ml/h 30000 U/24 h, and so on.

After insertion of catheter, venography, and start of iv UFH and iv rt-PA infusion, treatment will continue in medical wards. Blood pressure and pulse and the puncture site are assessed 4 times a day. Hemostasis is also monitored by daily analysis of hemoglobin, fibrinogen, D-dimer, INR, and platelet counts. APTT is monitored twice daily for adjustment of heparin dose. The patient will be encouraged to use the muscle pump of the leg while in bed. No food and drink restrictions.

Effect of treatment will be assessed by venography at least every 24 hrs, and catheters repositioned accordingly. Treatment should normally not continue for >96 h. At the end of treatment, the catheters will be removed immediately and hemostasis obtained by manual compression of the puncture site. Pressure will be continued for 2 hrs with a roll while the patient is immobilized.

- ***Stents.*** Balloon dilatation and placement of venous stents will be performed at the discretion of the operator to establish flow and to obtain <50% residual stenosis.

- ***Concomitant medication during procedure.*** During the interventional procedure concomitant use of other antithrombotic agents should be avoided because of increased risk of bleeding. This includes antiplatelet agents (e.g., acetylsalicylic acid, thienopyridines, GPIIb/IIIa inhibitors, non steroidal anti-inflammatory agents, or other) or anticoagulants (e.g., low molecular weight heparin, pentasaccharide, warfarin, or other). Concomitant use of ACE-inhibitors appears to increase the risk of anafylactoid reactions.

6.4.3 Group II – conventional treatment with LMWH

Patients allocated the conventional treatment arm will be given sc LMWH, either dalteparin (Fragmin®), 200 U/kg od, or enoxaparin (Klexane®), 1.5 mg/kg od, according to local hospital routines, and simultaneous warfarin (Marevan®) according to local routines. LMWH will be discontinued when INR has been in therapeutic range (2.0-3.0) for at least 24 hours, but should not be given for less than total 4-5 days.

6.4.4 Subacute and chronic phase after DVT

Patients will be treated with warfarin for at least 6 months with target INR 2.0-3.0. All patients will be adviced to use knee-high compression stockings, grade II, for 6 months.

6.5 VISITS AND PROCEDURES DURING FOLLOW-UP

End-point assessment will be performed by a vascular surgeon with no previous contact or knowledge of patients' medical history or treatment allocation. At each visit the patients will explicitly be told not to reveal treatment allocation.

6.5.1 Visit 1 (trial entry – at hospital admission/)

6.5.1.1 Case history and general clinical examination.

6.5.1.2 Compression ultrasonography or venography, alternatively CT or MRI angiography diagnosing acute iliofemoral DVT.

6.5.1.3 Laboratory screening (hemoglobin, platelets, leukocytes, creatinine, ASAT, ALAT, GT, bilirubin, INR, APTT, D-Dimer, cholesterol, and CRP).

6.5.1.4 Thrombophilia screening (collection of blood samples).

6.5.1.5 Assessment of baseline QoL before treatment using VEINES-QoL and EQ-D5 (Appendix 2).

6.5.1.6 Assessment of baseline clinical score using Villalta[5;43] score and the C classification of CEAP, see Definitions.

6.5.2 Visit 2 (hospital stay)

6.5.2.1 Daily assessment of hemoglobin, platelets, fibrinogen, APTT, INR, and D-Dimer, and bilateral leg circumference.

6.5.2.2 Daily venography will be performed in patients allocated CDT.

6.5.2.4 Bleeding complications.

6.5.3 Visit 3 – 6 m ± 2 weeks

6.5.3.1 Clinical history – recurrent thrombosis – malignancy.

6.5.3.2 Clinical PTS scores according to Villalta and CEAP. Bilateral leg circumference.

6.5.3.3 Assessment of functional venous obstruction by air-plethysmography.

6.5.3.4 Ultrasonographic assessment of postthrombotic changes, patency, and reflux [44-47].

6.5.3.5 Quality of Life (QoL) assessment (Appendix 2).

6.5.3.6 D-dimer testing, INR, thrombophilia screening (if previously inconclusive).

6.5.4 VISIT 4 – 12 m ± 4 weeks

Telephone interview – recurrent thrombosis – malignancy.

6.5.5 VISIT 5 – 24 m ± 4 weeks

6.5.5.1 Clinical history – recurrent thrombosis – malignancy.

6.5.5.2 Clinical PTS scores according to Villalta and CEAP. Bilateral leg circumference..

6.5.5.3 Assessment of functional venous obstruction by air-plethysmography.

6.5.5.4 Ultrasonographic assessment of postthrombotic changes, patency, and reflux

6.5.5.5 Quality of Life (QoL) assessment (Appendix 2).

6.5.5.6 D-dimer, INR, thrombophilia screening (if previously inconclusive).

6.5.6 VISIT 6 – 36 m ± 4 weeks

Telephone interview – recurrent thrombosis – malignancy.

6.5.7 VISIT 7 – 48 m ± 4 weeks

Telephone interview – PTS screening – recurrent thrombosis – malignancy.

6.5.8 VISIT 8 – 60 m ± 8 weeks

6.5.8.1 Clinical history – recurrent thrombosis – malignancy.

6.5.8.2 Clinical PTS scores according to Villalta and CEAP. Bilateral leg circumference.

6.5.8.3 Ultrasonographic assessment of postthrombotic changes, patency, and reflux.

6.5.8.4 Assessment of functional venous obstruction by air-plethysmography.

6.5.8.5 Quality of Life (QoL) assessment (Appendix 2).

7 DEFINITIONS

7.1 Post-Thrombotic Syndrome (PTS)

7.1.1 The Villalta Score[5;43]

PTS will be evaluated using the Villalta score, which scores PTS based on five symptoms and six objective signs (each item graded from 0 to 3):

Five symptoms: heaviness, pain (spontaneous or during deambulation), cramps, pruritus, and paresthesia.

Six signs: pretibial edema, induration of the skin, hyperpigmentation, new venous ectasia, redness, pain during calf compression

A total score of 5-14 indicates mild to moderate PTS, whereas a score of 15 or more indicates severe PTS. A lower limb venous ulcer indicates severe PTS regardless of the sum of the remaining signs and symptoms. The Villalta Score is quantitative and useful for longitudinal assessment of PTS.

7.1.2 The Clinical-Etiology-Anatomic-Pathophysiologic (CEAP) classification[48;49]

This is a classification of Clinical (dermatological) signs, Etiology, Anatomic distribution and Pathophysiologic dysfunction:

Clinical signs	**Class 0**	**No visible or palpable signs of venous disease**
	Class 1	**Teleangiectases or reticular veins**
	Class 2	**Varicose veins**
	Class 3	**Edema**
	Class 4	**a. pigmentation, eczema** **b. lipodermatosclerosis, atrophia blanche**
	Class 5	**Healed ulceration (and skin changes as defined above)**
	Class 6	**Active ulceration (and skin changes as defined above)**
Etiological classification	**Congenital, primary, secondary**	
Anatomic distribution	**Superficial, deep, or perforator, alone or in combination**	
Pathophysiological dysfunction	**Reflux or obstruction, alone or in combination**	

7.2 Non-invasive assessment of veins

7.2.1 Deep vein thrombosis[50]

7.2.1.1 Acute deep vein thrombosis

The principal criterion is inability to completely compress the vein lumen when examining the vein in the transverse plane. Other possible findings are distention of the vein, absence of flow, loss of phasic flow, and visualization of clot.

7.2.1.2 Chronic thrombosis and postthrombotic changes

Absence of complete incompressibility indicates residual thrombosis. Other postthrombotic features are wall-thickening and intraluminal hyperechoic structure.

7.2.2 Flow

Using Doppler-ultrasound, flow will be graded as spontaneous flow, forced flow (on peripheral compression), and no flow (obstruction)[38]. Flow will also be examined in supine position.

7.2.3 Reflux

Using Doppler-ultrasound and a distal inflation cuff with the patient in standing position, reflux is defined as reversal of the velocity curve after distal pneumatic decompression lasting longer than 0.5 second[51-53].

7.2.4 Assessment of functional venous obstruction

Venous obstruction will be assessed by using air plethysmography[54;55]. The patients will lie supine with the calf elevated (by a cushion) to the level of the heart. An occlusion cuff will be placed proximally on the thigh, and a recording cuff with a pressure of 6 mmHg will be placed on the calf. The proximal cuff will be inflated to 50 mmHg for 1 min. A venous outflow curve will be recorded when this cuff is deflated, and maximum outflow can then be calculated (delta mm/sec). Low outflow rates indicate presence of functional venous obstruction. The procedure will be performed on both legs.

7.2.5 Assessment of venous patency

Assessment of venous patency will include compressibility, flow and functional venous obstruction.

7.3 Evaluation of thrombolysis

Based on venography before and after CDT, thrombolysis will be graded by a scoring system[38]. Score=0 indicates an open vein, score=1 a partly occluded vein, and score=2 a completely occluded vein.

Each of the following 7 venous segments will be given a grade (0-2): IVC, the common iliac vein, the external iliac vein, the common femoral vein, the proximal and distal superficial femoral veins, and the popliteal vein. A total thrombus score before and after lysis will be calculated by adding the 7 scores. The difference between the pre- and postlysis thrombus scores divided by the prelysis score gives the grade of thrombolysis. Grade I=<50%; grade II=50-90%, and grade III=complete thrombolysis

7.4 Bleeding Complications

7.4.1 ***Major bleeding*** – any bleeding associated with a reduction in hemoglobin by ≥2 g/100 mL or bleeding requiring transfusion of ≥2 U pack red blood cells or whole blood or bleeding in a critical organ, intracranial, retroperitoneal or pericardial or bleeding contributing to death.

7.4.2 ***Clinically relevant non-major bleeding*** – overt bleeding not meeting criteria for major bleeding but satisfying a priori criteria defined by the safety monitoring committee including for example skin hematomas >100 cm^2, epistaxis lasting >5 min, being repetitive (≥2/24 h) or requiring intervention (packing, electrocoagulation), macroscopic hematuria – either spontaneous or lasting >24 h after instrumentation (catheter or surgery) of the urogenital tract, or any other bleeding type that is considered to have clinical consequences for the patient.

7.4.3 ***Trivial bleeding*** - all other overt bleeding episodes not meeting the criteria for clinically relevant bleeding.

7.5 Thrombophilia screening

Includes screening for antithrombin, protein C- and protein S deficiencies, factor V Leiden mutation, the prothrombin gene 20210GA allele variation and the methylene tetrahydrofolate reductase (MTHFR) mutation, homocystein, lupus anticoagulants and anticardiolipin antibodies.

8 STATISTICS

8.1 Sample size

Numerous studies indicate that conventional treatment, i.e., UFH or LMWH followed by oral anticoagulants is associated with PTS in more than 60-80% of the cases, whereas systemic thrombolytic therapy is associated with PTS in approximately 30% of the patients[5;21;56]. More recent studies employing systematic use of elastic compression stockings suggest PTS in approximately 25% of the patients.[11] In the present study, we will assume that the rate of PTS after 2 years will be at least 25% in those allocated conventional therapy as compared with less than 10% in those given CDT. For patency after 6 m we assume that the rate is less than 50% in those allocated conventional treatment as compared with at least 80% in those given CDT. With a significance level of $\alpha \leq 5\%$ and a statistical power (1-β) of $\geq 80\%$, we will need to randomize approximately 100 patients in each group.

Also as presented in our hypotheses, we assume that venous patency after 6 months occurs in less than 50% in those allocated conventional treatment as compared to at least 80% in those given adjunctive CDT. It may then be shown that with a significance level of 5% and a statistical power ≥80%, 76 patients must be included to test this short-term hypothesis. We plan to analyse patency rates after 6 months based on the first 100 patients with 6 months patency data. This analysis will be repeated when 200 patients have 6 months patency data.

8.2 Statistical methods

All statistical analysis will be performed according to the intention-to-treat principle. If ineligible patients are mistakenly included, they may be excluded (ref Ferguson et al BMJ 2002), apart from this, no other post-randomization exclusions will be made. The effect of treatment will be determined using 2x2 tables with assessment of the difference between patent vessels and prevalence of PTS, relative risks, and odds ratios with 95% confidence limits. The prevalence of clinically relevant bleeding, PTS, vein anomalies, thrombophilia, recurrent DVT will be determined using point estimates with 95% confidence intervals. A stratification analysis will be carried out using the Mantel-Haenzel method. Differences in baseline characteristics may be adjusted for using a multivariate logistic model. This may be done if there are substantial differences between the two groups, and if the variable(s) is probably or certainly associated with the outcome measure, e.g., age and previous VTE. Missing data on end-point variables will be scored as previous score or last/worst score carried forward.

9 ETHICAL CONSIDERATIONS

This study will recruit patients with proximal DVT. Even though the efficacy and safety of CDT for the treatment of acute proximal DVT remains to be established, some hospitals in many countries now offer CDT to selected patients with severe DVT, especially when the DVT extends into the caval vein. In the present study, non-trial CDT to selected patients with severe DVT will be left to the discretion of the responsible physician.

The study will be performed in accordance with the revised Helsinki Declaration and Good Clinical Practice (GCP). The study will only start after approval with the Regional Ethical Committee and the Norwegian Medical Agency. All patients will be given study specific identification codes and all data will be stored in a secured database on a secured server for research at the Ullevål University Hospital. This server as well as data management will be controlled by the Patient Protection Ombud at the Ullevål University Hospital. A non-linked database will provide information on the patients' contact information to allow follow-up. A biobank will be established at Ullevål University Hospital after approval.

10 MILESTONES

Q1-2006	First patient randomized
Q4-2007	Last patient randomized
Q2-2008	Six months follow-up of all patients for primary efficacy parameter patency
Q2-3-2008	Reporting of study design and primary efficacy parameter patency
Q4-2009	Two-years follow-up of all patients for primary efficacy parameter PTS
Q4-Q1-09-10	Reporting of primary efficacy parameter PTS
Q4-2012	Five years follow-up of last patient for patency and PTS.

11 TRIAL ORGANIZATION

11.1 GENERAL ORGANIZATION

The study is an investigator initiated study which will be run independently of the pharmaceutical industry. The study is financially supported by a grant from Eastern Norway Health Authority (doctoral fellow; Helse Øst grant no 2005-090).

The study will be a major collaborative effort among hospitals of the Eastern and Southern Norway Health Authorities (Helse Øst and Sør). All hospitals will be invited to participate in the study. Patients allocated to conventional treatment will be treated at the local hospital, whereas patients allocated CDT will be treated at Ullevål and Aker University Hospitals, the National Hospital and the Central Hospital in Østfold.

11.2 COMMITTES

11.2.1 Executive committee

- Per Morten Sandset (chair) – UUS – Hematologist
- Nils-Einar Kløw – UUS – Radiologist
- Leiv Sandvik – UUS – Statistician
- Tone Enden – UUS – Research fellow – Resident in Radiology
- Carl-Erik Slagsvold – AUS – Angiologist
- Anne Mette Njåstad – AUS – Hematologist
- Gunnar Sandbaek – AUS – Radiologist
- Pål Andre Holme – RR – Hematologist
- Geir Hafsahl – RR – Radiologist
- Waleed Ghanima – Østfold Hospital Trust Fredrikstad – Hematologist
- Lars Olav Holmen – Østfold Hospital Trust Fredrikstad – Radiologist

11.2.2 Steering committee

- Executive committee (chair Per Morten Sandset)
- One member from each collaborating hospital

11.2.3 Safety and monitoring committee

- Professor emeritus Ulrich Abildgaard
- Professor Frank Brosstad, Rikshospitalet-Radiumhospitalet, Oslo

12 PUBLICATION

Results of this study will be published in international medical journals, but will also be communicated to the general population whenever appropriate. The results may potentially have great interest for the scientific community, for health-providers in decision making, and for the general population. Publication will follow the Vancouver convention. Tone Enden will be the first author of these publications.

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Appendix 1

FORESPØRSEL OM Å DELTA I EN FORSKNINGSSTUDIE:

CaVenT-studien – kateterbasert trombolyse ved akutt dyp venetrombose

Denne forespørselen om å delta i forskningsprosjektet "CaVenT" går til pasienter som legges inn med akutt blodpropp i lår- og bekkenvener ved sykehus i Helseregion Sør og Øst.

Du bestemmer selv

Det er frivillig å delta i studien. Dersom du velger å ikke delta, trenger du ikke oppgi noen grunn for dette. Dersom du ikke ønsker å delta i studien, vil behandlingen din være den vanlige behandlingen som pasienter med din sykdom mottar. Du kan når som helst trekke deg underveis uten begrunnelse.

Bakgrunn

Undersøkelsene viser at du har fått en blodpropp i en samleblodåre (vene) i låret og/eller i bekkenet. Tilstanden kalles dyp venetrombose. Standardbehandlingen ved akutt dyp venetrombose er blodfortynnende medisin, først sprøyter med lavmolekylært heparin (inneholder legemidlene Fragmin eller Klexane) i 4-8 dager og deretter tabletter (legemidlet Marevan) i minst 3-6 måneder. Målet med behandlingen er å stoppe utviklingen av blodproppen, forhindre at blodproppen løsner og går til lungene og å redusere plagsomme senfølger i form av smerter, hevelse og hudforandringer. Slike senfølger kalles posttrombotisk syndrom. Om lag en fjerdedel av pasientene utvikler posttrombotisk syndrom i løpet av de første 2 årene etter standardbehandling for blodropp.

De siste årene er det utviklet en ny behandling for å løse opp blodpropp som kalles kateterbasert trombolyse. Behandlingen er beskrevet i detalj under. Foreløpige resultater tyder på at denne behandlingen kan løse opp blodproppen raskere og forebygge senplagene, men så langt har det ikke vært gjennomført studier som kan gi gode svar på dette.

Prosjektets formål

Hensikten med dette forskningsprosjektet er å avklare om tilleggsbehandling med kateterbasert trombolyse gir bedre resultat i akutt fase og færre plager på lang sikt uten økt risiko for bivirkninger sammenliknet med standard blodfortynnende medisin alene.

Om kateterbasert trombolyse/blodproppløsende behandling

Behandlingen gjennomføres i samarbeid mellom hematologisk/indremedisinsk avdeling og røntgenavdelingen. Selve prosedyren blir utført ved røntgenavdelingen. Du får først lokalbedøvelse. Deretter fører vi inn et 2 mm tykt plastrør i venen (blodåren) i knehasen og inn i selve blodproppen. Så gir vi kontinuerlig en lav dose av et blodproppløsende medikament (legemidlet Actilyse) gjennom plastrøret i inntil 3-4 dager. Samtidig gir vi også en lav dose blodfortynnende medisin (legemidlet heparin) som drypp intravenøst. Blodproppen løser seg langsomt opp, og tidspunktet for å avslutte behandlingen blir bestemt ut fra daglige kontroller med røntgen kontrastundersøkelse. Mens behandlingen pågår må man holde sengen.

Dersom det i forløpet av behandlingen påvises en unormal blodåre (vene), oftest en medfødt innsnevring, som kan forklare hvorfor blodpropp oppsto, vil vi vurdere å gi tilleggsbehandling ved å

utvide blodåren ved hjelp av et ballongkateter, eventuelt legge inn en stent (forsterkning). Dette vil sikre normal blodstrøm etter behandlingen.

Behandling med blodpropp-oppløsning utføres ved flere av de store sykehusene i regionen, og dersom ditt sykehus ikke kan utføre behandlingen, vil du bli overført til et av disse.

Etter avsluttet kateterbasert behandling vil du få vanlig behandling med lavmolekylært heparin og Marevan og bli fulgt opp etter gjeldende retningslinjer ved ditt lokalsykehus.

Gjennomføring

For å kunne gjøre en vitenskapelig sammenlikning av resultatene, vil det bli foretatt en trekning slik at halvparten av pasientene vil få standard behandling, mens den andre halvparten vil få kateterbasert trombolyse i tillegg. Du gis skriftlig og muntlig informasjon om forskningsprosjektet når du legges inn.

Deltagelse i studien medfører i tillegg til vanlig behandling og oppfølging, ekstra samtaler med lege (noen som telefonkonsultasjon) og enkelte undersøkelser (ultralyd, blodprøver) ved ulike tidspunkt i de påfølgende 2 år. Uansett behandling vil vi kontakte deg regelmessig, enten per telefon (etter 12, 36 og 48 måneder) eller ved kontrollundersøkelse (etter 6, 24 og 60 måneder). Undersøkelsene omfatter ultralydundersøkelse og blodprøver.

Risiko ved behandlingen

Kateterbasert trombolyse medfører en litt økt risiko for blødning sammenliknet med den vanlige behandlingen. Det vanligste er mindre blødning ved innstikksstedet der plastrøret er lagt inn. Hos noen få pasienter har det vært rapportert blødninger andre steder, mest alvorlig er blødninger i tarm og hode. Dersom slik blødning oppstår, vil vi stoppe den trombolytiske behandlingen og sette i gang tiltak for å behandle blødningen etter gjeldende rutiner ved sykehusene.

Blodprøver og biobank

Blodprøvene som blir tatt og informasjonen utledet av dette materialet vil bli lagret i en såkalt "forskningsbiobank" ved Ullevål universitetssykehus HF. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Blodprøvene vil bli lagret i fryseboks ved hematologisk forskningslaboratorium i tråd med interne retningslinjer. Viseadministrerende direktør ved sykehuset er ansvarlig for biobanken. Biobanken planlegges å vare til 2027. Etter dette vil materiale og opplysninger bli destruert/slettet etter interne retningslinjer.

Slik ivaretas dine prøver og personopplysninger

Personvernet ivaretas i samsvar med betingelser gitt i konsesjon fra Datatilsynet/melding til sykehusets personvernombud. Forskningsdata, inklusive opplysninger utledet av det biologiske materialet, lagres på eget, sikret datasystem ved sykehuset. Alle opplysningene vil bli behandlet konfidensielt. I prosjektet har du et prosjektnummer som knytter deg som person til prosjektet gjennom en adresseliste. Kun prosjektansvarlig har adgang til adresselisten.

Hvem som har vurdert prosjektet

Regional komité for medisinsk forskningsetikk, Øst-Norge, har vurdert prosjektet, og har ingen innvendinger mot at det gjennomføres. Forskningsbiobanken er meldt til Sosial- og helsedirektoratet, som ikke har innsigelser til opprettelse av biobanken.

Økonomi

Forskningsprosjektet er et samarbeid mellom sykehusavdelinger i Helse Sør og Øst. Prosjektet er delvis finansiert gjennom forskningsmidler fra Helse Øst. Det er ikke aktuelt å samarbeide med industri, og det er heller ikke aktuelt med kommersialisering av produkter. Prosjektansvarlig og andre som arbeider med prosjektet har ingen form for økonomisk vinning knyttet til prosjektet.

Dine rettigheter

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert evt. feil i de opplysningene vi har registrert. Hvis du senere trekker deg fra studien, kan du kreve at materialet destrueres. Du kan også kreve å få slettet opplysninger vi har registrert. Ved henvendelse til prosjektansvarlig kan du få nærmere opplysninger om dette. Du kan ikke få slettet opplysninger eller destruert materiale dersom de er anonymisert, er viderebehandlet og inngår i et annet biologisk produkt eller dersom opplysningene allerede har inngått i et vitenskapelig arbeid. Adgangen til destruksjon gjelder heller ikke dersom det ved lov er fastsatt at materialet eller opplysningene skal oppbevares.

Prosjektansvarlig – mer informasjon

Dersom du har flere spørsmål om studien eller biobanken kan du kontakte en av de prosjektansvarlige legene (se under) eller legen som er ansvarlig for oppfølging ved ditt sykehus (se under).

Per Morten Sandset
Avd. overlege, professor, dr. med
Prosjektansvarlig
Hematologisk avdeling, UUS

Nils Einar Kløw
Seksjonsoverlege, professor, dr. med

Hjerte- og karradiologisk avdeling, UUS

Tone Enden
Lege, stipendiat
Prosjektleder, UUS
Tlf UUS 22 11 80 80, calling nr. 581 78389
e-mail: tone.enden@uus.no

Prosjektansvarlig lege ved ditt sykehus er:

Navn:
Tittel:
Adresse:
Telefon:

CaVenT-studien

Samtykke – prosjektdeltaker

Deltakelse i studien er basert på ditt frivillige, informerte samtykke. Dersom du ønsker informasjon utover det som framkommer i dette informasjonsskrivet og den muntlige informasjonen du har mottatt/vil få, har du full anledning til å be om dette.

Dersom du etter å ha fått den informasjon du synes er nødvendig, sier ja til å delta i studien, må du signere samtykkeerklæringen.

Jeg,_____(navn med blokkbokstaver), bekrefter at jeg har mottatt skriftlig informasjon om studien, har fått anledning til å innhente den informasjon jeg har hatt behov for, og er villig til å delta i prosjektet.

*Signatur*_____ *Dato*_____.

(sign. prosjektdeltaker) *(datert av prosjektdeltaker)*

Informasjon om studien er gitt av:

*Lege,*_____*(navn med blokkbokstaver)*

*Signatur*_____ *Dato*_____.

(sign. lege)

Appendix 2: VEINES-QoL and EQ-D5

Spørreskjema om helse

Opplysningene vil være til hjelp for å holde rede på hvordan du har det, og om hvordan du klarer å utføre dine vanlige aktiviteter.

Vis hvilke utsagn som passer best på **din helsetilstand i dag** ved å sette et kryss i en av rutene utenfor hver av gruppene nedenfor.

Gange

Jeg har ingen problemer med å gå omkring. ☐

Jeg har litt problemer med å gå omkring. ☐

Jeg er sengeliggende. ☐

Personlig stell

Jeg har ingen problemer med personlig stell. ☐

Jeg har litt problemer med å vaske meg eller kle meg. ☐

Jeg er ute av stand til å vaske meg eller kle meg. ☐

Vanlige gjøremål *(f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter).*

Jeg har ingen problemer med å utføre mine vanlige gjøremål ☐

Jeg har litt problemer med å utføre mine vanlige gjøremål. ☐

Jeg er ute av stand til å utføre mine vanlige gjøremål. ☐

Smerte/ubehag

Jeg har verken smerte eller ubehag. ☐

Jeg har moderat smerte eller ubehag. ☐

Jeg har sterk smerte eller ubehag. ☐

Angst/depresjon

Jeg er verken engstelig eller deprimert. ☐

Jeg er noe engstelig eller deprimert. ☐

Jeg er svært engstelig eller deprimert. ☐

Besvar hvert spørsmål nedenfor ved å krysse av svaret som angitt. Hvis du er usikker på hva du skal svare, vennligst svar etter beste evne.

Disse spørsmålene er om din oppfatning av **beina dine**.

1. I løpet av de 4 siste ukene, hvor ofte har du hatt noen av disse plagene i beina?

(Sett ett kryss på hver linje)	**Daglig**	**Flere ganger i uka**	**Omtrent én gang i uka**	**Sjeldnere enn én gang i uka**	**Aldri**
1. Tunge bein	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Vondt i beina	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Hevelse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Kramper om natta	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Varme eller brennende følelse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Urolige bein	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Banking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Kløe	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. Prikking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Når på dagen er **plagene i beina** mest uttalte? *(Sett ett kryss)*

☐ 1 Når jeg våkner
☐ 2 Midt på dagen
☐ 3 På slutten av dagen
☐ 4 Om natta
☐ 5 Når som helst i løpet av dagen
☐ 6 Aldri

3. Sammenlignet med for ett år siden, hvordan vil du vurdere dine **plager i beina** nå? *(Sett ett kryss)*

☐ 1 Mye bedre nå enn for ett år siden
☐ 2 Noe bedre nå enn for ett år siden
☐ 3 Omtrent det samme nå som for ett år siden
☐ 4 Noe verre nå enn for ett år siden
☐ 5 Mye verre nå enn for ett år siden
☐ 6 Jeg hadde ingen plager i beina i fjor

4. Følgende spørsmål gjelder daglige aktiviteter. Setter **plagene i beina** begrensninger for dine daglige aktiviteter? Hvis « ja », i hvilken grad?

	(Sett ett kryss på hver linje)	Jeg jobber ikke	JA, begrenser meg mye	JA, begrenser meg litt	NEI, begrenser meg ikke
a.	Daglige aktiviteter på jobb.	☐ 0	☐ 1	☐ 2	☐ 3
b.	Daglige aktiviteter hjemme (husarbeid, småjobber, hagearbeid, o.l.)		☐ 1	☐ 2	☐ 3
c.	Fritidsaktiviteter hvor du må stå lenge (selskap, ta buss, handle o.l.)		☐ 1	☐ 2	☐ 3
d.	Fritidsaktiviteter hvor du må sitte lenge (kino, teater, på reise o.l.)		☐ 1	☐ 2	☐ 3

5. 3. I løpet av de 4 siste ukene, har du hatt noen av disse problemene i jobb eller i daglige aktiviteter på grunn av **plagene i beina**?

	(Sett ett kryss på hver linje)	**JA**	**NEI**
a.	Redusert arbeids**tid** eller **tid** til andre aktiviteter	☐ 1	☐ 2
b.	**Gjennomført mindre** enn du skulle ønsket	☐ 1	☐ 2
c.	Blitt begrenset i **type** jobb eller aktiviteter	☐ 1	☐ 2
d.	Hatt **vanskeligheter** med å utføre jobben eller andre aktiviteter (f eks det krevde større anstrengelse)	☐ 1	☐ 2

6. I løpet av de 4 siste ukene, i hvilken grad har **plagene i beina** kommet i veien for samvær med familie, venner, naboer eller grupper? *(Sett ett kryss)*

☐ 1 Ikke i det hele tatt
☐ 2 Lett
☐ 3 Moderat
☐ 4 Ganske stor
☐ 5 Svær

7. Hvor mye smerter har du hatt i beina i løpet av de 4 siste ukene? *(sett ett kryss)*

☐ 1 Ingen
☐ 2 Svært lite
☐ 3 Lite
☐ 4 Moderat
☐ 5 Mye
☐ 6 Svært mye

8. Disse spørsmålene er om hvordan du føler deg, og om hvordan du har hatt det de siste 4 ukene som følge av **plagene i beina**. For hvert spørsmål, kryss av for det svaret som passer best med hvordan du har følt deg. Hvor mye i løpet av de 4 siste ukene-

(Sett ett kryss på hver linje)	**Hele tiden**	**Det meste av tiden**	**Ganske ofte**	**Av og til**	**Sjelden**	**Aldri**

a.	har du vært bekymret for hvordan beina dine ser ut?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b.	har du følt deg irritabel	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c.	har du følt at du har vært til byrde for familie eller venner?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d.	har du vært bekymret for å skumpe borti ting?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e.	har dine beins utseende påvirket ditt klesvalg ?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Vennligst oppgi dato for utfyllingen:_____/_____/_____ *(dag/måned/år)*

Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis; from the CaVenT study (an open RCT)

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Secondary Subject Heading:	Haematology (incl blood transfusion), Patient-centred medicine
Keywords:	Bleeding disorders & coagulopathies < HAEMATOLOGY, Vascular medicine < INTERNAL MEDICINE, Interventional radiology < RADIOLOGY & IMAGING

Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis: secondary outcomes of the randomised, non-blinded, parallel-group CaVenT study

~~Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis; from the CaVenT study (an open RCT)~~

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Keywords: health outcomes, post-thrombotic syndrome, quality of life, venous thrombosis, thrombolytic therapy

Word count: 2309 words in main text

Summary:

Objectives: To investigate whether additional catheter-directed thrombolysis (CDT) improves long-term ~~patient reported~~ quality of life (QOL) compared to standard treatment with anticoagulation and compression stockings alone in patients with proximal deep vein thrombosis (DVT).

Design: Open-label randomised controlled trial.

Setting: 19 hospitals in the Norwegian southeastern health region.

Participants: Patients (18-75 years) with a high proximal DVT, symptoms <21 days, and no increased risk of bleeding were eligible. 189 of 209 recruited patients completed 24 months follow-up.

Interventions: Participants were randomized to additional CDT with alteplase for 1-4 days or to standard treatment only with 6 months anticoagulation and 24 months of compression stockings.

Primary and secondary outcome measures: Planned secondary outcome measures included QOL as assessed with the generic instrument EQ-5D and the disease specific instrument VEINES-QOL/Sym. Primary outcome measure was post-thrombotic syndrome (PTS) after 24 months.

Results: After 24 months there were no differences in QOL between the additional CDT and standard treatment arms; mean difference for the EQ-5D index was 0.~~80~~04 (95% CI ~~0.746-0.849~~—0.10-0.17) ~~and 0.84 (95% CI 0.807-0.875)~~, for the VEINES-QOL score ~~was 50.1~~0.2 (95% CI ~~47.9-52.3~~-2.8-3.0) ~~and 49.9 (95% CI 48.0-51.8)~~, and for the VEINES-Sym score ~~was 50.3~~ 0.5 (95% CI ~~48.0-52.5~~-2.4-3.4); ~~and 49.8 (95% CI 47.9-51.6), respectively~~ (p-values >0.37). Independent of treatment arms, patients with PTS had poorer outcomes than patient without PTS; mean difference for EQ-5D ~~index~~ was ~~0.77~~0.09 (95% CI ~~0.730-0.819~~0.03-0.15) ~~vs. 0.86 (95% CI 0.823-0.903)~~, for VEINES-QOL score ~~was 45.6~~8.6 (95% CI ~~43.4-47.9~~5.9-11.2) ~~vs. 54.2 (95% CI 52.8-55.6)~~, and for VEINES-Sym score ~~was 45.0~~9.8 (95% CI 7.3-12.3~~42.7-47.2~~) ~~vs. 54.8 (95% CI 53.5-56.0), respectively;~~ (p-values <0.001).

Conclusions: QOL did not differ between patients treated with additional CDT compared to standard treatment alone. Patients who developed PTS reported poorer QOL and more symptoms than patients without PTS. QOL should be included as an outcome measure in clinical studies on patients at risk of PTS.

Trial registration: NCT00251771

Article summary

Article Focus

- Assessment of ~~patient reported~~ quality of life may provide meaningful information not captured by clinical scores and other traditional health outcome measures.
- Additional catheter-directed thrombolysis for proximal deep vein thrombosis improves long-term clinical outcome by reducing post-thrombotic syndrome and is likely to be a cost-effective alternative to standard treatment alone.
- Our objective was to investigate whether additional thrombolysis also improves long-term quality of life compared to standard treatment alone.

Key Messages

- Quality of life did not differ between patients allocated thrombolytic therapy compared to control patients who receive standard anticoagulation and compression stockings only.
- Patients who developed post-thrombotic syndrome had poorer generic and disease specific quality of life scores compared to patients without post-thrombotic syndrome.
- Quality of life assessment should be among the long-term outcome measures in clinical research on patients who are at risk of developing post-thrombotic syndrome.

Strengths and Limitations

- A robust study design where patient reported quality of life was assessed using validated generic and disease-specific instruments within the setting of a multicenter open-label randomized controlled trial.
- The study was designed to detect a difference in the frequency of post-thrombotic syndrome between the two treatment arms and may have been underpowered to detect a clinically meaningful difference in quality of life. Other possible explanations include a relatively small effect on the reduction in post-thrombotic syndrome and the smaller proportion presenting with iliofemoral DVT relative to infrainguinal DVT.
- More frequent study visits and longitudinal assessments of quality of life would have allowed for better explanatory analyses, and may have added to the interpretation of clinically meaningful differences in the disease specific quality of life scores.

Introduction

Following standard treatment including anticoagulation and compression stockings, still at least 1 in 4 are at risk of developing a post-thrombotic syndrome (PTS) after suffering a proximal deep vein thrombosis (DVT), i.e., DVT in the popliteal vein or above [1-3]. PTS is characterized by persistent pain, heaviness, swelling, and deterioration of the skin. Previously in the CaVenT Study we have shown that additional catheter-directed thrombolysis (CDT) in patients with a high proximal DVT localized in the mid-thigh level or above, and a low risk of bleeding, reduced the frequency of PTS from 56% to 41% (p=0.047) after 2 years and that CDT is likely to be a cost-effective alternative to standard treatment only [4,5]. However, as PTS is a chronic condition associated with substantial morbidity and with no healing treatment options, ~~patient reported~~ assessment of both generic and disease-specific health-related quality of life (QOL) including the impact on health and daily functioning may provide meaningful information not captured by clinical scores and other traditional health outcome measures. Development of PTS has been shown to be a principal determinant of QOL following DVT of the lower limb; however, there is currently no gold standard for the PTS diagnosis [6]. We aimed at investigating whether additional CDT for a high proximal DVT improved long-term QOL compared to standard treatment alone.

Materials and methods

Study population

Patients were recruited as part of the CaVenT study, an open randomized controlled trial (RCT), from 19 hospitals within the South-Eastern Norway Regional Health Authority, which serves a population of 2.6 million people. Patients aged 18–75 years with a first-time objectively verified acute high proximal DVT, defined as thrombus in mid-thigh level or higher, and with a low risk of bleeding, were eligible for

inclusion if symptoms had lasted <21 days. Complete eligibility criteria and trial profile have been reported previously [5,7]. Patients were randomly assigned, using sealed numbered envelopes, to standard treatment with at least 6 months of anticoagulation and compression stockings for 24 months or to CDT with alteplase for 1-4 days in addition to standard treatment; the treatment strategies have previously been reported in detail [5,8]. Prior to treatment allocation, written informed consent was obtained by the local trial site investigator. The study protocol was approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Medicines Agency, and was registered at www.clinicaltrials.gov with the unique trial identifier NCT00251771.

Variables and instruments

Long-term quality of life

After 6 and 24 months follow-up the patients completed a self-reporting questionnaire including the validated Norwegian versions of the generic instrument EQ-5D (www.euroqol.org) and the disease-specific QOL instrument VEINES-QOL/Sym [9,10]. The VEINES-QOL/Sym comprises 26 items regarding problems of the lower limbs [4]. The instrument measures symptoms, limitations in daily activity and psychological impact during the previous 4 weeks, and change over the past year. Responses are rated on 2- to 7-point descriptive scales, and two summary scores are computed. The VEINES-QOL summary score assesses QOL, and the VEINES-Sym score is a subscale that measures symptom severity only. Higher scores represent better QOL and/or fewer symptoms, and a difference or change of ≥4 points has been suggested to represent a clinically meaningful difference [10].

The EQ-5D is a preference-based generic instrument for describing and valuing QOL, and is a widely used health measure outcome in clinical trials and cost-effectiveness and cost-utility analyses. This descriptive classification system comprises the five items mobility, self-care, activity, pain, and anxiety; each with the three levels reflecting the patient's status that particular day. The scoring gives a single

number/health status index ranging from 0 (dead) to 1 (best possible health). A difference or change in this index of ≥0.08 is likely to represent a clinically meaningful difference [11,12].

Assessment of post-thrombotic syndrome

In the absence of a gold standard for a PTS diagnosis, the Villalta score has been recommended for PTS assessment in clinical trials [13]. This score includes the five patient-rated symptoms pain, cramps, heaviness, paresthesia, pruritus, and the six clinician-rated signs edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, and redness. Each sign or symptom is rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and summed to produce a total score, where less than 5 indicates no PTS, 5–14 indicates mild or moderate PTS, and 15 or more (or presence of venous ulcer) indicates severe PTS.

Statistical analysis and sample size

Health related QOL was among the pre-specified secondary outcomes of the CaVenT Study, while the primary outcome of PTS after 2 years was the basis for the sample size calculation [7]. For all patients a EQ-5D summary index was calculated based on values from a Danish population as no Norwegian algorithm exists [14]. Scores for VEINES-QOL and VEINES-Sym were computed using standard scoring algorithms obtained from the authors [10]. Statistical analyses were by intention to treat. Any ineligible patients mistakenly included were excluded. Missing outcome data because of withdrawal of consent or death from cancer or other causes not related to CDT or anticoagulation were assumed to be missing independently of treatment received and were not included in the analyses [5]. When comparing dichotomous variables between groups, a two-sided chi-square test was used. Normal distribution was tested visually using plots, followed by comparing non-normally distributed continuous variables between independent groups with a two-sided Mann-Whitney U test. Findings with p-values less than

0.05 were deemed statistically significant. The statistical analyses were performed using the statistical package SPSS, version 18.0 (SPSS Inc, Chicago, IL, USA).

Results

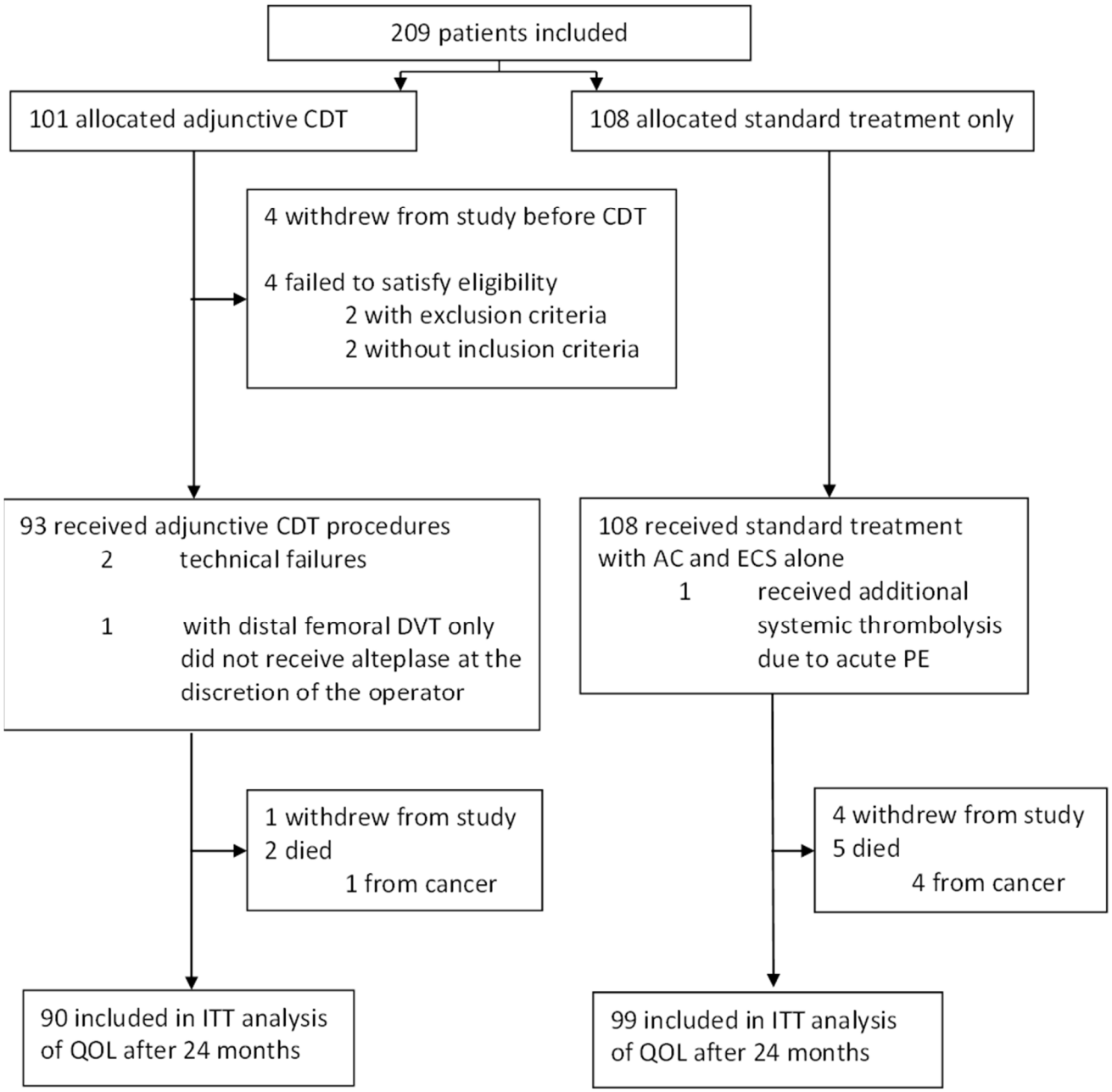
209 patients with a high proximal DVT were recruited and randomized to additional CDT or to standard treatment alone during 2006-2009. Table 1 shows the demographic and clinical characteristics of the 189 patients with complete 2 years follow-up included in the present analysis; 90 in the CDT group and 99 controls. Mean age was 51.5 years (SD 15.8) and 70 (37%) participants were female. Mean duration of symptoms before diagnosis and start of treatment was 6.6 days (SD 4.6). Most baseline demographic and clinical characteristics, including VEINES-QOL/Sym and EQ-5D scores, were fairly equally distributed between the two treatment groups. Figure 1 presents ~~D~~details on the study participants ~~including~~ and the complete trial profile ~~have been reported elsewhere~~ [5].

Table 1 Demographic and clinical characteristics

	Adjunctive catheter-directed thrombolysis (n=90)		Standard treatment only (n=99)	
Baseline				
Age (years)	53.3	(15.7)	50.0	(15.8)
Women	32	(35.6)	38	(38.4)
Duration of symptoms of acute DVT (days)	6.4	(4.4)	6.8	(4.8)
EQ-5D index	0.46 (~~0.372-0.548~~0.39)		0.63 (~~0.422-0.844~~0.99)	
VEINES-QOL score	50.2 (~~48.2-52.3~~9.3)		50.1 (~~47.8-52.4~~10.7)	
VEINES-Sym score	50.4 (~~48.4-52.5~~9.3)		49.5 (~~47.2-51.8~~10.7)	
No risk factor for venous thrombosis	31	(34.4)	26	(26.3)
Transient risk factors for venous thrombosis				
Surgery previous 3 months	15	(16.7)	13	(13.1)
Trauma previous 3 months	10	(11.1)	15	(15.2)
Short term immobility	20	(22.2)	19	(19.2)
Infection previous 6 weeks	6	(6.7)	9	(9.1)
Pregnancy previous 3 months	5	(5.6)	3	(3.0)
Hormonal replacement therapy	4	(4.4)	6	(6.1)
Oral contraceptive pill	3	(3.3)	11	(11.1)
Permanent risk factors for venous thrombosis				
Previous venous thrombosis	9	(10.0)	9	(9.1)
Cancer	3	(3.3)	1	(1.0)
Obesity	9	(10.0)	11	(11.1)
Inflammatory bowel disease	0	(0.0)	3	(3.0)
1st degree relative with venous thrombosis	9	(10.0)	13	(13.1)
Two risk factors for venous thrombosis	26	(28.9)	18	(18·2)
Three risk factors for venous thrombosis	10	(11.1)	14	(14.1)
Thrombophilia				
Heterozygous F5 6025 polymorphism	23	(25.6)	22	(22.2)
Homozygous F5 6025 polymorphism	1	(1.1)	4	(4.0)
Other thrombophilic factor(s)	15	(16.7)	13	(13.1)
~~At 24 months follow-up~~				
~~Daily wear of compression stockings class II~~	~~57~~	~~(63.3)~~	~~51~~	~~(51.5)~~
~~Recurrent venous thromboembolism~~	~~10~~	~~(11.1)~~	~~18~~	~~(18.2)~~
~~Diagnosed with cancer~~	~~4~~	~~(4.4)~~	~~7~~	~~(7.1)~~

DVT=deep vein thrombosis. Data are mean (SD) ~~for time, mean (95% CI) for scores,~~ or n (%)

Figure 1. Trial Profile



CDT=catheter-directed thrombolysis. VCI=vena cava inferior. AC=anticoagulation. ECS=elastic compression stockings. PE=pulmonary embolism. ITT=intention to treat. QOL=quality of life.

There were no differences between the two treatments groups in mean generic QOL scores, disease-specific QOL scores, or symptom severity score after 24 months follow-up (Table 2). Both VEINES-QOL and VEINES-Sym scores obtained at 6 months follow-up were higher in the CDT arm compared to control patients (p=0.048 and p=0.016, respectively), however, the mean differences of 2.4~~3.2~~ and 3.2~~2.4~~ points, respectively, were below the ≥4 points cut-off for a clinically meaningful difference. The 6 months' EQ-5D score did not differ between the treatment groups. After 24 months follow-up 57 (63.3%) of patients allocated additional CDT reported to wear compression stocking daily vs 51 (51.5%) controls. In the CDT arm 10 (11.1%) experienced a recurrent venous thromboembolism and 4 (4.4%) were diagnosed with cancer. The corresponding numbers among control arm patients were 18 (18.2%) and 7 (7.1%), respectively [5].

Table 2 Generic and disease-specific quality of life and symptom severity according to treatment allocation

		~~Additional catheter-directed thrombolysis (n=90)~~	~~Standard treatment only (n=99)~~	~~P-value*~~
~~24 months~~				
~~Generic QOL~~	~~EQ-5D~~	~~0.80 (0.746-0.849)~~	~~0.84 (0.807-0.875)~~	~~0.705~~
~~Disease-specific QOL~~	~~VEINES-QOL~~	~~50.1 (47.9-52.3)~~	~~49.9 (48.0-51.8)~~	~~0.595~~
	~~VEINES-Sym~~	~~50.3 (48.0-52.5)~~	~~49.8 (47.9-51.6)~~	~~0.368~~
~~6-months~~				
~~Generic QOL~~	~~EQ-5D~~	~~0.82 (0.780-0.856)~~	~~0.81 (0.777-0.852)~~	~~0.893~~
~~Disease-specific QOL~~	~~VEINES-QOL~~	~~51.3 (49.2-53.4)~~	~~48.9 (46.8-50.9)~~	~~0.048~~
	~~VEINES-Sym~~	~~51.7 (49.8-53.7)~~	~~48.5 (46.4-50.6)~~	~~0.016~~

~~Data are mean scores (95% CI). *Mann Whitney U test~~

		Additional catheter-directed thrombolysis (n=90)	Standard treatment only (n=99)	Mean difference	P-value*
24 months					
Generic QOL	EQ-5D	0.80 (0.746-0.849)	0.84 (0.807-0.875)	0.04 (-0.01-0.17)	0.705
Disease-specific QOL	VEINES-QOL	50.1 (47.9-52.3)	49.9 (48.0-51.8)	0.2 (-2.8-3.0)	0.595
	VEINES-Sym	50.3 (48.0-52.5)	49.8 (47.9-51.6)	0.5 (-2.4-3.4)	0.368
6 months					
Generic QOL	EQ-5D	0.82 (0.780-0.856)	0.81 (0.777-0.852)	0.01 (-0.05-0.06)	0.893
Disease-specific QOL	VEINES-QOL	51.3 (49.2-53.4)	48.9 (46.8-50.9)	2.4 (-0.5-5.3)	0.048
	VEINES-Sym	51.7 (49.8-53.7)	48.5 (46.4-50.6)	3.2 (0.4-6.1)	0.016

Data are mean values (95% CI). *Mann Whitney U test

Independent of treatment allocation, the mean VEINES-QOL and VEINES–Sym scores were lower in patients who developed PTS compared to patients without PTS at both 6 and 24 months follow-up (p-values <0.001) (Table 3). The mean differences were 6.0 points after 6 month, and increased to 8.6 and 9.8 points, respectively, after 24 months. The mean EQ-5D index was 0.09 points lower in PTS patients at 24 months follow-up (p<0.001); however, there was no mean difference after 6 months. When looking at the PTS cases only at 24 months follow-up the three scores did not differ between the two treatment groups (p-value >0.8, data not shown).

Table 3 Generic and disease-specific quality of life and symptom severity according to PTS development

		PTS (n=92)	No PTS (n=97)	P value*
24 months				
Generic QOL	EQ-5D	0.77 (0.730-0.819)	0.86 (0.823-0.903)	<0.001
Disease-specific QOL	VEINES-QOL	45.6 (43.4-47.9)	54.2 (52.8-55.6)	<0.001
	VEINES-Sym	45.0 (42.7-47.2)	54.8 (53.5-56.0)	<0.001
6 months				
Generic QOL	EQ-5D	0.80 (0.770-0.837)	0.82 (0.788-0.869)	0.062
Disease-specific QOL	VEINES-QOL	46.8 (44.6-49.0)	53.0 (51.3-54.7)	<0.001
	VEINES-Sym	46.9 (44.6-49.1)	53.0 (51.4-54.6)	<0.001

Data are mean scores (95% CI). * Mann Whitney U test

		PTS (n=92)	No PTS (n=97)	Mean difference	P-value*
24 months					
Generic QOL	EQ-5D	0.77 (0.730-0.819)	0.86 (0.823-0.903)	0.09 (0.03-0.15)	<0.001
Disease-specific QOL	VEINES-QOL	45.6 (43.4-47.9)	54.2 (52.8-55.6)	8.6 (5.9-11.2)	<0.001
	VEINES-Sym	45.0 (42.7-47.2)	54.8 (53.5-56.0)	9.8 (7.3-12.3)	<0.001
6 months					
Generic QOL	EQ-5D	0.80 (0.770-0.837)	0.82 (0.788-0.869)	0.02 (-0.08-0.28)	0.062
Disease-specific QOL	VEINES-QOL	46.8 (44.6-49.0)	53.0 (51.3-54.7)	6.2 (3.4-9.09)	<0.001
	VEINES-Sym	46.9 (44.6-49.1)	53.0 (51.4-54.6)	6.1 (3.4-8.9)	<0.001

Data are mean values (95% CI). * Mann Whitney U test

Looking at individual items concerning problems with mobility (EQ-5D) and limitations in daily activities at home, work or during leisure time (VEINES-QOL) there was no differences between the two treatment groups; however patients with PTS reported more problems and limitations than patients without PTS (data not shown).

The proportions of patients that reported clinically meaningful changes over time during the 6 to 24 months follow-up did not differ between the two treatment groups with regards to the two QOL scores, and the majority of patients reported no QOL change (table 4). In both groups 1 in 5 patients reported worsening of the Sym score, and 32% of control patients reported improved symptom severity compared to 16% treated with CDT (p=0.029).

Table 4 Changes in generic and disease-specific quality of life and symptom severity during 6 to 24 months follow-up*

		Additional catheter-directed thrombolysis (n=90)		Standard treatment only (n=99)		P-value**
		n	% (95% CI)	n	% (95% CI)	
Generic QOL	EQ-5D improved	15	16.7 (10.0-24.4)	24	24.5 (16.6-33.4)	0.233
	EQ-5D worsened	22	24.4 (16.4-34.1)	16	16.3 (9.9-24.4)	
Disease-specific QOL	VEINES-QOL improved	17	19.5 (11.8-28.0)	27	27.3 (19.2-36.7)	0.462
	VEINES-QOL worsened	19	21.8 (13.6-30.4)	19	19.2 (12.3-27.8)	
	VEINES-Sym improved	14	15.9 (9.1-24.2)	32	32.3 (23.7-42.0)	0.029
	VEINES-Sym worsened	20	22.7 (14.5-31.7)	21	21.2 (14.0-30.1)	
		PTS (n=92)		No PTS (n=97)		P-value*
		n	% (95% CI)	n	% (95% CI)	
Generic QOL	EQ-5D improved	15	16.5 (9.8-24.9)	24	24.7 (16.9-34.0)	0.041
	EQ-5D worsened	25	27.5 (18.8-36.9)	13	13.4 (7.7-21.3)	
Disease-specific QOL	VEINES-QOL improved	21	23.3 (15.1-32.2)	23	24.0 (16.1-32.9)	0.017
	VEINES-QOL worsened	26	28.9 (19.8-38.1)	12	12.5 (6.9-20.1)	
	VEINES-Sym improved	20	22.0 (14.2-31.0)	26	27.1 (18.7-36.3)	0.017
	VEINES-Sym worsened	28	30.8 (21.7-40.4)	12	13.5 (7.7-21.3)	

*A meaningful change was defined as ≥4 points for VEINES-QOL/Sym scores and ≥0.08 for the EQ-5D index; improvement or worsening below this was registered as no change. **chi-square test

Correspondingly, when comparing proportions with meaningful changes in the three different scores during follow-up in patients with and without development of PTS independent of treatment allocation, the EQ-5D and VEINES-QOL scores worsened in nearly 30% of patients with PTS compared to 13% of patients who did not develop PTS (p=0.041 and p=0.017, respectively)(table 4). Finally, 31% patients with PTS reported worsening of the Sym score compared to 14% of patients without PTS (p=0.017).

Discussion

We have previously shown that after a high proximal DVT additional CDT reduces the frequency of PTS [5]. Nevertheless, in the present report we found no differences in long-term QOL between patients

treated with additional CDT compared to patients who received standard treatment with anticoagulation and compression stockings alone. However, patients who developed PTS after 24 months reported poorer QOL with both EQ-5D and VEINES-QOL, and more symptoms on Sym score compared to patients without PTS. This finding is in line with other reports, and the VEINES-QOL/Sym scores were in similar ranges as previously reported in DVT populations [6,15-17].

To our knowledge we are the first to investigate QOL after CDT in a well-designed study using validated QOL instruments and PTS assessment. We have recently in a retrospective study of 71 patients previously treated with CDT shown that VEINES-QOL/Sym scores were poorer in patients with established PTS compared to no PTS (median) 6 years after the index DVT, and poorer in patients compared to a control group without previous DVT [17]. Another retrospective study of corresponding size found improved QOL and less post-thrombotic symptoms in patients treated with CDT compared to similar patients treated with anticoagulation only; however, this study did not use a disease-specific QOL instrument or a validated assessment of PTS [18]. This finding was not supported in our RCT, and long-term QOL may not represent a significant secondary efficacy outcome after CDT.

The baseline scores were obtained within 1-2 days following the verification of the acute DVT, and the low EQ-5D scores are likely to reflect the patients' medical emergency situation at that time point. The items of the VEINES instrument are concerned with "the last 4 weeks" and mean symptom duration among study participants was only 6-7 days and, as indicated by the relatively better scores, the VEINES-QOL/Sym baseline results are likely to reflect a longer period including time before symptom onset. Finally, QOL is a more appropriate outcome for chronic conditions, and together with our lack of more frequent study visits and longitudinal assessments, we did not include baseline scores in our analyses.

The finding that more control patients reported a meaningful improvement in the Sym score during follow-up than patients treated with CDT, should be interpreted with caution as the 6 months Sym score

was higher in the CDT arm, though this difference did not reach a meaningful difference of at least 4 points.

We regard our study population to be representative and the CDT procedure to be applicable in a clinical setting [5]. However, due to the open label design, bias in patient reported outcomes like QOL cannot be excluded, and it is uncertain in what direction such bias would impact the results. As our eligibility criteria allowed for study participants to enroll with up to 21 days of symptoms, this meant that patients with sub-acute DVT, that is more than 14 days of symptoms, may have entered the study and possibly contributed to the overall high PTS frequency and lack of treatment group differences in the QOL scores [19]. However, as the mean symptom duration was less than 7 days and only 15 patients (hereunder 8 controls) had more than 14 days of symptom, we find this unlikely. Finally, two ongoing RCTs; the American ATTRACT study and the DUTCH CAVA trial, will provide additional data to the field of QOL after CDT treatment (www.clinicaltrials.gov; NCT 00790335 and NCT 00970619).

The Villalta scale has been validated and recommended for assessment of PTS [13,20], however, as no gold standard exists and a relatively high frequency of PTS was found in both treatment arms, concerns have been raised about the clinical benefit of CDT as shown in the CaVenT study [5,21]. The present findings of poorer QOL in those who developed PTS, as obtained within an appropriately designed RCT, underpin our perception that the 15% absolute reduction in PTS as assessed with the Villalta scale and shown in ~~CavenT~~CaVenT, does represent a clinically meaningful effect of additional CDT [5].

It has been recommended to include QOL as part of the long-term follow-up assessment of patients at risk of PTS [6], and a recent review "recommend(s) that the Villalta score combined with a venous disease-specific quality-of-life questionnaire be considered as the "gold standard" for the diagnosis and classification of PTS" [22]. The VEINES questionnaire would be a candidate, but such a combination must be validated in properly designed studies and take into account the apparent overlap between the

Villalta score and the VEINES-scores; all items in the Sym score are covered in the QOL score, 2/3 of Sym items are covered in Villalta, and 1/4 of the QOL items are covered in Villalta. Finally, 5 of 11 items in Villalta score, i.e., the symptom rating, are in fact patient reported outcomes (PRO), and combining with another patient PRO instrument should seek to avoid assessing the same thing twice over.

The generic instrument EQ-5D showed a clinically meaningful and statistically significant poorer QOL measure in patients who developed PTS, indicating that this preference based questionnaire can be included in studies on PTS and thereby allowing analyses on utilities and cost-effectiveness for decision making [23]. However, the sample size was powered to detect a 15% reduction in PTS after additional CDT, not improvement in QOL, which was among the secondary outcome measures. Accordingly, the negative finding in terms of no difference in QOL between the treatment arms, may relate to the sensitivity of the instruments, the prevalence of PTS, and the lack of power to detect a statistically significant difference. Finally, the VEINES scores differed significantly between patients with PTS vs. no PTS, and the magnitude of the mean difference was 6 points or higher. This has been reported to represent meaningful differences, but a well-established definition or cut-off for a clinically meaningful difference in VEINES scores is lacking, and also this limitation must be taken into account when interpreting the results [10].

In conclusion, there was no difference in long-term QOL between patients with a high proximal DVT treated with additional CDT compared to those treated with anticoagulation and compression therapy alone. Patients who developed PTS reported poorer QOL and more symptoms than patients without PTS. This is in line with previous reports, and supports the use of QOL as an outcome measure in clinical research on patients who are at risk of PTS.

Addendum: role of each author

T Enden: Design of study, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript, obtaining funding

H S Wik: Acquisition of data, interpretation of data, critical revision of manuscript

A K Kvam: Interpretation of data, and critical revision of manuscript

Y Haig: Acquisition of data and critical revision of manuscript

N E Kløw: Design of study, acquisition of data, critical revision of manuscript, obtaining funding

P M Sandset: Design of study, acquisition of data, critical revision of manuscript, obtaining funding

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Disclosure of Conflicts of Interests

The authors state that they have no conflict of interest.

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Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis: secondary outcomes of the randomised, non-blinded, parallel-group CaVenT study

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Summary:

Objectives: To investigate whether additional catheter-directed thrombolysis (CDT) improves long-term quality of life (QOL) compared to standard treatment with anticoagulation and compression stockings alone in patients with proximal deep vein thrombosis (DVT).

Design: Open-label randomised controlled trial.

Setting: 19 hospitals in the Norwegian southeastern health region.

Participants: Patients (18-75 years) with a high proximal DVT, symptoms <21 days, and no increased risk of bleeding were eligible. 189 of 209 recruited patients completed 24 months follow-up.

Interventions: Participants were randomized to additional CDT with alteplase for 1-4 days or to standard treatment only with 6 months anticoagulation and 24 months of compression stockings.

Primary and secondary outcome measures: Planned secondary outcome measures included QOL as assessed with the generic instrument EQ-5D and the disease specific instrument VEINES-QOL/Sym. Primary outcome measure was post-thrombotic syndrome (PTS) after 24 months.

Results: After 24 months there were no differences in QOL between the additional CDT and standard treatment arms; mean difference for the EQ-5D index was 0.04 (95% CI —0.10-0.17), for the VEINES-QOL score 0.2 (95% CI -2.8-3.0), and for the VEINES-Sym score 0.5 (95% CI -2.4-3.4);(p-values >0.37). Independent of treatment arms, patients with PTS had poorer outcomes than patient without PTS; mean difference for EQ-5D was 0.09 (95% CI 0.03-0.15) , for VEINES-QOL score 8.6 (95% CI 5.9-11.2) , and for VEINES-Sym score 9.8 (95% CI 7.3-12.3); (p-values <0.001).

Conclusions: QOL did not differ between patients treated with additional CDT compared to standard treatment alone. Patients who developed PTS reported poorer QOL and more symptoms than patients without PTS. QOL should be included as an outcome measure in clinical studies on patients at risk of PTS.

Trial registration: NCT00251771

Article summary

Article Focus

- Assessment of quality of life may provide meaningful information not captured by clinical scores and other traditional health outcome measures.
- Additional catheter-directed thrombolysis for proximal deep vein thrombosis improves long-term clinical outcome by reducing post-thrombotic syndrome and is likely to be a cost-effective alternative to standard treatment alone.
- Our objective was to investigate whether additional thrombolysis also improves long-term quality of life compared to standard treatment alone.

Key Messages

- Quality of life did not differ between patients allocated thrombolytic therapy compared to control patients who receive standard anticoagulation and compression stockings only.
- Patients who developed post-thrombotic syndrome had poorer generic and disease specific quality of life scores compared to patients without post-thrombotic syndrome.
- Quality of life assessment should be among the long-term outcome measures in clinical research on patients who are at risk of developing post-thrombotic syndrome.

Strengths and Limitations

- A robust study design where patient reported quality of life was assessed using validated generic and disease-specific instruments within the setting of a multicenter open-label randomized controlled trial.
- The study was designed to detect a difference in the frequency of post-thrombotic syndrome between the two treatment arms and may have been underpowered to detect a clinically meaningful difference in quality of life. Other possible explanations include a relatively small effect on the reduction in post-thrombotic syndrome and the smaller proportion presenting with iliofemoral DVT relative to infrainguinal DVT.
- More frequent study visits and longitudinal assessments of quality of life would have allowed for better explanatory analyses, and may have added to the interpretation of clinically meaningful differences in the disease specific quality of life scores.

Introduction

Following standard treatment including anticoagulation and compression stockings, still at least 1 in 4 are at risk of developing a post-thrombotic syndrome (PTS) after suffering a proximal deep vein thrombosis (DVT), i.e., DVT in the popliteal vein or above [1-3]. PTS is characterized by persistent pain, heaviness, swelling, and deterioration of the skin. Previously in the CaVenT Study we have shown that additional catheter-directed thrombolysis (CDT) in patients with a high proximal DVT localized in the mid-thigh level or above, and a low risk of bleeding, reduced the frequency of PTS from 56% to 41% (p=0.047) after 2 years and that CDT is likely to be a cost-effective alternative to standard treatment only [4,5]. However, as PTS is a chronic condition associated with substantial morbidity and with no healing treatment options, assessment of both generic and disease-specific health-related quality of life (QOL) including the impact on health and daily functioning may provide meaningful information not captured by clinical scores and other traditional health outcome measures. Development of PTS has been shown to be a principal determinant of QOL following DVT of the lower limb; however, there is currently no gold standard for the PTS diagnosis [6]. We aimed at investigating whether additional CDT for a high proximal DVT improved long-term QOL compared to standard treatment alone.

Materials and methods

Study population

Patients were recruited as part of the CaVenT study, an open randomized controlled trial (RCT), from 19 hospitals within the South-Eastern Norway Regional Health Authority, which serves a population of 2.6 million people. Patients aged 18–75 years with a first-time objectively verified acute high proximal DVT, defined as thrombus in mid-thigh level or higher, and with a low risk of bleeding, were eligible for inclusion if symptoms had lasted <21 days. Complete eligibility criteria and trial profile have been

reported previously [5,7]. Patients were randomly assigned, using sealed numbered envelopes, to standard treatment with at least 6 months of anticoagulation and compression stockings for 24 months or to CDT with alteplase for 1-4 days in addition to standard treatment; the treatment strategies have previously been reported in detail [5,8]. Prior to treatment allocation, written informed consent was obtained by the local trial site investigator. The study protocol was approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Medicines Agency, and was registered at www.clinicaltrials.gov with the unique trial identifier NCT00251771.

Variables and instruments

Long-term quality of life

After 6 and 24 months follow-up the patients completed a self-reporting questionnaire including the validated Norwegian versions of the generic instrument EQ-5D (www.euroqol.org) and the disease-specific QOL instrument VEINES-QOL/Sym [9,10]. The VEINES-QOL/Sym comprises 26 items regarding problems of the lower limbs [4]. The instrument measures symptoms, limitations in daily activity and psychological impact during the previous 4 weeks, and change over the past year. Responses are rated on 2- to 7-point descriptive scales, and two summary scores are computed. The VEINES-QOL summary score assesses QOL, and the VEINES-Sym score is a subscale that measures symptom severity only. Higher scores represent better QOL and/or fewer symptoms, and a difference or change of ≥4 points has been suggested to represent a clinically meaningful difference [10].

The EQ-5D is a preference-based generic instrument for describing and valuing QOL, and is a widely used health measure outcome in clinical trials and cost-effectiveness and cost-utility analyses. This descriptive classification system comprises the five items mobility, self-care, activity, pain, and anxiety; each with the three levels reflecting the patient's status that particular day. The scoring gives a single

number/health status index ranging from 0 (dead) to 1 (best possible health). A difference or change in this index of ≥0.08 is likely to represent a clinically meaningful difference [11,12].

Assessment of post-thrombotic syndrome

In the absence of a gold standard for a PTS diagnosis, the Villalta score has been recommended for PTS assessment in clinical trials [13]. This score includes the five patient-rated symptoms pain, cramps, heaviness, paresthesia, pruritus, and the six clinician-rated signs edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, and redness. Each sign or symptom is rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and summed to produce a total score, where less than 5 indicates no PTS, 5–14 indicates mild or moderate PTS, and 15 or more (or presence of venous ulcer) indicates severe PTS.

Statistical analysis and sample size

Health related QOL was among the pre-specified secondary outcomes of the CaVenT Study, while the primary outcome of PTS after 2 years was the basis for the sample size calculation [7]. For all patients a EQ-5D summary index was calculated based on values from a Danish population as no Norwegian algorithm exists [14]. Scores for VEINES-QOL and VEINES-Sym were computed using standard scoring algorithms obtained from the authors [10]. Statistical analyses were by intention to treat. Any ineligible patients mistakenly included were excluded. Missing outcome data because of withdrawal of consent or death from cancer or other causes not related to CDT or anticoagulation were assumed to be missing independently of treatment received and were not included in the analyses [5]. When comparing dichotomous variables between groups, a two-sided chi-square test was used. Normal distribution was tested visually using plots, followed by comparing non-normally distributed continuous variables between independent groups with a two-sided Mann-Whitney U test. Findings with p-values less than

0.05 were deemed statistically significant. The statistical analyses were performed using the statistical package SPSS, version 18.0 (SPSS Inc, Chicago, IL, USA).

Results

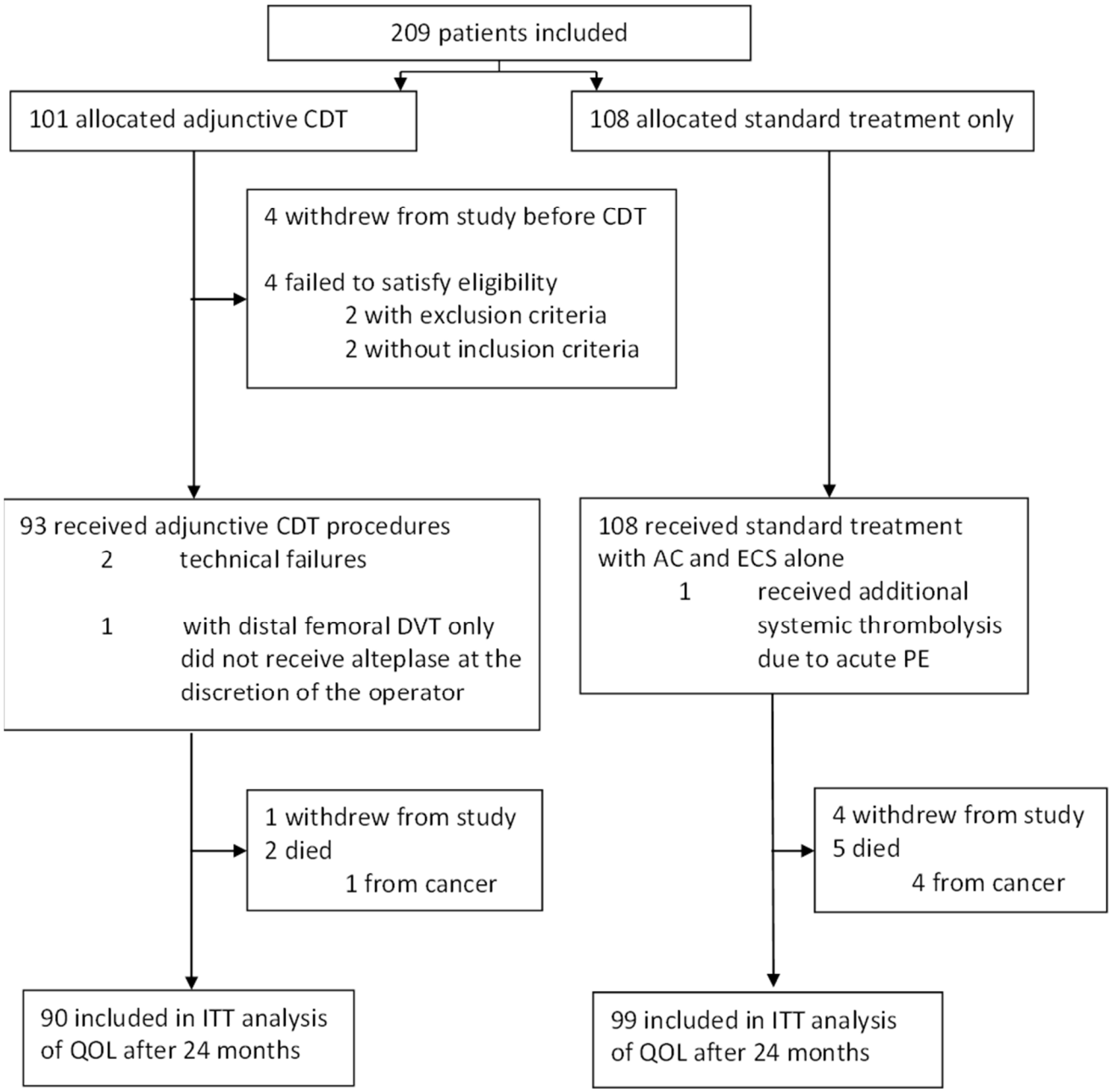
209 patients with a high proximal DVT were recruited and randomized to additional CDT or to standard treatment alone during 2006-2009. Table 1 shows the demographic and clinical characteristics of the 189 patients with complete 2 years follow-up included in the present analysis; 90 in the CDT group and 99 controls. Mean age was 51.5 years (SD 15.8) and 70 (37%) participants were female. Mean duration of symptoms before diagnosis and start of treatment was 6.6 days (SD 4.6). Most baseline demographic and clinical characteristics, including VEINES-QOL/Sym and EQ-5D scores, were fairly equally distributed between the two treatment groups. Figure 1 presents details on the study participants and the complete trial profile [5].

Table 1 Demographic and clinical characteristics

	Adjunctive catheter-directed thrombolysis (n=90)		Standard treatment only (n=99)	
Baseline				
Age (years)	53.3	(15.7)	50.0	(15.8)
Women	32	(35.6)	38	(38.4)
Duration of symptoms of acute DVT (days)	6.4	(4.4)	6.8	(4.8)
EQ-5D index	0.46 (0.39)		0.63 (0.99)	
VEINES-QOL score	50.2 (9.3)		50.1 (10.7)	
VEINES-Sym score	50.4 (9.3)		49.5 (10.7)	
No risk factor for venous thrombosis	31	(34.4)	26	(26.3)
Transient risk factors for venous thrombosis				
Surgery previous 3 months	15	(16.7)	13	(13.1)
Trauma previous 3 months	10	(11.1)	15	(15.2)
Short term immobility	20	(22.2)	19	(19.2)
Infection previous 6 weeks	6	(6.7)	9	(9.1)
Pregnancy previous 3 months	5	(5.6)	3	(3.0)
Hormonal replacement therapy	4	(4.4)	6	(6.1)
Oral contraceptive pill	3	(3.3)	11	(11.1)
Permanent risk factors for venous thrombosis				
Previous venous thrombosis	9	(10.0)	9	(9.1)
Cancer	3	(3.3)	1	(1.0)
Obesity	9	(10.0)	11	(11.1)
Inflammatory bowel disease	0	(0.0)	3	(3.0)
1st degree relative with venous thrombosis	9	(10.0)	13	(13.1)
Two risk factors for venous thrombosis	26	(28.9)	18	(18·2)
Three risk factors for venous thrombosis	10	(11.1)	14	(14.1)
Thrombophilia				
Heterozygous F5 6025 polymorphism	23	(25.6)	22	(22.2)
Homozygous F5 6025 polymorphism	1	(1.1)	4	(4.0)
Other thrombophilic factor(s)	15	(16.7)	13	(13.1)

DVT=deep vein thrombosis. Data are mean (SD) or n (%)

Figure 1. Trial Profile



CDT=catheter-directed thrombolysis. VCI=vena cava inferior. AC=anticoagulation. ECS=elastic compression stockings. PE=pulmonary embolism. ITT=intention to treat. QOL=quality of life.

There were no differences between the two treatments groups in mean generic QOL scores, disease-specific QOL scores, or symptom severity score after 24 months follow-up (Table 2). Both VEINES-QOL and VEINES-Sym scores obtained at 6 months follow-up were higher in the CDT arm compared to control patients (p=0.048 and p=0.016, respectively), however, the mean differences of 2.4 and 3.2 points, respectively, were below the ≥4 points cut-off for a clinically meaningful difference. The 6 months' EQ-5D score did not differ between the treatment groups. After 24 months follow-up 57 (63.3%) of patients allocated additional CDT reported to wear compression stocking daily vs 51 (51.5%) controls. In the CDT arm 10 (11.1%) experienced a recurrent venous thromboembolism and 4 (4.4%) were diagnosed with cancer. The corresponding numbers among control arm patients were 18 (18.2%) and 7 (7.1%), respectively [5].

Table 2 Generic and disease-specific quality of life and symptom severity according to treatment allocation

		Additional catheter-directed thrombolysis (n=90)	Standard treatment only (n=99)	Mean difference	P-value*
24 months					
Generic QOL	EQ-5D	0.80 (0.746-0.849)	0.84 (0.807-0.875)	0.04 (-0.01-0.17)	0.705
Disease-specific QOL	VEINES-QOL	50.1 (47.9-52.3)	49.9 (48.0-51.8)	0.2 (-2.8-3.0)	0.595
	VEINES-Sym	50.3 (48.0-52.5)	49.8 (47.9-51.6)	0.5 (-2.4-3.4)	0.368
6 months					
Generic QOL	EQ-5D	0.82 (0.780-0.856)	0.81 (0.777-0.852)	0.01 (-0.05-0.06)	0.893
Disease-specific QOL	VEINES-QOL	51.3 (49.2-53.4)	48.9 (46.8-50.9)	2.4 (-0.5-5.3)	0.048
	VEINES-Sym	51.7 (49.8-53.7)	48.5 (46.4-50.6)	3.2 (0.4-6.1)	0.016

Data are mean values (95% CI). *Mann Whitney U test

Independent of treatment allocation, the mean VEINES-QOL and VEINES–Sym scores were lower in patients who developed PTS compared to patients without PTS at both 6 and 24 months follow-up (p-

values <0.001) (Table 3). The mean differences were 6 points after 6 month, and increased to 8.6 and 9.8 points, respectively, after 24 months. The mean EQ-5D index was 0.09 points lower in PTS patients at 24 months follow-up (p<0.001); however, there was no mean difference after 6 months. When looking at the PTS cases only at 24 months follow-up the three scores did not differ between the two treatment groups (p-value >0.8, data not shown).

Table 3 Generic and disease-specific quality of life and symptom severity according to PTS development

		PTS (n=92)	No PTS (n=97)	Mean difference	P-value*
24 months					
Generic QOL	EQ-5D	0.77 (0.730-0.819)	0.86 (0.823-0.903)	0.09 (0.03-0.15)	<0.001
Disease-specific QOL	VEINES-QOL	45.6 (43.4-47.9)	54.2 (52.8-55.6)	8.6 (5.9-11.2)	<0.001
	VEINES-Sym	45.0 (42.7-47.2)	54.8 (53.5-56.0)	9.8 (7.3-12.3)	<0.001
6 months					
Generic QOL	EQ-5D	0.80 (0.770-0.837)	0.82 (0.788-0.869)	0.02 (-0.08-0.28)	0.062
Disease-specific QOL	VEINES-QOL	46.8 (44.6-49.0)	53.0 (51.3-54.7)	6.2 (3.4-9.09)	<0.001
	VEINES-Sym	46.9 (44.6-49.1)	53.0 (51.4-54.6)	6.1 (3.4-8.9)	<0.001

Data are mean values (95% CI). * Mann Whitney U test

Looking at individual items concerning problems with mobility (EQ-5D) and limitations in daily activities at home, work or during leisure time (VEINES-QOL) there was no differences between the two treatment groups; however patients with PTS reported more problems and limitations than patients without PTS (data not shown).

The proportions of patients that reported clinically meaningful changes over time during the 6 to 24 months follow-up did not differ between the two treatment groups with regards to the two QOL scores, and the majority of patients reported no QOL change (table 4). In both groups 1 in 5 patients reported worsening of the Sym score, and 32% of control patients reported improved symptom severity compared to 16% treated with CDT (p=0.029).

Table 4 Changes in generic and disease-specific quality of life and symptom severity during 6 to 24 months follow-up*

		Additional catheter-directed thrombolysis (n=90)		Standard treatment only (n=99)		P-value**
		n	% (95% CI)	n	% (95% CI)	
Generic QOL	EQ-5D improved	15	16.7 (10.0-24.4)	24	24.5 (16.6-33.4)	0.233
	EQ-5D worsened	22	24.4 (16.4-34.1)	16	16.3 (9.9-24.4)	
Disease-specific QOL	VEINES-QOL improved	17	19.5 (11.8-28.0)	27	27.3 (19.2-36.7)	0.462
	VEINES-QOL worsened	19	21.8 (13.6-30.4)	19	19.2 (12.3-27.8)	
	VEINES-Sym improved	14	15.9 (9.1-24.2)	32	32.3 (23.7-42.0)	0.029
	VEINES-Sym worsened	20	22.7 (14.5-31.7)	21	21.2 (14.0-30.1)	
		PTS (n=92)		No PTS (n=97)		P-value*
		n	% (95% CI)	n	% (95% CI)	
Generic QOL	EQ-5D improved	15	16.5 (9.8-24.9)	24	24.7 (16.9-34.0)	0.041
	EQ-5D worsened	25	27.5 (18.8-36.9)	13	13.4 (7.7-21.3)	
Disease-specific QOL	VEINES-QOL improved	21	23.3 (15.1-32.2)	23	24.0 (16.1-32.9)	0.017
	VEINES-QOL worsened	26	28.9 (19.8-38.1)	12	12.5 (6.9-20.1)	
	VEINES-Sym improved	20	22.0 (14.2-31.0)	26	27.1 (18.7-36.3)	0.017
	VEINES-Sym worsened	28	30.8 (21.7-40.4)	12	13.5 (7.7-21.3)	

*A meaningful change was defined as ≥4 points for VEINES-QOL/Sym scores and ≥0.08 for the EQ-5D index; improvement or worsening below this was registered as no change. **chi-square test

Correspondingly, when comparing proportions with meaningful changes in the three different scores during follow-up in patients with and without development of PTS independent of treatment allocation, the EQ-5D and VEINES-QOL scores worsened in nearly 30% of patients with PTS compared to 13% of patients who did not develop PTS (p=0.041 and p=0.017, respectively)(table 4). Finally, 31% patients with PTS reported worsening of the Sym score compared to 14% of patients without PTS (p=0.017).

Discussion

We have previously shown that after a high proximal DVT additional CDT reduces the frequency of PTS [5]. Nevertheless, in the present report we found no differences in long-term QOL between patients

treated with additional CDT compared to patients who received standard treatment with anticoagulation and compression stockings alone. However, patients who developed PTS after 24 months reported poorer QOL with both EQ-5D and VEINES-QOL, and more symptoms on Sym score compared to patients without PTS. This finding is in line with other reports, and the VEINES-QOL/Sym scores were in similar ranges as previously reported in DVT populations [6,15-17].

To our knowledge we are the first to investigate QOL after CDT in a well-designed study using validated QOL instruments and PTS assessment. We have recently in a retrospective study of 71 patients previously treated with CDT shown that VEINES-QOL/Sym scores were poorer in patients with established PTS compared to no PTS (median) 6 years after the index DVT, and poorer in patients compared to a control group without previous DVT [17]. Another retrospective study of corresponding size found improved QOL and less post-thrombotic symptoms in patients treated with CDT compared to similar patients treated with anticoagulation only; however, this study did not use a disease-specific QOL instrument or a validated assessment of PTS [18]. This finding was not supported in our RCT, and long-term QOL may not represent a significant secondary efficacy outcome after CDT.

The baseline scores were obtained within 1-2 days following the verification of the acute DVT, and the low EQ-5D scores are likely to reflect the patients' medical emergency situation at that time point. The items of the VEINES instrument are concerned with "the last 4 weeks" and mean symptom duration among study participants was only 6-7 days and, as indicated by the relatively better scores, the VEINES-QOL/Sym baseline results are likely to reflect a longer period including time before symptom onset. Finally, QOL is a more appropriate outcome for chronic conditions, and together with our lack of more frequent study visits and longitudinal assessments, we did not include baseline scores in our analyses.

The finding that more control patients reported a meaningful improvement in the Sym score during follow-up than patients treated with CDT, should be interpreted with caution as the 6 months Sym score

was higher in the CDT arm, though this difference did not reach a meaningful difference of at least 4 points.

We regard our study population to be representative and the CDT procedure to be applicable in a clinical setting [5]. However, due to the open label design, bias in patient reported outcomes like QOL cannot be excluded, and it is uncertain in what direction such bias would impact the results. As our eligibility criteria allowed for study participants to enroll with up to 21 days of symptoms, this meant that patients with sub-acute DVT, that is more than 14 days of symptoms, may have entered the study and possibly contributed to the overall high PTS frequency and lack of treatment group differences in the QOL scores [19]. However, as the mean symptom duration was less than 7 days and only 15 patients (hereunder 8 controls) had more than 14 days of symptom, we find this unlikely. Finally, two ongoing RCTs; the American ATTRACT study and the DUTCH CAVA trial, will provide additional data to the field of QOL after CDT treatment (www.clinicaltrials.gov; NCT 00790335 and NCT 00970619).

The Villalta scale has been validated and recommended for assessment of PTS [13,20], however, as no gold standard exists and a relatively high frequency of PTS was found in both treatment arms, concerns have been raised about the clinical benefit of CDT as shown in the CaVenT study [5,21]. The present findings of poorer QOL in those who developed PTS, as obtained within an appropriately designed RCT, underpin our perception that the 15% absolute reduction in PTS as assessed with the Villalta scale and shown in CaVenT, does represent a clinically meaningful effect of additional CDT [5].

It has been recommended to include QOL as part of the long-term follow-up assessment of patients at risk of PTS [6], and a recent review "recommend(s) that the Villalta score combined with a venous disease-specific quality-of-life questionnaire be considered as the "gold standard" for the diagnosis and classification of PTS" [22]. The VEINES questionnaire would be a candidate, but such a combination must be validated in properly designed studies and take into account the apparent overlap between the

Villalta score and the VEINES-scores; all items in the Sym score are covered in the QOL score, 2/3 of Sym items are covered in Villalta, and 1/4 of the QOL items are covered in Villalta. Finally, 5 of 11 items in Villalta score, i.e., the symptom rating, are in fact patient reported outcomes (PRO), and combining with another patient PRO instrument should seek to avoid assessing the same thing twice over.

The generic instrument EQ-5D showed a clinically meaningful and statistically significant poorer QOL measure in patients who developed PTS, indicating that this preference based questionnaire can be included in studies on PTS and thereby allowing analyses on utilities and cost-effectiveness for decision making [23]. However, the sample size was powered to detect a 15% reduction in PTS after additional CDT, not improvement in QOL, which was among the secondary outcome measures. Accordingly, the negative finding in terms of no difference in QOL between the treatment arms, may relate to the sensitivity of the instruments, the prevalence of PTS, and the lack of power to detect a statistically significant difference. Finally, the VEINES scores differed significantly between patients with PTS vs. no PTS, and the magnitude of the mean difference was 6 points or higher. This has been reported to represent meaningful differences, but a well-established definition or cut-off for a clinically meaningful difference in VEINES scores is lacking, and also this limitation must be taken into account when interpreting the results [10].

In conclusion, there was no difference in long-term QOL between patients with a high proximal DVT treated with additional CDT compared to those treated with anticoagulation and compression therapy alone. Patients who developed PTS reported poorer QOL and more symptoms than patients without PTS. This is in line with previous reports, and supports the use of QOL as an outcome measure in clinical research on patients who are at risk of PTS.

Addendum: role of each author

T Enden: Design of study, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript, obtaining funding

H S Wik: Acquisition of data, interpretation of data, critical revision of manuscript

A K Kvam: Interpretation of data, and critical revision of manuscript

Y Haig: Acquisition of data and critical revision of manuscript

N E Kløw: Design of study, acquisition of data, critical revision of manuscript, obtaining funding

P M Sandset: Design of study, acquisition of data, critical revision of manuscript, obtaining funding

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Disclosure of Conflicts of Interests

The authors state that they have no conflict of interest.

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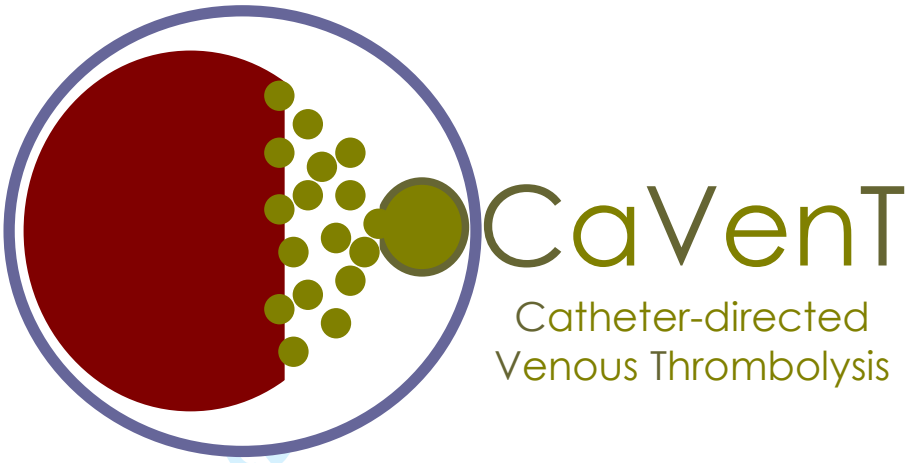
CONSORT Statement 2001 - Checklist

Items to include when reporting a randomized trial

PAPER SECTION And topic	Item	Descriptor	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	2
INTRODUCTION Background	2	Scientific background and explanation of rationale.	3
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	3
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	4
Objectives	5	Specific objectives and hypotheses.	3
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	5
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	5
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	3,4
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	3
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	4
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	3
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	5
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	6
Recruitment	14	Dates defining the periods of recruitment and follow-up.	5
Baseline data	15	Baseline demographic and clinical characteristics of each group.	6 + table 1
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	5 + table 2
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	8 + tables 2,3,4
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	3
Adverse events	19	All important adverse events or side effects in each intervention group.	Previous publication(s)
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	11-13
Generalizability	21	Generalizability (external validity) of the trial findings.	12
Overall evidence	22	General interpretation of the results in the context of current evidence.	11-13

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; **357**:1191-1194.



Protocol

Catheter-directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis - an open Randomized, Controlled, Clinical Trial

The CaVenT Study Group

Working Protocol - Amendment 04 – August 2007

CONTENTS

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1 SYNOPSIS

Deep vein thrombosis (DVT) is a severe disease which may cause severe disability and which is sometimes fatal. Conventional treatment with low molecular weight heparin (LMWH) and oral antiocoagulants is associated with some degree of long-term sequalae, i.e., post-thrombotic syndrome (PTS), in more than 60-80% of the patients. Systemic thrombolytic therapy reduces the risk of PTS, but is associated with an unacceptably high risk of bleeding complications, many being disabling or fatal. Catheter-directed thrombolytic (CDT) therapy is a novel treatment modality which has been introduced in many hospitals worldwide. Low dose fibrinolytic agents are delivered continuously and directly into the thrombus through a catheter until thrombus has dissolved. Although many, mostly small series, have suggested a beneficial effect of this costly treatment in terms of increased patency of the veins and improved short term functional outcome, there are no randomized clinical trials documenting its short and long-term efficacy and safety.

The present study is a randomized, open-label, multi-center clinical trial among hospitals in the Eastern and Southern Norway Health Authorities (Helse Øst and Sør). Patients with acute iliofemoral vein thrombosis will be randomized to either conventional treatment or CDT in addition to conventional treatment. Main outcome parameters are patency rates at 6 months and prevalence of PTS at 24 months. A number of secondary outcomes include bleeding complications, recurrent thrombosis, quality of life (QoL), markers of importance for successful lysis and recurrent thrombosis, and whether PTS is related to patency at the end of treatment.

Our main short-term hypothesis is that CDT of first-time acute DVT will increase patency of the affected iliofemoral vein segments after 6 months from <50% on conventional therapy to >80% after CDT. Our main long-term hypothesis is that CDT will improve long-term functional outcome, i.e., risk of PTS, assessed after 2 years, from >25% on conventional treatment to <10% after CDT. The estimated sample size is at least 100 evaluable patients in each group using a statistical significance (α) = 5% and a statistical power (1-β) = 80%.

2 BACKGROUND

Deep vein thrombosis (DVT) of the lower extremities is a common disease, which is associated with significant morbidity. The incidence of DVT is estimated as 1 event per 1,000 per year, which ranks it as one of the more common cardiovascular disorders [1]. Furthermore, DVT is associated with several important short- and long-term outcomes [2]. Short-term there are symptoms of pain and swelling due to inflammation and obstruction. In a small minority of cases, the condition leads to phlegmasia cerulea dolens in which extensive venous obstruction leads to ischemia or infarction of the extremity. Lastly, DVT can also lead to pulmonary embolism (PE), which can be fatal. Long-term sequelae of DVT include recurrent venous thromboembolism (VTE), post-thrombotic syndrome (PTS), and chronic thromboembolic pulmonary hypertension.

Anticoagulation therapy is the basic treatment of DVT[3], which purpose is to inhibit the thrombotic process and the inflammatory response so that the thrombus can be cleared by endogenous fibrinolysis. Anticoagulation therapy thereby alleviates acute symptoms, prevents PE, and recurrent events. In most cases, anticoagulation is achieved acutely with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) therapy, followed by long term anticoagulation with oral vitamin K antagonists (eg warfarin).

Anticoagulation therapy is highly efficacious for the prevention of recurrent VTE, PE, and death[3;4], but the ability to prevent PTS as an outcome is less clear[5]. PTS is thought to be a result of residual venous stenosis and damage to the venous valves which together cause venous hypertension. Venous hypertension leads to chronic edema and fibrin deposition in the interstitial tissues, which in turn bring about poor oxygen exchange. Insufficient oxygenation induces skin changes, pain and, in severe cases, chronic ulceration.

Several studies have addressed the epidemiology of PTS[5;6], i.e., the incidence of PTS over time, its risk factors, the relationship between vein patency and development of PTS, and the usefulness of compression stockings to prevent PTS following a first episode of acute DVT treated with anticoagulation alone[5;7-10]. The incidence of moderate or severe PTS varied across these studies, but in general increased over time. Moderate to severe PTS developed in 2% to 11% of patients with DVT provided that compression stockings were worn at some early point after the acute DVT. Elastic compression stockings may reduce the risk of PTS by approximately 50%[11;12]. Risk factors for severe PTS identified by some, but not all of these studies, were recurrent ipsilateral DVT, extent of initial thrombus, and obesity. Although the role of return of vein patency has not been established, it may still be an appropriate surrogate for long-term outcomes.

Thrombolytic agents, such as streptokinase (SK), urokinase (UK), and recombinant tissue plasminogen activator (rt-PA) are, theoretically, ideal adjuvants to standard anticoagulation therapy because they potentially dissolve thrombi, promote early vein recanalization, and thereby, minimize vein stenosis and valve dysfunction[13;14]. Therefore, treatment strategies incorporating these agents with anticoagulation may be more effective than those using anticoagulation alone for the prevention of PTS. In addition, in the minority of cases with phlegmasia cerulea dolens, thrombolytic therapies may prove limb saving. However, despite the theoretical advantages and a history of more than 30 years of use, thrombolytic therapy has not been widely embraced for DVT treatment due to poor

Table 1 Summary results for the trials comparing streptokinase (SK) to intravenous unfractionated heparin (UFH); Values in parentheses are percent of cases.

Study	**SK**		**UFH**		**Odds Ratio (95% CI)**	
	Events/N	**(%)**	**Events/N**	**(%)**		
	Efficacy = significant lysis					
Robertson 1[15]	5/8	(63)	1/8	(13)	9.4	(0.9, 98.1)
Kakkar[16]	7/10	(70)	2/20	(20)	8.2	(1.1, 58.7)
Robertson 2[17]	5/9	(56)	1/7	(14)	6.2	(0.6, 62.1)
Tsapogas[18]	10/19	(53)	1/15	(7)	12.6	(1.7, 96.5)
Porter[19]	13/24	(54)	8/26	(31)	2.6	(0.8, 8.2)
Elliot[20]	17/26	(65)	0/25	(0)	188.4	(3.4, 10494)
Arnesen[21]	15/21	(71)	5/21	(24)	7.6	(1.9, 29.3)
Total	**72/117**	**(62)**	**18/112**	**(16)**	**8.5**	**(4.4, 16.3)**
	Major Hemorrhage					
Robertson	2/8	(25)	0/8	(0)	11.9	(0.2, 843)
Kakkar	3/30	(39)	2/10	(20)	1.6	(0.2, 11.8)
Tsapogas	4/19	(21)	0/15	(0)	17.0	(0.3, 1022)
Porter	4/24	(17)	1/26	(4)	4.2	(0.5, 34)
Elliot	2/26	(8)	0/25	(0)	9.4	(0.1, 607)
Schulman[22]	3/17	(18)	1/19	(5)	3.3	(0.4, 29.4)
Arnesen	2/21	(10)	2/21	(10)	1.0	(0.1, 7.1)
Total	**20/115**	**(16)**	**6/124**	**(5)**	**3.9**	**(1.5, 10.3)**

Table 2 Summary results for the trials comparing urokinase (UK) to intravenous unfractionated heparin (UFH); Values in parentheses are percent of cases.

Study	UK Events/N	(%)	UFH Events/N	(%)	Odds Ratio (95% CI)	
	Efficacy = significant lysis					
Goldhaber[23]	1/8	(13)	1/9	(11)	1.1	(0.1, 2.9)
Kiil[24]	1/11	(9)	1/9	(11)	0.8	(0, 14.9)
Total	**2/19**	**(11)**	**2/18**	**(11)**	**1.0**	**(0.1, 7.2)**
	Major Hemorrhage					
Goldhaber	0/8	(0)	1/9	(11)	0.2	(0, 16.3)
Kiil	0/11	(0)	3/9	(33)	0.8	(0, 2.8)
Total	**0/19**	**(0)**	**4/18**	**(22)**		

Table 3 Summary results for the trials comparing recombinant tissue plasminogen activator (rt-PA) to intravenous unfractionated heparin (UFH); Values in parentheses are percent of cases.

Study	rt-PA Events/N	(%)	UFH Events/N	(%)	Odds Ratio (95% CI)	
	Efficacy = significant lysis					
Goldhaber[23]	15/53	(28)	0/12	(0)	10.1	(0.8, 999)
Turpie 2[25]	6/29	(21)	2/30	(7)	3.7	(0.6, 29)
Turpie 1[25]	7/12	(58)	0/12	(0)	34.1	(2.0, 999)
Total	**28/94**	**(30)**	**2/54**	**(4)**	**11.7**	**(2.6, 53)**
	Major Hemorrhage					
Goldhaber	1/53	(2)	0/12	(0)	0.7	(0.01, 999)
Turpie 2	0/29	(0)	0/30	(0)	0.3	(0, 22000)
Turpie 1	1/12	(0)	0/12	(0)	1.0	(0.02, 43)
Verahaeghe[26]	0/11	(0)	3/9	(33)	7.3	(0, 2.8)
Total	**0/105**	**(2)**	**3/63**	**(48)**	**0.4**	

documentation of its efficacy and high short-term risk of bleeding[27]. Overall only a few hundred patients have been evaluated in randomized clinical trials. The effects of SK treatment versus heparin are summarized in Table I, the effects of urokinase versus heparin in Table II, and that of rt-PA versus heparin in Table III. The overall clinical effects are shown in Table IV.

Table 4 Summary results of all trials of thrombolytic therapy for acute DVT (after[13]).

Treatment	Success rate (% with significant lysis)	Major hemorrhage (%)
Unfractionated heparin	12	6
SK	62	16
SK high dose	Uninterpretable	Uninterpretable
SK low dose	27	15
UK	11	0
rt-PA	30	8
rt-PA high dose	6	29
rt-PA local administration	27	10
Catheter directed (UK and rt-PA) (no randomized clinical trials)	83	11

Several published studies using ultrasound imaging have demonstrated considerable endogenous ability to lyse thrombi after conventional anticoagulation therapy[2]. One year after acute DVT, somewhere between 30% and 73% of patients will normalize their ultrasound findings. Earlier in the disease course, patency rates are lower, demonstrating that over time there is continued recanalization of the vein. The studies do not describe PTS incidence and whether or not development of the condition correlates with recanalization status. Without this information, it is difficult to answer the important question of whether or not early recanalization protects against development of PTS.

Catheter-directed thrombolytic therapy (CDT) is a relatively new technique for treatment of DVT[13;28] and its efficacy has recently been reviewed[29]. It involves application of the thrombolytic agent directly into the thrombus using a catheter with multiple side holes. The catheter is passed into the clot under radiographic guidance. The venous puncture may be central or peripheral to the thrombosed vein. For thrombolysis of the pelvic and the femoral veins, the access was in the early studies of the internal jugular, or the contralateral or ipsilateral femoral veins. Subsequent investigators have used the ipsilateral popliteal vein with success and this appears to be the site of choice. The thrombolytic agent is administered over 1-4 days until dissolution of the clot is apparent. Both UK, alteplase (Actilyse®), reteplase (Rapilysin®) and tenecteplase (Metalyse®) has been used, but UK is no longer available in the market, and only alteplase may be given as a continuous iv infusion, preferably at 0.001-0.02 mg/kg/hour[30;31]. Heparin therapy should be given concomitantly intravenously probably at subtherapeutic doses[29;30;32;33], corresponding to a 1.2-1.7 times prolongation of aPTT.

The decision to discontinue the drug is based on daily venographic examinations through the indwelling catheter. Depending on the findings the catheter may be pulled out, the infusion continued, or the catheter repositioned. To obtain flow in the veins balloon inflation may be performed at the follow-up. Thrombolytic agents are given until there is no more evidence of thrombosis or until there is little improvement in venographic appearance. After 72-96 hours thrombolysis is discontinued. Adjuvant therapies include angioplasty, angioplasty with stents, thrombectomy, and surgically created arterio-venous fistulas.

So far, there are no randomized clinical trials with long-term follow-up on the efficacy of CDT therapy, but at least 15 case series have been reported[29;34-37]. Combining the studies, 263 patients received this type of therapy for thrombosis of the iliofemoral veins or inferior vena cava. 221 (84%) patients were considered to have successful short-term outcomes based on venographic appearance and 13 (4.9%) patients had bleeding severe enough to warrant transfusion. Long term outcomes were not reported, and the authors did not describe the proportion of patients requiring adjuvant therapy.

A National DVT Registry was established in North-America to analyze results in a large number of patients treated with CDT[38]. This registry included 473 patients with documented lower extremity DVT treated with CDT, but follow-up data included only 287 patients who received 312 treatments. Thrombi subjected to lysis included either ilio-femoral vein thrombosis in 71% of cases and femoro-popliteal vein thrombosis in 25% of cases. The mean age of patients was 47.5 years and the mean duration of infusion was 53 h. All patients had six months of therapy with oral anticoagulants following CDT and many had heparin as well. Complete lysis was obtained in 31% of patients, 50-99% lysis in 52% and <50% lysis in 17%. Successful lysis was not related to location of the thrombus. The overall primary patency rate was 80% at 12 months, with better patency for ilio-femoral segments than the femoro-popliteal segments. Major bleeding complications occurred in 11% of patients; 39% of these at the venous insertion site, 13% were retroperitoneal hematoma. Minor bleeding events occurred in 16% of patients, again most often at the venous entry site. There was one fatal intracranial hemorrhage, one subdural hematoma, and 6 pulmonary emboli of which one was fatal. Thus, the overall mortality rate from lysis was 0.4%. There was no data on PTS.

If the PTS differs between standard therapy and thrombolytic therapy then the quality of life may differ between patients also. Comerota assessed health-related quality of life in patients after CDT therapy compared to a group of patients treated with standard anticoagulation therapy[39]. The delayed functional outcome and wellbeing scores were significantly better in the thrombolytic therapy group. Although this study had some methodological shortcomings[13], the findings are still suggestive that thrombolytic therapy may offer improved quality of life in patients who achieve successful thrombolysis.

Compared to historical data of anticoagulation and intravenous thrombolysis, CDT probably has higher recanalization rates. The studies so far, indcluding one RCT with 6 months follow-up and 35 patients[40], have been promising, but unfortunately no high-quality randomized studies with long-term follow-up have been performed. Experimental data indicate that valves of the femoral veins may be preserved[41;42]. It is therefore possible that PTS may be reduced. However, long term studies have not been performed. In the absence of well-designed randomized clinical studies both for early findings, the implications of early patency for long-term clinical results, the complications, and the costs related to treatment, CDT therapy for DVT should at present be considered experimental treatment. Still, some Norwegian hospitals including Aker and Ullevål University Hospitals, Rikshospitalet, and the Østfold Hospital Trust Fredrikstad, do provide this high-intensive treatment to selected patients. A case-series with careful follow-up at Aker University Hospital has recently been published[31].

In the present study, we aim to investigate the role of CDT therapy for treatment of acute DVT as compared with established treatment with low molecular weight heparin. The study will be an open-label, randomized study of patients with first-time acute DVT of the affected limb, and our major outcome parameter will be the frequency of PTS as related to early venographic patency. The results of this study have the potential to properly define the role of this costly treatment in the future.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVES

To investigate whether catheter-directed thrombolytic therapy for first-time acute DVT of the iliofemoral veins may:

3.1.1 increase patency rate at 6 months.

3.1.2 reduce the risk of PTS at 2 years.

3.2 SECONDARY OBJECTIVES

3.2.1 To investigate frequency of clinically relevant bleeding related to the procedure.

3.2.2 To investigate effects on quality of life (QoL).

3.2.3 To investigate cost-effectiveness of treatment.

3.2.4 To investigate the procedural success of CDT.

3.2.5 To identify markers of importance for successful thrombolysis.

3.2.6 To investigate patency at 2 years.

3.2.7 To investigate PTS at 6 and 60 months.

3.2.8 To investigate whether presence or absence of PTS at any time point is related to patency at end of treatment.

3.2.9 To investigate prevalence of vein anomalies (and need for angioplasty or stents).

3.2.10 To investigate prevalence of underlying thrombophilia.

3.2.11 To investigate frequency of recurrent VTE during follow-up.

3.2.12 To identify markers of importance for recurrent thrombosis.

4 HYPOTHESES

Our main short-term hypothesis is that CDT of first-time acute DVT will increase patency of the affected iliofemoral vein segments after 6 months from <50% on conventional therapy to >80% after CDT. Our main long-term hypothesis is that CDT will improve long-term functional outcome, i.e., risk of PTS, assessed after 2 years, from >25% on conventional treatment to <10% after CDT.

5 PATIENT POPULATION

5.1 INCLUSION CRITERIA

5.1.1 Age 18-75 years.

5.1.2 Onset of symptoms <21 days.

5.1.3 Objectively verified DVT (ultrasonography, venography, computed tomography, or magnetic resonance imaging) localized in the upper half of the thigh, the common iliac vein or the combined iliofemoral segment.

5.1.4 Informed consent (Appendix 1).

5.2 EXCLUSION CRITERIA

5.2.1 Anticoagulant therapy prior to trial entry for >7 days.

5.2.2 Contraindications to thrombolytic therapy, including bleeding diathesis.

5.2.3 Indications for thrombolytic therapy, e.g., phlegmacia coerolia dolens or isolated vena cava thrombosis.

5.2.4 Severe anemia (hemoglobin <8 g/dL).

5.2.5 Thrombocytopenia (platelets $<80 \cdot 10^9$/L).

5.2.6 Severe renal failure – creatinine clearance <30 ml/min. Creatinine clearance will be calculated according to the following formula:

$$\text{Creatinine clearance (ml/min)} = \frac{b \times (140 - \text{age (yrs)}) \times \text{body weight (kg)}}{\text{serum creatinine (µmol/L}}$$

b=1.23 (females); 1.04 (males)

5.2.7 Severe hypertension, i.e. persistent systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg.

5.2.8 Pregnancy and thrombosis ≤7 days post-partum (may be included after 7 days post-partum).

5.2.9 Less than 14 days post-surgery or post-trauma (may be included after 14 days).

5.2.10 History of subarachnoidal or intracerebral bleeding.

5.2.11 Disease with life expectancy <24 months.

5.2.12 Drug abuse or mental disease that may interfere with treatment and follow-up.

5.2.13 Former ipsilateral proximal DVT.

5.2.14 Malignant disease requiring chemotherapy.

5.2.15 Any thrombolytic therapy within 7 days prior to trial inclusion.

6 METHODS

6.1 DESIGN

Multi-center, open-label, randomized clinical study on the effect and safety of CDT therapy as compared with conventional therapy for the treatment of acute, first-time ilio-femoral DVT. The study will be a collaborative study of hospitals belonging to the Eastern and Southern Norway Health Authorities (Helse Øst and Sør).

6.2 PATIENT RECRUITMENT

Eligible patients (section 5) will be invited to participate in the study. Informed consent (Appendix 1) in accordance with the revised Helsinki Declaration must be obtained from the patient before randomization.

6.3 RANDOMIZATION

Patients will be randomized by sealed numbered envelopes using block randomization. Each envelope will contain information on treatment allocation. A new patient will be allocated the lowest numbered envelope. Treatment will be open-label, but stratified for extension of DVT, i.e., only femoral or iliofemoral DVT.

6.4 TREATMENT

6.4.1 Acute treatment

Patients will be randomized to one of the following treatment groups:

Group I	Catheter-directed thrombolytic therapy with rt-PA in addition to conventional treatment with low molecular weight heparin (for details – see 6.4.2)
Group II	Conventional treatment with low molecular weight heparin (see 6.4.3)

Drugs will be ordered from the hospital's pharmacy according to local routines.

- Group I will be given rt-PA (Actilyse®) combined with unfractionated heparin and followed by low molecular weight heparin (LMWH) and warfarin.

- Group II, the conventional treatment arm, will be given LMWH, either sc dalteparin (Fragmin®), 200 IU/kg od, or enoxaparin (Klexane®), 1.5 mg/kg od, according to local routines, and warfarin.

6.4.2 Group I - Catheter-Directed Thrombolytic (CDT) therapy – procedures

- ***Anticoagulant and fibrinolytic therapy***
  - Discontinue oral anticoagulants - INR should be <1.5 before the procedure.
  - In case of prior sc LMWH therapy treatment should be discontinued at least 8 h before the procedure, and in case of prior UFH treatment APTT (Cephotest®) should be adjusted to 40-60 sec during the procedure (see below).
  - An iv bolus dose of UFH, 5000 U, should be given followed by continuous iv UFH[1] infusion at 15 U/kg/h. Adjust dose to keep APTT (Cephotest®) at 40-60 sec, first adjustment 6-12 h after start of treatment.
  - During the thrombolytic treatment keep APTT (Cephotest®) at 40-60 sec.
  - At the completion of thrombolytic treatment:
    - ✓ discontinue UFH
    - ✓ give sc LMWH after 1 h, (either dalteparin, Fragmin®, 200 U/kg bid, or enoxaparin, Klexane®, 1,5 mg/kg bid).
    - ✓ Oral warfarin (Marevan®) will be initiated according to local routines.
    - ✓ LMWH will be discontinued when INR has been in therapeutic range (2.0-3.0) for at least 24 hours, but should not be given for less than total 4-5 days.

- ***Interventional procedures.*** In an interventional radiology unit, an introducer will be inserted into an appropriate vein, preferentially the popliteal vein, guided by ultrasound to prevent puncture of the artery or laceration of the vein wall and to secure only a single puncture. If possible, the wire and catheter should be introduced above the proximal part of the thrombus (use fitting-sized perfusion catheters, e.g., 10, 20, 30, or 50 cm). A venography should then be performed to disclose the topography of the thrombus. CDT may be discontinued if introduction of the catheter through the occluded segment is not successful. Catheters should be properly fixed to the skin.

  The perfusion catheter (and the perfusion wire) should cover the central to peripheral part of the thrombus. Rt-PA (Actilyse®), 20 mg diluted in 500 ml 0.9% NaCl, will be infused at 0.01 mg/kg/h. Maximal dose infused will be 20 mg/24 h. The rt-PA dosage may be split into two catheters using lower consentration, keeping flow the same.

[1] A suitable working solution should be made to contain UFH 40 U/ml in 0.9% NaCl, e.g., mix 20000 U of UFH in 500 ml 0.9% NaCl or 40000 U in 1000 ml 0.9% NaCl. The infusion rate (ml/h) then reflects total units of UFH per 24 hrs in thousands, e.g., 25 ml/h corresponds to 25000 U/24 h, 30 ml/h 30000 U/24 h, and so on.

After insertion of catheter, venography, and start of iv UFH and iv rt-PA infusion, treatment will continue in medical wards. Blood pressure and pulse and the puncture site are assessed 4 times a day. Hemostasis is also monitored by daily analysis of hemoglobin, fibrinogen, D-dimer, INR, and platelet counts. APTT is monitored twice daily for adjustment of heparin dose. The patient will be encouraged to use the muscle pump of the leg while in bed. No food and drink restrictions.

Effect of treatment will be assessed by venography at least every 24 hrs, and catheters repositioned accordingly. Treatment should normally not continue for >96 h. At the end of treatment, the catheters will be removed immediately and hemostasis obtained by manual compression of the puncture site. Pressure will be continued for 2 hrs with a roll while the patient is immobilized.

- ***Stents.*** Balloon dilatation and placement of venous stents will be performed at the discretion of the operator to establish flow and to obtain <50% residual stenosis.

- ***Concomitant medication during procedure.*** During the interventional procedure concomitant use of other antithrombotic agents should be avoided because of increased risk of bleeding. This includes antiplatelet agents (e.g., acetylsalicylic acid, thienopyridines, GPIIb/IIIa inhibitors, non steroidal anti-inflammatory agents, or other) or anticoagulants (e.g., low molecular weight heparin, pentasaccharide, warfarin, or other). Concomitant use of ACE-inhibitors appears to increase the risk of anafylactoid reactions.

6.4.3 Group II – conventional treatment with LMWH

Patients allocated the conventional treatment arm will be given sc LMWH, either dalteparin (Fragmin®), 200 U/kg od, or enoxaparin (Klexane®), 1.5 mg/kg od, according to local hospital routines, and simultaneous warfarin (Marevan®) according to local routines. LMWH will be discontinued when INR has been in therapeutic range (2.0-3.0) for at least 24 hours, but should not be given for less than total 4-5 days.

6.4.4 Subacute and chronic phase after DVT

Patients will be treated with warfarin for at least 6 months with target INR 2.0-3.0. All patients will be adviced to use knee-high compression stockings, grade II, for 6 months.

6.5 VISITS AND PROCEDURES DURING FOLLOW-UP

End-point assessment will be performed by a vascular surgeon with no previous contact or knowledge of patients' medical history or treatment allocation. At each visit the patients will explicitly be told not to reveal treatment allocation.

6.5.1 Visit 1 (trial entry – at hospital admission/)

6.5.1.1 Case history and general clinical examination.

6.5.1.2 Compression ultrasonography or venography, alternatively CT or MRI angiography diagnosing acute iliofemoral DVT.

6.5.1.3 Laboratory screening (hemoglobin, platelets, leukocytes, creatinine, ASAT, ALAT, GT, bilirubin, INR, APTT, D-Dimer, cholesterol, and CRP).

6.5.1.4 Thrombophilia screening (collection of blood samples).

6.5.1.5 Assessment of baseline QoL before treatment using VEINES-QoL and EQ-D5 (Appendix 2).

6.5.1.6 Assessment of baseline clinical score using Villalta[5;43] score and the C classification of CEAP, see Definitions.

6.5.2 Visit 2 (hospital stay)

6.5.2.1 Daily assessment of hemoglobin, platelets, fibrinogen, APTT, INR, and D-Dimer, and bilateral leg circumference.

6.5.2.2 Daily venography will be performed in patients allocated CDT.

6.5.2.4 Bleeding complications.

6.5.3 Visit 3 – 6 m ± 2 weeks

6.5.3.1 Clinical history – recurrent thrombosis – malignancy.

6.5.3.2 Clinical PTS scores according to Villalta and CEAP. Bilateral leg circumference.

6.5.3.3 Assessment of functional venous obstruction by air-plethysmography.

6.5.3.4 Ultrasonographic assessment of postthrombotic changes, patency, and reflux [44-47].

6.5.3.5 Quality of Life (QoL) assessment (Appendix 2).

6.5.3.6 D-dimer testing, INR, thrombophilia screening (if previously inconclusive).

6.5.4 VISIT 4 – 12 m ± 4 weeks

Telephone interview – recurrent thrombosis – malignancy.

6.5.5 VISIT 5 – 24 m ± 4 weeks

6.5.5.1 Clinical history – recurrent thrombosis – malignancy.

6.5.5.2 Clinical PTS scores according to Villalta and CEAP. Bilateral leg circumference..

6.5.5.3 Assessment of functional venous obstruction by air-plethysmography.

6.5.5.4 Ultrasonographic assessment of postthrombotic changes, patency, and reflux

6.5.5.5 Quality of Life (QoL) assessment (Appendix 2).

6.5.5.6 D-dimer, INR, thrombophilia screening (if previously inconclusive).

6.5.6 VISIT 6 – 36 m ± 4 weeks

Telephone interview – recurrent thrombosis – malignancy.

6.5.7 VISIT 7 – 48 m ± 4 weeks

Telephone interview – PTS screening – recurrent thrombosis – malignancy.

6.5.8 VISIT 8 – 60 m ± 8 weeks

6.5.8.1 Clinical history – recurrent thrombosis – malignancy.

6.5.8.2 Clinical PTS scores according to Villalta and CEAP. Bilateral leg circumference.

6.5.8.3 Ultrasonographic assessment of postthrombotic changes, patency, and reflux.

6.5.8.4 Assessment of functional venous obstruction by air-plethysmography.

6.5.8.5 Quality of Life (QoL) assessment (Appendix 2).

7 DEFINITIONS

7.1 Post-Thrombotic Syndrome (PTS)

7.1.1 The Villalta Score[5;43]

PTS will be evaluated using the Villalta score, which scores PTS based on five symptoms and six objective signs (each item graded from 0 to 3):

Five symptoms: heaviness, pain (spontaneous or during deambulation), cramps, pruritus, and paresthesia.

Six signs: pretibial edema, induration of the skin, hyperpigmentation, new venous ectasia, redness, pain during calf compression

A total score of 5-14 indicates mild to moderate PTS, whereas a score of 15 or more indicates severe PTS. A lower limb venous ulcer indicates severe PTS regardless of the sum of the remaining signs and symptoms. The Villalta Score is quantitative and useful for longitudinal assessment of PTS.

7.1.2 The Clinical-Etiology-Anatomic-Pathophysiologic (CEAP) classification[48;49]

This is a classification of Clinical (dermatological) signs, Etiology, Anatomic distribution and Pathophysiologic dysfunction:

Clinical signs	**Class 0**	**No visible or palpable signs of venous disease**
	Class 1	**Teleangiectases or reticular veins**
	Class 2	**Varicose veins**
	Class 3	**Edema**
	Class 4	**a. pigmentation, eczema** **b. lipodermatosclerosis, atrophia blanche**
	Class 5	**Healed ulceration (and skin changes as defined above)**
	Class 6	**Active ulceration (and skin changes as defined above)**
Etiological classification	**Congenital, primary, secondary**	
Anatomic distribution	**Superficial, deep, or perforator, alone or in combination**	
Pathophysiological dysfunction	**Reflux or obstruction, alone or in combination**	

7.2 Non-invasive assessment of veins

7.2.1 Deep vein thrombosis[50]

7.2.1.1 Acute deep vein thrombosis

The principal criterion is inability to completely compress the vein lumen when examining the vein in the transverse plane. Other possible findings are distention of the vein, absence of flow, loss of phasic flow, and visualization of clot.

7.2.1.2 Chronic thrombosis and postthrombotic changes

Absence of complete incompressibility indicates residual thrombosis. Other postthrombotic features are wall-thickening and intraluminal hyperechoic structure.

7.2.2 Flow

Using Doppler-ultrasound, flow will be graded as spontaneous flow, forced flow (on peripheral compression), and no flow (obstruction)[38]. Flow will also be examined in supine position.

7.2.3 Reflux

Using Doppler-ultrasound and a distal inflation cuff with the patient in standing position, reflux is defined as reversal of the velocity curve after distal pneumatic decompression lasting longer than 0.5 second[51-53].

7.2.4 Assessment of functional venous obstruction

Venous obstruction will be assessed by using air plethysmography[54;55]. The patients will lie supine with the calf elevated (by a cushion) to the level of the heart. An occlusion cuff will be placed proximally on the thigh, and a recording cuff with a pressure of 6 mmHg will be placed on the calf. The proximal cuff will be inflated to 50 mmHg for 1 min. A venous outflow curve will be recorded when this cuff is deflated, and maximum outflow can then be calculated (delta mm/sec). Low outflow rates indicate presence of functional venous obstruction. The procedure will be performed on both legs.

7.2.5 Assessment of venous patency

Assessment of venous patency will include compressibility, flow and functional venous obstruction.

7.3 Evaluation of thrombolysis

Based on venography before and after CDT, thrombolysis will be graded by a scoring system[38]. Score=0 indicates an open vein, score=1 a partly occluded vein, and score=2 a completely occluded vein.

Each of the following 7 venous segments will be given a grade (0-2): IVC, the common iliac vein, the external iliac vein, the common femoral vein, the proximal and distal superficial femoral veins, and the popliteal vein. A total thrombus score before and after lysis will be calculated by adding the 7 scores. The difference between the pre- and postlysis thrombus scores divided by the prelysis score gives the grade of thrombolysis. Grade I=<50%; grade II=50-90%, and grade III=complete thrombolysis

7.4 Bleeding Complications

7.4.1 ***Major bleeding*** – any bleeding associated with a reduction in hemoglobin by ≥2 g/100 mL or bleeding requiring transfusion of ≥2 U pack red blood cells or whole blood or bleeding in a critical organ, intracranial, retroperitoneal or pericardial or bleeding contributing to death.

7.4.2 ***Clinically relevant non-major bleeding*** – overt bleeding not meeting criteria for major bleeding but satisfying a priori criteria defined by the safety monitoring committee including for example skin hematomas >100 cm^2, epistaxis lasting >5 min, being repetitive (≥2/24 h) or requiring intervention (packing, electrocoagulation), macroscopic hematuria – either spontaneous or lasting >24 h after instrumentation (catheter or surgery) of the urogenital tract, or any other bleeding type that is considered to have clinical consequences for the patient.

7.4.3 ***Trivial bleeding*** - all other overt bleeding episodes not meeting the criteria for clinically relevant bleeding.

7.5 Thrombophilia screening

Includes screening for antithrombin, protein C- and protein S deficiencies, factor V Leiden mutation, the prothrombin gene 20210GA allele variation and the methylene tetrahydrofolate reductase (MTHFR) mutation, homocystein, lupus anticoagulants and anticardiolipin antibodies.

8 STATISTICS

8.1 Sample size

Numerous studies indicate that conventional treatment, i.e., UFH or LMWH followed by oral anticoagulants is associated with PTS in more than 60-80% of the cases, whereas systemic thrombolytic therapy is associated with PTS in approximately 30% of the patients[5;21;56]. More recent studies employing systematic use of elastic compression stockings suggest PTS in approximately 25% of the patients.[11] In the present study, we will assume that the rate of PTS after 2 years will be at least 25% in those allocated conventional therapy as compared with less than 10% in those given CDT. For patency after 6 m we assume that the rate is less than 50% in those allocated conventional treatment as compared with at least 80% in those given CDT. With a significance level of $\alpha \leq 5\%$ and a statistical power (1-β) of $\geq 80\%$, we will need to randomize approximately 100 patients in each group.

Also as presented in our hypotheses, we assume that venous patency after 6 months occurs in less than 50% in those allocated conventional treatment as compared to at least 80% in those given adjunctive CDT. It may then be shown that with a significance level of 5% and a statistical power ≥80%, 76 patients must be included to test this short-term hypothesis. We plan to analyse patency rates after 6 months based on the first 100 patients with 6 months patency data. This analysis will be repeated when 200 patients have 6 months patency data.

8.2 Statistical methods

All statistical analysis will be performed according to the intention-to-treat principle. If ineligible patients are mistakenly included, they may be excluded (ref Ferguson et al BMJ 2002), apart from this, no other post-randomization exclusions will be made. The effect of treatment will be determined using 2x2 tables with assessment of the difference between patent vessels and prevalence of PTS, relative risks, and odds ratios with 95% confidence limits. The prevalence of clinically relevant bleeding, PTS, vein anomalies, thrombophilia, recurrent DVT will be determined using point estimates with 95% confidence intervals. A stratification analysis will be carried out using the Mantel-Haenzel method. Differences in baseline characteristics may be adjusted for using a multivariate logistic model. This may be done if there are substantial differences between the two groups, and if the variable(s) is probably or certainly associated with the outcome measure, e.g., age and previous VTE. Missing data on end-point variables will be scored as previous score or last/worst score carried forward.

9 ETHICAL CONSIDERATIONS

This study will recruit patients with proximal DVT. Even though the efficacy and safety of CDT for the treatment of acute proximal DVT remains to be established, some hospitals in many countries now offer CDT to selected patients with severe DVT, especially when the DVT extends into the caval vein. In the present study, non-trial CDT to selected patients with severe DVT will be left to the discretion of the responsible physician.

The study will be performed in accordance with the revised Helsinki Declaration and Good Clinical Practice (GCP). The study will only start after approval with the Regional Ethical Committee and the Norwegian Medical Agency. All patients will be given study specific identification codes and all data will be stored in a secured database on a secured server for research at the Ullevål University Hospital. This server as well as data management will be controlled by the Patient Protection Ombud at the Ullevål University Hospital. A non-linked database will provide information on the patients' contact information to allow follow-up. A biobank will be established at Ullevål University Hospital after approval.

10 MILESTONES

Q1-2006	First patient randomized
Q4-2007	Last patient randomized
Q2-2008	Six months follow-up of all patients for primary efficacy parameter patency
Q2-3-2008	Reporting of study design and primary efficacy parameter patency
Q4-2009	Two-years follow-up of all patients for primary efficacy parameter PTS
Q4-Q1-09-10	Reporting of primary efficacy parameter PTS
Q4-2012	Five years follow-up of last patient for patency and PTS.

11 TRIAL ORGANIZATION

11.1 GENERAL ORGANIZATION

The study is an investigator initiated study which will be run independently of the pharmaceutical industry. The study is financially supported by a grant from Eastern Norway Health Authority (doctoral fellow; Helse Øst grant no 2005-090).

The study will be a major collaborative effort among hospitals of the Eastern and Southern Norway Health Authorities (Helse Øst and Sør). All hospitals will be invited to participate in the study. Patients allocated to conventional treatment will be treated at the local hospital, whereas patients allocated CDT will be treated at Ullevål and Aker University Hospitals, the National Hospital and the Central Hospital in Østfold.

11.2 COMMITTES

11.2.1 Executive committee

- Per Morten Sandset (chair) – UUS – Hematologist
- Nils-Einar Kløw – UUS – Radiologist
- Leiv Sandvik – UUS – Statistician
- Tone Enden – UUS – Research fellow – Resident in Radiology
- Carl-Erik Slagsvold – AUS – Angiologist
- Anne Mette Njåstad – AUS – Hematologist
- Gunnar Sandbaek – AUS – Radiologist
- Pål Andre Holme – RR – Hematologist
- Geir Hafsahl – RR – Radiologist
- Waleed Ghanima – Østfold Hospital Trust Fredrikstad – Hematologist
- Lars Olav Holmen – Østfold Hospital Trust Fredrikstad – Radiologist

11.2.2 Steering committee

- Executive committee (chair Per Morten Sandset)
- One member from each collaborating hospital

11.2.3 Safety and monitoring committee

- Professor emeritus Ulrich Abildgaard
- Professor Frank Brosstad, Rikshospitalet-Radiumhospitalet, Oslo

12 PUBLICATION

Results of this study will be published in international medical journals, but will also be communicated to the general population whenever appropriate. The results may potentially have great interest for the scientific community, for health-providers in decision making, and for the general population. Publication will follow the Vancouver convention. Tone Enden will be the first author of these publications.

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Appendix 1

FORESPØRSEL OM Å DELTA I EN FORSKNINGSSTUDIE:

CaVenT-studien – kateterbasert trombolyse ved akutt dyp venetrombose

Denne forespørselen om å delta i forskningsprosjektet "CaVenT" går til pasienter som legges inn med akutt blodpropp i lår- og bekkenvener ved sykehus i Helseregion Sør og Øst.

Du bestemmer selv

Det er frivillig å delta i studien. Dersom du velger å ikke delta, trenger du ikke oppgi noen grunn for dette. Dersom du ikke ønsker å delta i studien, vil behandlingen din være den vanlige behandlingen som pasienter med din sykdom mottar. Du kan når som helst trekke deg underveis uten begrunnelse.

Bakgrunn

Undersøkelsene viser at du har fått en blodpropp i en samleblodåre (vene) i låret og/eller i bekkenet. Tilstanden kalles dyp venetrombose. Standardbehandlingen ved akutt dyp venetrombose er blodfortynnende medisin, først sprøyter med lavmolekylært heparin (inneholder legemidlene Fragmin eller Klexane) i 4-8 dager og deretter tabletter (legemidlet Marevan) i minst 3-6 måneder. Målet med behandlingen er å stoppe utviklingen av blodproppen, forhindre at blodproppen løsner og går til lungene og å redusere plagsomme senfølger i form av smerter, hevelse og hudforandringer. Slike senfølger kalles posttrombotisk syndrom. Om lag en fjerdedel av pasientene utvikler posttrombotisk syndrom i løpet av de første 2 årene etter standardbehandling for blodropp.

De siste årene er det utviklet en ny behandling for å løse opp blodpropp som kalles kateterbasert trombolyse. Behandlingen er beskrevet i detalj under. Foreløpige resultater tyder på at denne behandlingen kan løse opp blodproppen raskere og forebygge senplagene, men så langt har det ikke vært gjennomført studier som kan gi gode svar på dette.

Prosjektets formål

Hensikten med dette forskningsprosjektet er å avklare om tilleggsbehandling med kateterbasert trombolyse gir bedre resultat i akutt fase og færre plager på lang sikt uten økt risiko for bivirkninger sammenliknet med standard blodfortynnende medisin alene.

Om kateterbasert trombolyse/blodproppløsende behandling

Behandlingen gjennomføres i samarbeid mellom hematologisk/indremedisinsk avdeling og røntgenavdelingen. Selve prosedyren blir utført ved røntgenavdelingen. Du får først lokalbedøvelse. Deretter fører vi inn et 2 mm tykt plastrør i venen (blodåren) i knehasen og inn i selve blodproppen. Så gir vi kontinuerlig en lav dose av et blodproppløsende medikament (legemidlet Actilyse) gjennom plastrøret i inntil 3-4 dager. Samtidig gir vi også en lav dose blodfortynnende medisin (legemidlet heparin) som drypp intravenøst. Blodproppen løser seg langsomt opp, og tidspunktet for å avslutte behandlingen blir bestemt ut fra daglige kontroller med røntgen kontrastundersøkelse. Mens behandlingen pågår må man holde sengen.

Dersom det i forløpet av behandlingen påvises en unormal blodåre (vene), oftest en medfødt innsnevring, som kan forklare hvorfor blodpropp oppsto, vil vi vurdere å gi tilleggsbehandling ved å

utvide blodåren ved hjelp av et ballongkateter, eventuelt legge inn en stent (forsterkning). Dette vil sikre normal blodstrøm etter behandlingen.

Behandling med blodpropp-oppløsning utføres ved flere av de store sykehusene i regionen, og dersom ditt sykehus ikke kan utføre behandlingen, vil du bli overført til et av disse.

Etter avsluttet kateterbasert behandling vil du få vanlig behandling med lavmolekylært heparin og Marevan og bli fulgt opp etter gjeldende retningslinjer ved ditt lokalsykehus.

Gjennomføring

For å kunne gjøre en vitenskapelig sammenlikning av resultatene, vil det bli foretatt en trekning slik at halvparten av pasientene vil få standard behandling, mens den andre halvparten vil få kateterbasert trombolyse i tillegg. Du gis skriftlig og muntlig informasjon om forskningsprosjektet når du legges inn.

Deltagelse i studien medfører i tillegg til vanlig behandling og oppfølging, ekstra samtaler med lege (noen som telefonkonsultasjon) og enkelte undersøkelser (ultralyd, blodprøver) ved ulike tidspunkt i de påfølgende 2 år. Uansett behandling vil vi kontakte deg regelmessig, enten per telefon (etter 12, 36 og 48 måneder) eller ved kontrollundersøkelse (etter 6, 24 og 60 måneder). Undersøkelsene omfatter ultralydundersøkelse og blodprøver.

Risiko ved behandlingen

Kateterbasert trombolyse medfører en litt økt risiko for blødning sammenliknet med den vanlige behandlingen. Det vanligste er mindre blødning ved innstikksstedet der plastrøret er lagt inn. Hos noen få pasienter har det vært rapportert blødninger andre steder, mest alvorlig er blødninger i tarm og hode. Dersom slik blødning oppstår, vil vi stoppe den trombolytiske behandlingen og sette i gang tiltak for å behandle blødningen etter gjeldende rutiner ved sykehusene.

Blodprøver og biobank

Blodprøvene som blir tatt og informasjonen utledet av dette materialet vil bli lagret i en såkalt "forskningsbiobank" ved Ullevål universitetssykehus HF. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Blodprøvene vil bli lagret i fryseboks ved hematologisk forskningslaboratorium i tråd med interne retningslinjer. Viseadministrerende direktør ved sykehuset er ansvarlig for biobanken. Biobanken planlegges å vare til 2027. Etter dette vil materiale og opplysninger bli destruert/slettet etter interne retningslinjer.

Slik ivaretas dine prøver og personopplysninger

Personvernet ivaretas i samsvar med betingelser gitt i konsesjon fra Datatilsynet/melding til sykehusets personvernombud. Forskningsdata, inklusive opplysninger utledet av det biologiske materialet, lagres på eget, sikret datasystem ved sykehuset. Alle opplysningene vil bli behandlet konfidensielt. I prosjektet har du et prosjektnummer som knytter deg som person til prosjektet gjennom en adresseliste. Kun prosjektansvarlig har adgang til adresselisten.

Hvem som har vurdert prosjektet

Regional komité for medisinsk forskningsetikk, Øst-Norge, har vurdert prosjektet, og har ingen innvendinger mot at det gjennomføres. Forskningsbiobanken er meldt til Sosial- og helsedirektoratet, som ikke har innsigelser til opprettelse av biobanken.

Økonomi

Forskningsprosjektet er et samarbeid mellom sykehusavdelinger i Helse Sør og Øst. Prosjektet er delvis finansiert gjennom forskningsmidler fra Helse Øst. Det er ikke aktuelt å samarbeide med industri, og det er heller ikke aktuelt med kommersialisering av produkter. Prosjektansvarlig og andre som arbeider med prosjektet har ingen form for økonomisk vinning knyttet til prosjektet.

Dine rettigheter

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert evt. feil i de opplysningene vi har registrert. Hvis du senere trekker deg fra studien, kan du kreve at materialet destrueres. Du kan også kreve å få slettet opplysninger vi har registrert. Ved henvendelse til prosjektansvarlig kan du få nærmere opplysninger om dette. Du kan ikke få slettet opplysninger eller destruert materiale dersom de er anonymisert, er viderebehandlet og inngår i et annet biologisk produkt eller dersom opplysningene allerede har inngått i et vitenskapelig arbeid. Adgangen til destruksjon gjelder heller ikke dersom det ved lov er fastsatt at materialet eller opplysningene skal oppbevares.

Prosjektansvarlig – mer informasjon

Dersom du har flere spørsmål om studien eller biobanken kan du kontakte en av de prosjektansvarlige legene (se under) eller legen som er ansvarlig for oppfølging ved ditt sykehus (se under).

Per Morten Sandset
Avd. overlege, professor, dr. med
Prosjektansvarlig
Hematologisk avdeling, UUS

Nils Einar Kløw
Seksjonsoverlege, professor, dr. med

Hjerte- og karradiologisk avdeling, UUS

Tone Enden
Lege, stipendiat
Prosjektleder, UUS
Tlf UUS 22 11 80 80, calling nr. 581 78389
e-mail: tone.enden@uus.no

Prosjektansvarlig lege ved ditt sykehus er:

Navn:
Tittel:
Adresse:
Telefon:

CaVenT-studien

Samtykke – prosjektdeltaker

Deltakelse i studien er basert på ditt frivillige, informerte samtykke. Dersom du ønsker informasjon utover det som framkommer i dette informasjonsskrivet og den muntlige informasjonen du har mottatt/vil få, har du full anledning til å be om dette.

Dersom du etter å ha fått den informasjon du synes er nødvendig, sier ja til å delta i studien, må du signere samtykkeerklæringen.

Jeg,_____(navn med blokkbokstaver), bekrefter at jeg har mottatt skriftlig informasjon om studien, har fått anledning til å innhente den informasjon jeg har hatt behov for, og er villig til å delta i prosjektet.

Signatur_____Dato_____.

(sign. prosjektdeltaker) (datert av prosjektdeltaker)

Informasjon om studien er gitt av:

Lege,_____(navn med blokkbokstaver)

Signatur_____Dato_____.

(sign. lege)

Appendix 2: VEINES-QoL and EQ-D5

Spørreskjema om helse

Opplysningene vil være til hjelp for å holde rede på hvordan du har det, og om hvordan du klarer å utføre dine vanlige aktiviteter.

Vis hvilke utsagn som passer best på **din helsetilstand i dag** ved å sette et kryss i en av rutene utenfor hver av gruppene nedenfor.

Gange

Jeg har ingen problemer med å gå omkring. ☐

Jeg har litt problemer med å gå omkring. ☐

Jeg er sengeliggende. ☐

Personlig stell

Jeg har ingen problemer med personlig stell. ☐

Jeg har litt problemer med å vaske meg eller kle meg. ☐

Jeg er ute av stand til å vaske meg eller kle meg. ☐

Vanlige gjøremål *(f.eks. arbeid, studier, husarbeid, familie- eller fritidsaktiviteter).*

Jeg har ingen problemer med å utføre mine vanlige gjøremål ☐

Jeg har litt problemer med å utføre mine vanlige gjøremål. ☐

Jeg er ute av stand til å utføre mine vanlige gjøremål. ☐

Smerte/ubehag

Jeg har verken smerte eller ubehag. ☐

Jeg har moderat smerte eller ubehag. ☐

Jeg har sterk smerte eller ubehag. ☐

Angst/depresjon

Jeg er verken engstelig eller deprimert. ☐

Jeg er noe engstelig eller deprimert. ☐

Jeg er svært engstelig eller deprimert. ☐

Besvar hvert spørsmål nedenfor ved å krysse av svaret som angitt. Hvis du er usikker på hva du skal svare, vennligst svar etter beste evne.

Disse spørsmålene er om din oppfatning av **beina dine**.

1. I løpet av de 4 siste ukene, hvor ofte har du hatt noen av disse plagene i beina?

(Sett ett kryss på hver linje)	**Daglig**	**Flere ganger i uka**	**Omtrent én gang i uka**	**Sjeldnere enn én gang i uka**	**Aldri**
1. Tunge bein	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Vondt i beina	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Hevelse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Kramper om natta	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Varme eller brennende følelse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Urolige bein	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Banking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Kløe	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. Prikking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Når på dagen er **plagene i beina** mest uttalte? *(Sett ett kryss)*

☐ 1 Når jeg våkner
☐ 2 Midt på dagen
☐ 3 På slutten av dagen
☐ 4 Om natta
☐ 5 Når som helst i løpet av dagen
☐ 6 Aldri

3. Sammenlignet med for ett år siden, hvordan vil du vurdere dine **plager i beina** nå? *(Sett ett kryss)*

☐ 1 Mye bedre nå enn for ett år siden
☐ 2 Noe bedre nå enn for ett år siden
☐ 3 Omtrent det samme nå som for ett år siden
☐ 4 Noe verre nå enn for ett år siden
☐ 5 Mye verre nå enn for ett år siden
☐ 6 Jeg hadde ingen plager i beina i fjor

4. Følgende spørsmål gjelder daglige aktiviteter. Setter **plagene i beina** begrensninger for dine daglige aktiviteter? Hvis « ja », i hvilken grad?

	(Sett ett kryss på hver linje)	Jeg jobber ikke	JA, begrenser meg mye	JA, begrenser meg litt	NEI, begrenser meg ikke
a.	Daglige aktiviteter på jobb.	☐ 0	☐ 1	☐ 2	☐ 3
b.	Daglige aktiviteter hjemme (husarbeid, småjobber, hagearbeid, o.l.)		☐ 1	☐ 2	☐ 3
c.	Fritidsaktiviteter hvor du må stå lenge (selskap, ta buss, handle o.l.)		☐ 1	☐ 2	☐ 3
d.	Fritidsaktiviteter hvor du må sitte lenge (kino, teater, på reise o.l.)		☐ 1	☐ 2	☐ 3

5. 3. I løpet av de 4 siste ukene, har du hatt noen av disse problemene i jobb eller i daglige aktiviteter på grunn av **plagene i beina**?

	(Sett ett kryss på hver linje)	**JA**	**NEI**
a.	Redusert arbeids**tid** eller **tid** til andre aktiviteter	☐ 1	☐ 2
b.	**Gjennomført mindre** enn du skulle ønsket	☐ 1	☐ 2
c.	Blitt begrenset i **type** jobb eller aktiviteter	☐ 1	☐ 2
d.	Hatt **vanskeligheter** med å utføre jobben eller andre aktiviteter (f eks det krevde større anstrengelse)	☐ 1	☐ 2

6. I løpet av de 4 siste ukene, i hvilken grad har **plagene i beina** kommet i veien for samvær med familie, venner, naboer eller grupper? *(Sett ett kryss)*

☐ 1 Ikke i det hele tatt
☐ 2 Lett
☐ 3 Moderat
☐ 4 Ganske stor
☐ 5 Svær

7. Hvor mye smerter har du hatt i beina i løpet av de 4 siste ukene? *(sett ett kryss)*

☐ 1 Ingen
☐ 2 Svært lite
☐ 3 Lite
☐ 4 Moderat
☐ 5 Mye
☐ 6 Svært mye

8. Disse spørsmålene er om hvordan du føler deg, og om hvordan du har hatt det de siste 4 ukene som følge av **plagene i beina**. For hvert spørsmål, kryss av for det svaret som passer best med hvordan du har følt deg. Hvor mye i løpet av de 4 siste ukene-

(Sett ett kryss på hver linje)	**Hele tiden**	**Det meste av tiden**	**Ganske ofte**	**Av og til**	**Sjelden**	**Aldri**

a.	har du vært bekymret for hvordan beina dine ser ut?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b.	har du følt deg irritabel	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c.	har du følt at du har vært til byrde for familie eller venner?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d.	har du vært bekymret for å skumpe borti ting?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e.	har dine beins utseende påvirket ditt klesvalg ?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Vennligst oppgi dato for utfyllingen:_____/_____/_____ *(dag/måned/år)*