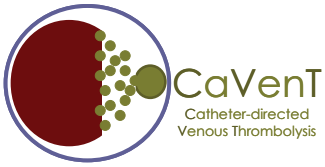
Towards improvement in deep vein thrombosis; studies on diagnostic MRI, thrombolytic therapy, and quality of life



PhD thesis

by

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… give love give love give love give love

give love give love give love give love give love.

"Under pressure"

David Bowie & Queen

1981

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Summary

Background:

Standard treatment for deep vein thrombosis includes anticoagulation and compression therapy. Accelerated lysis of venous thrombus by additional catheter-directed thrombolysis is suggested to reduce the development of postthrombotic syndrome. Large scale randomized controlled trials with long-term follow-up are needed to evaluate additional thrombolysis compared with standard treatment alone. Traditionally clinical trials on deep vein thrombosis have not employed functional outcomes with assessment of postthrombotic syndrome and quality of life, and this should be included. Routine diagnostic imaging with ultrasound for detection of acute deep vein thrombosis is not always feasible.

Aims:

The overall objective was to evaluate and improve diagnostic imaging and therapy of deep vein thrombosis of the lower limb with focus on catheter-directed thrombolysis and MRI. The first aim was to design and implement a well designed trial for the evaluation of additional catheter-directed thrombolysis. The second aim was translation and psychometric evaluation with assessment of data quality, reliability and validity, of a disease-specific questionnaire for patient reported quality of life following venous thrombosis of the lower limb. Final aim was to compare balanced MRI with contrast-enhanced MRI in visualisation of the deep veins and detection of acute deep vein thrombosis with ultrasound as reference method.

Materials and methods:

In the CaVenT Study a total of 200 patients with acute iliofemoral deep vein thrombosis will be recruited to detect a clinically relevant reduction in postthrombotic syndrome from 25 % to 10 % after 2 years. The patients are randomized to receive additional thrombolysis or standard treatment alone. The first 118 recruited patients were included in the analyses on short-term patency. Non-invasive assessment of veins, clinical assessment of postthrombotic syndrome, and patient-reported outcome on quality of life were performed after 6 and 24 months. The quality of life validation study was performed on a subset of 74 patients in the CaVenT Study using a novel Norwegian translation of the VEINES-QOL/Sym questionnaire. Balanced and contrast enhanced MRI were performed in 15 healthy volunteers and 6 patients with proximal deep vein thrombosis verified with ultrasound.

Results:

A psychometric evaluation of the Norwegian version of the VEINES-QOL/Sym questionnaire indicated satisfactory data quality, item-total correlations, internal consistency, test-retest reliability, and construct validity. Additional catheter-directed thrombolysis resulted in effective lysis in the great majority of patients. After 6 months venous patency was improved (64.0% vs. 35.8%) and venous obstruction was reduced (20.0% vs. 49.1%) when comparing additional thrombolysis with standard treatment alone. Venous incompetence was detected in the majority of patients, and did not differ between the two groups. Balanced and contrast-enhanced MRI techniques were comparable in visualizing the deep veins of the lower limb. Diagnostic properties and inter-observer reliability of both MRI sequences were good for proximal and poor for distal deep vein thrombosis.

Conclusions:

The CaVenT study is a considerable contribution towards a more evidence-based practice in the treatment of deep vein thrombosis, and future long-term results may lead to a modification of clinical guidelines. The psychometric properties of the Norwegian version of the VEINES-QOL/Sym questionnaire support its use in the evaluation of patient outcomes and burden of illness in clinical studies on deep vein thrombosis. Additional catheter-directed thrombolysis improved short-term venous patency compared to anticoagulation and compression therapy only. Both balanced and contrast-enhanced MRI may be used for the detection of proximal deep vein thrombosis in patients where ultrasound is not feasible.

Abbreviations

2D/3D	two/three dimensional (MRI)
ACCP	American College of Chest Physicians
aPTT	activated partial thromboplastin time
ARR	absolute risk reduction
CDT	catheter-directed thrombolysis
CI	confidence interval
CNR	contrast-to-noise ratio
DVT	deep vein thrombosis
ECS	elastic compression stockings
FISP	fast imaging with steady-state precession (MRI)
FVL	factor V Leiden mutation
iv	intravenous
ISTH	International Society of Thrombosis and Haemostasis
LMWH	low molecular weight heparin
MRDTI	magnetic resonance direct thrombus imaging
MRI	magnetic resonance imaging
NA	not applicable/not available
PE	pulmonary embolism
PTS	postthrombotic syndrome
QOL	health-related quality of life
RCT	randomized controlled trial
RR	relative risk
sc	subcutaneous
SD	standard deviation
SR	systematic review
TOF	time-of-flight (MRI)
US	ultrasound
VCI	vena cava inferior
VESPA	venous enhanced subtracted peak arterial (MRI)
VTE	venous thromboembolism

List of papers

The thesis is based on the following papers, referred to in the text by their Roman numerals.

Paper I

Enden T, Sandvik L, Kløw NE, Hafsahl G, Holme PA, Holmen PO, Ghanima W, Njaastad AM, Sandbæk G, Slagsvold CE, and Sandset PM. Catheter-directed Venous Thrombolysis in acute iliofemoral vein thrombosis - the CaVenT Study: Rationale and design of a multicenter, randomized, controlled, clinical trial (NCT00251771). American Heart Journal 2007;154:808-14.

Paper II

Enden T, Garratt AM, Kløw NE, and Sandset PM. Assessing burden of illness following acute deep vein thrombosis: data quality, reliability and validity of the Norwegian version of VEINES-QOL/Sym, a disease-specific questionnaire. Scandinavian Journal of Caring Sciences 2009;23:369-74

Paper III

Enden T, Sandvik L, Kløw NE, Hafsahl G, Holme PA, Holmen PO, Ghanima W, Njaastad AM, Sandbæk G, Slagsvold CE, and Sandset PM. Catheter-directed thrombolysis versus anticoagulant therapy alone in deep vein thrombosis: Results of an open randomized, controlled trial reporting on short term patency. Journal of Thrombosis and Haemostasis 2009;7:1268-75.

Paper IV

Enden T, Storaas T, Negaard A, Haig Y, Sandvik L, Gjesdal KI, Sandset PM, Kløw NE. Visualisation of the deep veins and detection of deep vein thrombosis with balanced TFE and contrast-enhanced T1 FFE using a blood pool agent. Submitted JMRI.

(Included for information only).

1. *Enden T, Sandset PM.* Lancet protocol Reviews, protocol 07PRT/295: Catheter-directed Venous Thrombolysis in acute iliofemoral vein thrombosis — the CaVenT study. http://www.thelancet.com/journals/lancet/misc/protocol/07PRT-295
2. *Schulman S.* Getting intimate with the venous thrombus (*editorial*) . Journal of Thrombosis and Haemostasis 2009;7:1266-7.
3. *Enden T, Kløw NE, Sandset PM*. Kateterbasert trombolytisk behandling ved akutt dyp venetrombose (*commentary*). (Catheter-directed thrombolysis in acute deep venous thrombosis). Tidsskrift for den Norske Lægeforening 2006; 126:1765
4. *Enden T, Kløw NE, Sandset PM, Aas E.* Cost-effectiveness of catheter-directed thrombolysis in iliofemoral deep vein thrombosis; a model based on the CaVenT study (RCT) (*abstract*). Health Technology Assessment international, Barcelona 2007 June.

1. Introduction

Deep vein thrombosis (DVT) of the lower limb is a common disease associated with substantial morbidity (1). In clinical practice acute DVT is routinely verified by diagnostic imaging using ultrasound, but in some patients ultrasound may not be feasible. Standard treatment of DVT includes anticoagulation (AC) for prevention of thrombus formation and compression therapy for reducing postthrombotic syndrome (PTS). Still, following adequate standard therapy a number of patients with proximal DVT will develop PTS with a chronically reduced functional outcome. To improve the clinical outcome for patients with DVT there is continued need for better diagnostic and therapeutic approaches, and the work of this thesis has examined the role of diagnostic MRI (magnetic resonance imaging) and thrombolytic therapy.

1.1 Deep vein thrombosis of the lower limb

DVT is acute abnormal clotting in deep veins hindering normal flow of venous blood. This may take place when at least one of the three following occurs; venous stasis, vessel wall injury and/or hypercoagulability, known as Virchow's triad since 1856 (2). The initial thrombus formation usually takes place in the paired calf veins, and if not recognized and treated may result in continuous clotting and more proximal extension of the clot (1). When attending medical help, 85% have developed proximal DVT affecting the popliteal or more proximal veins (3). Thrombotic material may embolize and finally lodge in the pulmonary arterial circulation causing pulmonary embolism (PE) in up to 50 % of patients with proximal DVT (4). DVT of the lower limb may cause substantial acute and chronic morbidity, and even death in cases of severe PE.

Estimated incidence of acute DVT is approximately 1/1000/year (5). Several risk factors for venous thromboembolism (VTE) have been identified and can be classified as acquired or inherited as summarized in table 1. From this follows that patients suffering from DVT are encountered in a wide range of medical specialties including oncology, haematology, obstetrics and gynaecology, orthopaedics, surgery, and emergency medicine. Approximately 40% have idiopathic VTE with no identified risk factor (5).

Table 1 Risk factors for venous thromboembolism, adapted from (6;7)

Acquired risk factors	
Age (especially >75 years)	
Surgery	Infection
Trauma	Heart failure
Malignancy	Respiratory failure, chronic obstructive lung disease
Cancer therapy (hormonal chemotherapy or radiotherapy)	Estrogen-containing oral contraception, or hormone replacement therapy or selective estrogen receptor modulator therapy
Prolonged immobility, paresis	Nephrotic syndrome
Previous venous thromboembolism	Myeloproliferative disorders
Increased age (especially > 75 yr)	Obesity
Pregnancy and postpartum status	Smoking
Inflammatory bowel disease	Varicose veins
Travel (long haul flights)	Central venous catheterization
Antiphospholipid antibodies	
Inherited risk factors	
1st degree relative with venous thromboembolism	
Thrombophilia: Factor V Leiden mutation	
Prothrombin gene (G20210A) mutation	
Antithrombin deficiency	
Protein C deficiency	
Protein S deficiency	

1.1.1 Chronic postthrombotic complications

Chronic changes of the leg following proximal DVT include swelling, pain, discomfort, deterioration of skin and possibly ulcers. This is recognized as the postthrombotic syndrome (PTS). The symptoms are typically most pronounced at the end of the day, and aggravated by standing and walking. PTS probably evolves from venous obstruction as a result of persistent postthrombotic changes and/or venous incompetence caused by inflammatory destruction of venous valves in response to acute thrombotic occlusion (8). Both obstruction and incompetence may lead to chronic venous hypertension, resulting in edema, pigmentation, fibrosis, and ulceration. However, the pathophysiologic mechanisms remain unclear (9). PTS develops in approximately every fourth patient

following adequate standard therapy (10;11). In addition to significant morbidity PTS is associated with reduced quality of life (QOL) and substantial costs (12-14).

1.2 Diagnostic imaging of deep vein thrombosis

The typical symptoms of DVT are acute onset of pain, swelling, and erythema of the lower limb, but the clinical presentation may be highly variable and misleading. Estimation of individual clinical probability of DVT using a prediction rule like the Wells' score (15), improves diagnostic accuracy. Combined with the high specificity and negative predictive value of D-dimer, a specific product of fibrin degradation, diagnostic imaging is not necessary in patients with low clinical probability and negative D-dimer (16). In all cases of high clinical probability, diagnostic imaging should be performed to objectively secure the diagnosis. In clinical practice compression ultrasound is the method of choice, possibly combined with Doppler (17;18). A meta-analysis of the diagnostic accuracy of ultrasound for symptomatic DVT included 100 cohorts where ultrasound was compared to venography, the former reference method (table 2) (17). Overall sensitivity was at least 94% for proximal DVT. Sensitivity for distal DVT was improved by using Doppler, while specificity was at least 94% independent of whether compression technique only and/or Doppler were used.

Table 2 Sensitivity and specificity of ultrasound in patients with suspected DVT of the lower limb (17)

Ultrasound technique	Sensitivity		Specificity
	Proximal DVT	Distal DVT	
Overall	94.2%	63.5%	93.8%
Duplex*	96.5%	71.2%	94.0%
Triplex**	96.4%	75.2%	94.3%
Compression only	93.8%	56.8%	97.8%

* Combined compression and color Doppler ultrasound

** Combined compression, color Doppler and continuous wave Doppler ultrasound

In some patients ultrasound is not feasible if obesity, severe oedema, plaster casts, wound dressings etc cause inadequate penetration of the ultrasound. The method also has limitations in diagnosing acute on chronic DVT and asymptomatic DVT (19;20). Finally, it may not be possible to completely visualise the iliac veins with any ultrasound technique because of their deep location in the pelvis and overlying disturbing bowel gas (21). Alternative, easily accessible imaging is venography and CT (computer tomography) when ultrasound is inconclusive. However, these examinations include radiation and injection of intravenous iodine-based contrast agent, causing discomfort to the patient and may carry adverse effects such as kidney failure, anaphylactoid reactions and increased risk for radiation induced malignancy. CT venography of the lower limb has so far not been shown to hold a

position in the primary diagnostic work up for acute DVT, but may be preferred for, e.g., intensive care patients (22). In patients with suspected PE, however, a CT pulmonary angiography should be carried out (4;23), and an immediately following ("follow-on") CT venography utilizing the already given contrast agent, may give additional information in this patient group (24).

Regarding visualisation of pelvic structures, it is known from general radiology that CT and MRI are superior to ultrasound. In addition, both methods have overall high technical efficacy, visualise deep structures practically independent of patients' constitution, and allow visualisation of secondary signs of acute thrombosis and ancillary findings, e.g., peri-venous inflammation, vein abnormalities, and other structural changes (tumours, strictures, etc.).

1.2.1 MRI

The search for an ideal imaging modality along with the fast developing and highly advanced MRI technology, have led to a number of MRI techniques for detection of acute DVT. Overall the results are promising, but implication in clinical practice has been slow. Reasons for this may be various, including high costs, restricted availability, long acquisition times, large variation in techniques developed and evaluated during the last two decades, and no large scale studies for confirmation of preliminary reports.

Studies on MRI detection of acute DVT report sensitivities of 87-100% and specificities of 82-100%, with results improving during the last decade (table 3). MRI venography has been performed with and without use of contrast agent, but also imaging of the thrombus itself has been demonstrated with a so-called direct thrombus imaging technique (MRDTI) (25). A systematic review (SR) with meta-analysis of 14 studies on the accuracy of MRI in diagnosis of suspected DVT showed similar results, and so far no particular MRI technique has proven superior (26). The authors concluded that the "meta-analysis suggests that MRI has similar diagnostic accuracy to ultrasound, although this is based upon a relatively small number of heterogeneous studies. Given the cost and inconvenience of performing MRI, it is clear that MRI will not replace ultrasound as a first-line investigation for DVT. MRI may offer an alternative for patients in whom ultrasound is inappropriate, not feasible, or yields inconclusive results". Part of the significant heterogeneity in the SR may be explained by the varying MRI methods, but the results should also be interpreted with caution because of high prevalence of DVT in several of the studies. In populations with suspected DVT undergoing diagnostic imaging, DVT is found in 20-25% (18), and a higher prevalence may indicate selection bias among recruited patients.

Up to recently the use of gadolinium based MRI contrast has been considered safe, however, it is now clear that in some cases of severe kidney failure, there is a risk of developing the chronic and non-curable condition nephrogenic systemic fibrosis (27). Whether this applies to the new "generation" of so called blood pool agents, is not unlikely. Blood pool agents has the advantage of remaining intravascular long enough to allow high resolution imaging up to 30-60 min after iv administration. With regards to rare and potentially serious complications and costs, a method not relying on MRI contrast is therefore beneficial.

Table 3. MRI techniques for detection of DVT

Year	1st author	Technique	n=	No. with DVT	Veins examined	Reference standard	Sensitivity (%)	Specificity (%)	Kappa§
1990	Spritzer (28)	Gradient-echo	66	24	Iliofemoral and popliteal	Venography or clinical follow-up	100	93	
1990	Erdman (29)	Contrast enhanced spin-echo	36	27	Iliofemoral and popliteal	Venography	90	100	**0.752**
1991	Arrivé (30)	Gradient-echo & spin-echo	72	NA	Abdominal	Surgery/CT/US	95	82	
1993	Spritzer (31)*	Gradient-echo	199	72		Venograpy/CT/US	97	98	
1993	Evans (32)*	Gradient-echo	61	21	Iliofemoral and calf	Venography	87-100	95-97	
1993	Carpenter (33)*	2D TOF spin-echo	85	NA	VCI, iliofemoral, popliteal	Venography (US)	100	96	
1995	Dupas (34)	2D TOF	25	25	VCI, iliofemoral	Venography (US)	100	98.5	
1995	Montgomery (35)	Gradient-echo & spin-echo	45	15	Iliofemoral (asymptomatic patients with pelvic fracture)	Venography	**MRI was superior to venography**		
1996	Laissy (36)*	Contrast-enhanced	21	15	iliofemoral	Venography	100	100	
1996	Evans (37)*	Gradient-echo	75	26	Iliofemoral (calf)	US	100	100	
1997	Lebowitz (38)	3D FISP +/- 2D TOF contrast enhanced	17	4	Iliofemoral and calf	Venography	100	100	
1997	Catalano (39)*	2D TOF	43	25	Ilial	Venography	100	94	
2002	Fraser (25)*	MRDTI	101	53	iliofemoral, popliteal and calf	Venography	92-100	90-100	**0.89-0.98**
2003	Fraser (40)*	2D TOF and VESPA contrast enhanced	55	20	Iliofemoral	Venography	100	97-100	**0.85-0.97**
2006	Cantwell (41)	True FISP	24	10	VCI to calf	venography	87	98	**0.64-0.97**

§ Kappa value indicates interobserver variability

*study also included in SR (26)

1.3 Testing efficacy of diagnostic imaging

In studies of diagnostic imaging the efficacy of the examination can be evaluated on different levels, and a hierarchical model of 6 levels has been suggested (42), as summarised in table 4 (43). A novel method of diagnostic imaging should initially be evaluated on level 1, followed by level 2. The measures on level 1 are mainly technical parameters allowing comparison of one image system with another based on physical attributes. In addition, assessment of inter-observer variation is included on this level. The measures of analyses on level 2 express diagnostic accuracy, and depending on the clinical setting various measures can be used (42;44;45).

Table 4 Levels of efficacy and typical measures of analyses in diagnostic imaging thornbury (42;43)

Level of efficacy	Typical measures of analyses	Comment
1 Technical, pre-clinical	Resolution, gray scale range, sharpness, signal-to-noise ratio, contrast-to-noise ratio, inter observer variation	Image quality
2 Clinical, diagnostic accuracy	Abnormal vs. normal findings, percentage correct diagnoses, sensitivity and specificity in defined clinical setting, positive and negative predictive value, area under the receiver-operation–characteristic (ROC) curve	Compare to reference method
3 Clinical, diagnostic-thinking	Impact on and change in diagnostic algorithm	
4 Clinical, therapeutic	Impact on and change in therapeutic decisions	
5 Patient-outcome	Mortality, morbidity, patient reported measures, QOL	Multicenter, controlled trials
6 Societal	Cost-effectiveness Implementation studies	Societal viewpoint

Previous reports indicating suboptimal quality of methods in studies of diagnostic accuracy led to the international STARD (Standards for Reporting of Diagnostic Accuracy) initiative and checklist (46), with the objective to improve “accuracy and completeness of reporting of studies of diagnostic accuracy, to allow readers to assess the potential for bias in the study (internal validity) and to evaluate its generalizability (external validity)” (www.stard-statement.org).

1.4 Standard treatment for deep vein thrombosis

Standard treatment for DVT is found in continually updated international guidelines (47). In summary, anticoagulation (AC) and compression therapy should be given to patients with verified acute DVT (Grade 1A recommendations[1]).

1.4.1 Anticoagulation

AC is given initially as heparin followed by oral warfarin for at least 6 months for iliofemoral DVT (47). AC prevents further formation of venous thrombus, recurrent thrombus formation and thrombus embolization (1). Consequently both morbidity and mortality are reduced. Adequate AC may play a role in reducing risk of PTS development (49). Following a first time VTE, all patients are at risk of experiencing recurrent thrombosis. As several known and unknown factors influence recurrence, the optimal duration of AC remains uncertain in several subgroups of patients (50). Patients with idiopathic thrombosis or a persistent risk factor experience recurrent VTE in at least 10% per year, compared to ≤ 3% per year in patients with transient risk factor(s) (1). The duration of AC has to be decided by balancing the individual patient's risk of recurrent VTE with and without treatment, and the risk of AC-related bleeding (50). A SR of 2006 estimated frequency of recurrent VTE per 100 patient years to be 4.9 (95% CI 3.5-6.2) when treated with AC for 4-12 months and 0.7 (95% CI 0.3-1-1) on continuous AC (51). Corresponding numbers for estimated frequency of bleeding were 0.7 (95% CI 0.4–1.0) and 1.6 (95% CI 0.5–2.7), respectively.

1.4.2 Elastic compression stockings

Elastic compression stockings (ECS) are recommended for 24 months following a proximal DVT, as this has been shown to reduce the risk of PTS with approximately 50% in 2 open randomized, controlled trials (RCT), see table 5 (10;11). The stockings should be knee-high, worn daily whenever out of bed, and execute an external pressure of approximately 30 mmHg (class II ECS). The external pressure from ECS reduces venous hypertension and reflux (10).

[1] Grade 1A recommendations: "Strong recommendation, high-quality evidence. Desirable effects clearly outweigh undesirable effects. Consistent evidence from RCTs without important limitations … Recommendations can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect" (1).

Table 5 ECS and frequency of PTS at 24 months following a proximal DVT of the lower limb

Year	1st author	Group	PTS	No PTS	*Duration of follow-up*
1997	Brandjes (11)	ECS	30 (31%)	66 (69%)	*Median 76 months*
		Control	69 (70%)	29 (30%)	*Range 60-96 months*
2004	Prandoni (10)	ECS	23 (26%)	67 (74%)	*Mean ≈ 50 months*
		Control	44 (49%)	46 (51%)	*Range 6-60 months*

1.5 Additional thrombolytic therapy

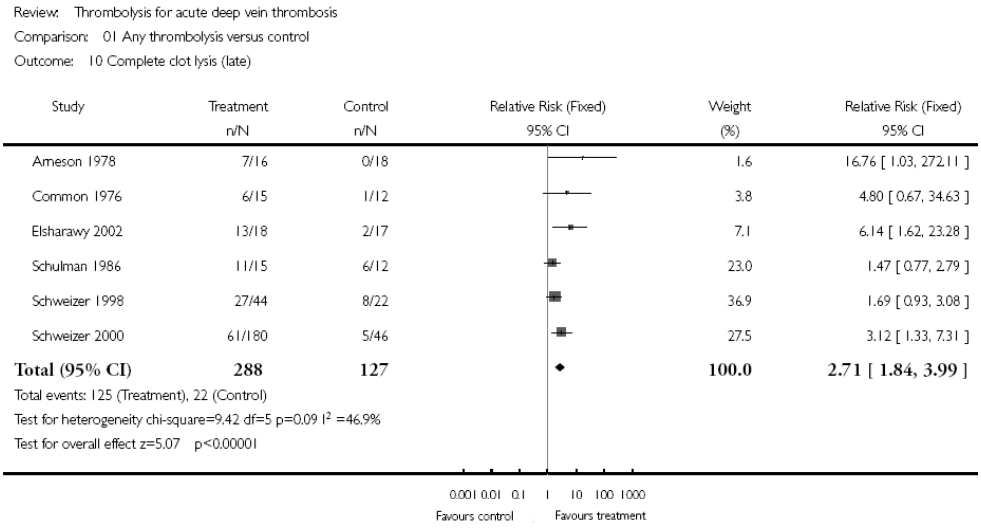
Table 5 shows that when applying the recommended standard therapy, still one in four patients suffering a proximal DVT is at risk of developing PTS (10;11). Accelerating the removal of venous thrombus by thrombolytic agents has been suggested to prevent the development of PTS. The current knowledge regarding the effects of additional venous thrombolysis is summarised in a Cochrane review from 2004 (52). Among the 12 studies included, only one made use of catheter-directed technique. In spite of being more effective than endogenous fibrinolysis in achieving thrombolysis (figure 1), documentation on clinically relevant outcomes is very sparse with results suggesting a positive effect with some reduction in PTS (figure 2). The conclusions of the Cochrane review were "Thrombolysis appears to offer advantages in terms of reducing PTS and maintaining venous patency after DVT", and "optimum drug, dose and route of administration have yet to be determined".

Additional thrombolysis implies an additional risk of bleeding. Following thrombolysis there were significantly more bleeding complications with early clinically relevant bleeding (cerebral bleeding excluded) in 44/440 in thrombolysis group and 18/228 of controls, corresponding to a pooled relative risk (RR) of 1.73 (95% CI 1.04-2.88) (52). Early cerebral bleeding was reported in 2/459 in thrombolysis group and 0/242 of controls, and pooled RR was 1.70 (95% CI 0.21-13.70). The authors stated that "the incidence of bleeding appears to have reduced over time with the introduction of stricter selection criteria".

Finally, regarding systemic thrombolysis the recent American College of Chest Physicians' (ACCP) guidelines suggest that "In selected patients with extensive proximal DVT (…) who have a low risk of bleeding, …may be used to reduce acute symptoms and postthrombotic morbidity if catheter-

directed thrombolysis (CDT) is not available" (Grade 2C recommendations[2]) (47). Systemic thrombolysis is in other words second to CDT due to unacceptably high risk of bleeding.

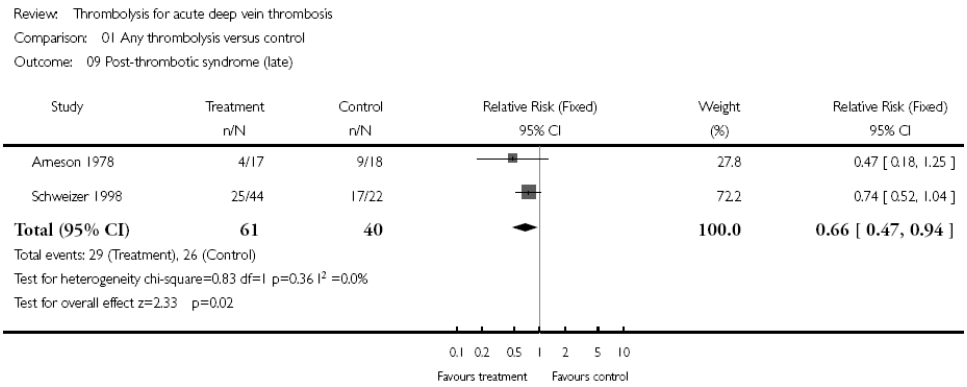
Figure 1 Complete clot lysis; meta-analysis of thrombolysis versus standard anticoagulation alone on (52)[3]



[2] Grade 2C recommendations: "Weak recommendation, low or very low-quality evidence. Desirable effects closely balanced with undesirable… Evidence for at least 1 critical outcome from observation studies, case series, or RCTs with serious flaws… Other alternatives may be equally reasonable, higher-quality research is likely to have important impact on our confidence in the estimate of effect an may…change the estimate"(1).

[3] Figure 1 has been modified by TE as the terms "Favours control" and "Favours treatment" were incorrectly interchanged in the figure compared to the results presented in the text of the Cochrane report. The author L. Watson has been informed about this error, but hitherto this has not been corrected in an update on their report.

Figure 2 Postthrombotic syndrome; meta-analysis of thrombolysis versus standard anticoagulation alone (52)



1.5.1 Catheter-directed thrombolysis

Using minimal-invasive percutaneous vascular technique the thrombolytic agent is delivered as a continuous low-dose infusion through a catheter directly into the thrombotic segments. A potential benefit of this technique is that systemic effects are minimised and frequency of bleeding is reduced. In an American national multicenter registry study with 287 patients receiving additional CDT, effective thrombolysis was achieved in approximately 80% (53). Major bleeding complications occurred in 11%, including 1 fatal intracranial haemorrhage. However, long-term follow up is scarce, and properly designed controlled trials are lacking (14;54). So far only one small RCT of 35 patients randomized to receive either additional CDT or AC alone has been reported (55). The results from 6 months follow-up showed improved patency rates following CDT; 13/18 vs 2/17, p<0.001. No results on late follow-up have been published.

Based on this limited documentation the ACCP changed their recommendations in Evidence-Based Clinical Practice Guidelines (8th Edition) regarding CDT for DVT from "We recommend against the routine use of CDT (Grade 1C recommendation[4])" and " We suggest that this treatment should be

[4] Grade 1C recommendations: Methodological strength of supporting evidence from observational studies. Implicate "intermediate–strength recommendation; may change when stronger evidence is available" (2).

confined to selected patients such as those requiring limb salvage (Grade 2C recommendation[5])" in 2004 (57) to "In selected patients with extensive acute proximal DVT (iliofemoral DVT, symptoms for <14 days, good functional status, life expectancy of >1 year) who have a low risk of bleeding, we suggest that CDT may be used to reduce acute symptoms and postthrombotic morbidity if appropriate expertise and resources are available (Grade 2B recommendation[6])" in 2008 (47).

With the CDT procedure a persisting venous stenosis following successful thrombolysis may be corrected with angioplasty and possibly stent before removing the catheter. Likewise, it is possible to identify and at the same time treat underlying vein abnormalities disposing for thrombus formation. Most commonly found is the iliac vein compression syndrome (also called May Thurner syndrome) which may be found in up to 50% of patients with left sided iliac DVT. In these patients chronic pulsating pressure from the right iliac artery riding across the left iliac vein reduces venous flow and damages vessel wall, eventually inducing a left-sided iliofemoral DVT (58).

1.5.2 Thrombolytic agents

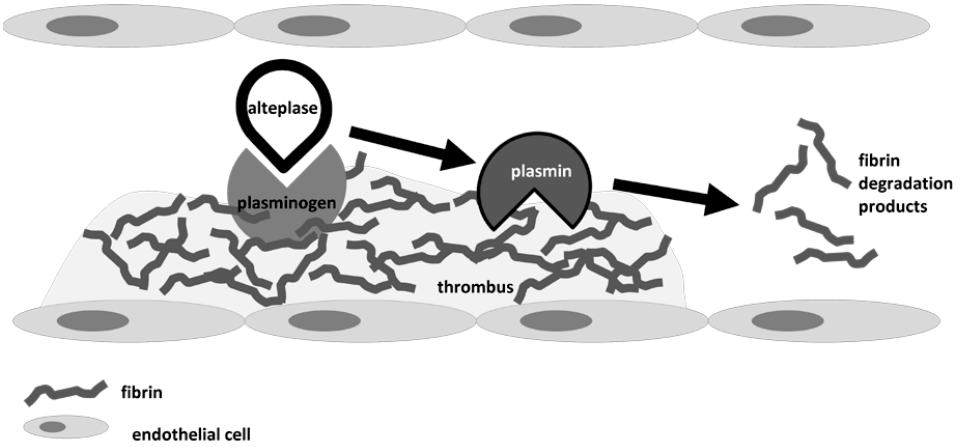
All thrombolytic agents work by inducing the conversion of plasminogen to plasmin, which again disintegrates the fibrin mesh of the clot resulting in lysis of thrombus material. All agents may cause bleeding. The previously reported thrombolytic agents in VTE studies are urokinase, streptokinase and alteplase (52). Urokinase has been used to a great extent in the US (53). Streptokinase has the disadvantage of inducing antibody formation. The recombinant tissue plasminogen activator (rt-PA) alteplase (Actilyse®, Boehringer Ingelheim, Ingelheim am Rhein, Germany) is the single thrombolytic agent registered for treatment of VTE in Norway (www.felleskatalogen.no, www.legemiddelhandboka.no). Alteplase has high affinity and specificity for fibrin, as fibrin-bound plasminogen on the clot surface accelerates the activity of alteplase substantially (figure 3). Theoretically this leads to less systemic effect compared to other thrombolytic agents. A previous SR

[5] Grade 2C recommendations: Risk/benefit is unclear. Methodological strength of supporting evidence from observational studies. Implicate "very weak recommendations; other alternatives may be equally reasonable" (2).

[6] Grade 2B recommendations: "Weak recommendation, moderate-quality evidence. Desirable effects closely balanced with undesirable… Evidence from RCTs with important limitations… Best action may differ depending on circumstances…; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate"(1).

on t-PA for the treatment of DVT identified one study comparing high-dose vs. low-dost rt-PA (n=32), one comparing systemic vs. local administration of rt-PA (n=151), and 3 RCTs comparing systemic rt-PA plus heparin vs. placebo infusions and heparin (n=169). (59). (These three trials were later included in the Cochrane review (52)). Use of rt-PA was found to increase chance of >50% lysis and complications compared to placebo. Increased dose did not increase efficacy. Local administration was neither more efficacious nor riskier than systemic. Based on this limited evidence the authors concluded that "the weight of evidence does not support routine use of rt-PA" and "there is insufficient evidence regarding its risks to discard this potentially effective treatment…"

Figure 3 Fibrin specific thrombolysis by alteplase



1.6 Testing treatments

"Comparisons are the key to all fair tests of treatments" (60).

1.6.1 Randomised controlled trials

The most powerful method for assessing the effect of a therapy is to perform an experimental clinical study designed as an RCT (61). With this design patients are randomly assigned to receive the treatment of interest or not, and this allows comparisons to be made between two or more groups of patients that principally differ only in whether they have received the intervention or not, thereby avoiding selection bias. Likewise, all known and unknown factors that may influence the outcome, so-called confounding variables, will be equally distributed between the groups.

To avoid observation bias in RCTs, treatment allocation can be blinded. The trial may be classified according to the level(s) of blinding, i.e., who is unaware of allocated treatment; patient, physician, study investigators and/or statistician. In many trials blinding may not be ethical or feasible, resulting in an open design where patients and investigators know the treatment. To reduce observation bias in open trials, the end-point evaluators can be blinded to treatment allocation, trial results at previous time-points, and results of parallel assessments at follow-up.

To improve and secure the transparency of clinical research worldwide, study protocols are since recently registered in open access online databases, e.g., www.clinicaltrials.gov, and a number of journals require studies to be registered before being considered for publication (http://resources.bmj.com/bmj/authors/article-submission/article-requirements).

Another internationally accepted and warranted improvement in quality and surveillance of clinical research is the development of reporting guidelines, with the CONSORT guidelines for RCTs as the most well-known (www.consort-statement.org). (All guidelines are found through the portal www.equator.org).

Finally, when designing a RCT, ethical and economic aspects have to be considered to secure patients rights, avoid excessive study participation and resource consumption. In addition to the principal investigators, this responsibility is secured through ethics committees and research sponsors. A new Norwegian Law in Health research comprising all existing regulations for health research was approved by Parliament in 2008 and aim for increasing the quality and efficiency of the research process.

1.6.2 Sample size calculation, statistical power and level of significance

To obtain reliable results from a RCT it is crucial that the study has adequate statistical power to be able to detect a clinically relevant difference in effect. Power indicates the probability of detecting this effect, and is usually set to 80% (or 90%) (62;63). This corresponds to a probability of doing a type II error, i.e., accepting a false null hypothesis (to conclude that there is no difference when a difference exists), of 20% (or 10%). Type II error is likely to occur if the sample size is insufficient. The estimated effect size is the main determinant of sample size as the required sample size is inversely proportional to the [estimated treatment effect]^2 (61). Sample size calculation also includes a chosen level of significance, which is usually set to 0.05, indicating acceptance of 5% chance for rejecting a true null hypothesis (to conclude that there is a difference when there is no difference), i.e., type I

error. Sample size calculation may then be carried out using simple formulas or computer programmes (62;63).

1.6.3 Systematic review and meta-analysis

Results of a number of RCTs evaluating the same therapy may be systematically collected into a SR and analysed using meta-analysis statistics. This approach leads to new information with a higher level of confidence than the results from single clinical studies. The rationale and advantages for SR are versatile, as summarised in table 6 (64;65). This synthesis of total research evidence is of great importance for decision makers, clinicians and researchers. The significance of systematically collected evidence is underlined by high-quality journals like the Lancet requiring authors to "…direct reference to an existing systematic review and meta-analysis. When a systematic review or meta-analysis does not exist, authors are encouraged to do their own" (66).

Table 6 Why do SR and meta-analysis? (64;65)

Rationale and advantages for SR and meta-analysis
▪ Condense large amounts of information
▪ Quickly assimilation by healthcare providers, researchers, and policymakers
▪ Explicit methods limit bias in identifying and rejecting studies
▪ Efficient scientific technique
▪ Show evidence that new trials are unnecessary
▪ Assess generalizability of results
▪ Assess consistency of results
▪ Explain inconsistencies in results
▪ Increase power
▪ Increase precision in effect estimates
▪ Improve accuracy
▪ Results can be reproduced
▪ Improve reliability of conclusions
▪ More quickly implementation of effective healthcare

1.6.4 An approach for treatment evaluation

In summary; to answer a research question like "Is this new treatment better than current treatment?" a structured approach for evaluating the effects of new treatments (or other interventions) are needed. This will lead to a robust conclusion with high level of evidence that

others can use for clinical policy making, clinical practice or further clinical research. The steps for such an approach are summarised in table 7.

Table 7 Steps for treatment evaluation

	Structural approach for treatment evaluation
1	Identify or write SR
2	Search for RCTs, if several new: update SR
3	Search for registered trials
4	Define protocol
5	Register study
6	Conduct study
7	Report study adhering to reporting guidelines
8	Describe main study results in trials registry
9	Update SR

1.7 Efficacy outcomes in clinical studies on deep vein thrombosis

Traditionally the primary outcome measures in studies on antithrombotic treatment of DVT have been recurrent VTE, bleeding complications, and mortality (47). The majority of recurrent VTE occurs during the first two years after discontinuation of AC (50). However, time of follow-up in a number of studies is limited to only 3-12 months (47). Studies on thrombolytic therapy have used surrogate endpoints like patency and reflux (table 14).

1.7.1 Postthrombotic syndrome

Studies on antithrombotic treatment of DVT rarely report on functional and patient reported outcome measures. The frequency of PTS, its impact on daily activities and quality of life (QOL), and the associated socioeconomic burden indicate that PTS is a significant and relevant outcome following DVT (12-14;67).

For assessment of PTS development, time of follow-up should be at least 2 years (8;10;11). Different clinical scales have been used for the diagnosis of PTS (e.g., in table 3). Most frequently employed is the Villalta score (68). This score has recently been discussed and recommended by the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) (69). For long-term functional assessment The Society of Interventional Radiology recommends the use of Villalta score, preferably together with Venous Clinical Severity Score, and/or Venous Disability Score. These are scores derived from the CEAP-classification, see section 3.4.6 (54).

1.7.2 Quality of life (QOL) following deep vein thrombosis of the lower limb

QOL is a patient reported outcome measure increasingly employed in clinical research (70), and can be used in both observational and experimental clinical studies (71). Patient reported outcomes are not only easy and reasonable to obtain, but may give relevant and valuable information on aspects considered of great importance from the patients' own point of view and which are not covered by use of traditional clinical outcome measures. QOL is of particular interest in chronic medical conditions, and may be a primary or, more commonly, secondary outcome measure.

Both generic and disease-specific QOL instruments aim at assessing multi-dimensional aspects of burden of disease regarding patients' functioning and daily life including impairment of function at work and home, and the subsequent psychological strains and limitations in social life. It is well recognised that generic QOL-instruments should be used in combination with disease-specific instruments in clinical studies (70;71). Generic instruments, e.g., SF-36 and EQ-5D, can be used in both healthy individuals and patients and can compare QOL between different populations irrespective of diagnosis. Disease-specific instruments often assess QOL within the same dimensions, but with focus on aspects closely related to the disease of interest. These instruments are therefore more sensitive than generic questionnaires in capturing clinically relevant changes in the patient population of interest (71).

To obtain reliable measures of the multi-dimensional impact of burden of disease scientifically rigorous measures are required (72). QOL instruments should be developed and evaluated to fulfil standard criteria for acceptability, reliability, validity and responsiveness in a psychometric evaluation (71;72). Table 8 presents a summary of the different psychometric properties that can be tested and their related criteria. A reliable questionnaire means that the construct of interest is measured consistently, as reliability describes the precision of the measurement. The validity of an instrument is the degree to which it measures what it was designed to measure. Responsiveness refers to the ability of an instrument to detect clinically important changes over time. Most Norwegian versions of QOL instruments are translated from English, and translation of QOL questionnaires should adhere to suggested guidelines (73).

Table 8 Psychometric evaluation of QOL measurements (71;72)

Property	Definition	Assessment	Criteria
Acceptability	Data quality Score distributions (Time for completion)	Missing data (summary scores) Frequency distribution Floor and ceiling effects	< 5% < 10%
Reliability			
Internal consistency	Homogeneity of scale; extent of items measuring the same construct	Cronbach's α Item-total correlations	> 0.70 > 0.20
Test-retest reliability	Stability over time	Correlations	> 0.80
Validity			
Content validity	Representative of the domain of interest	Qualitatively	None
Construct validity	Measure of a single construct Form a summary score	Cronbach's α Correlation	> 0.70 Moderate/large
Convergent validity	Correlation with other measures of similar constructs	Correlation	Moderate/large
Discriminant validity	No correlation with other measures of different constructs	Correlation	Small
Known-group differences	Ability to differentiate known groups	Scores groups	(p-value)
Responsiveness	Detection of clinically important change over time	Change scores	(p-value)

Patient reported QOL is recognized as a meaningful outcome measure in long-term follow-up in DVT studies as a supplement to investigator-assessed measures (74). Several disease-specific instruments for chronic venous disease have been developed and validated, including one specifically constructed for acute DVT (75). Table 9 presents conclusions and summary of study details from 1 case-control and 10 cohort studies, including 3 validation studies, assessing QOL in patients with DVT of the lower limb.

Table 9 Studies on QOL assessment following DVT of the lower limb

Year	1st author	Patient population	QOL instrument	Study design	N=	Follow-up	Conclusions
1995	Beyth (76)	DVT	3 domains of SF-36	Cohort	52	6-8 years	Symptoms in the affected leg were common and associated with worse health-related quality of life.
1999	Mathias (77)	Iliofemoral DVT	HUI SF-12 Additional DVT specific scales	Validation study	111	>6 months	Measure is reliable, valid and responsive
2000	Comerota (78)	CDT for iliofemoral DVT		Case-control	68+30	16 months	Better functioning in CDT group. Successful lysis correlated with improved QOL.
2001	Ziegler (79)	DVT 82% with PTS	CIVIQ(modified)	Prospective cohort	161	56 months	Estimated restriction in QOL was in accordance with clinical severity of PTS
2004	Van Korlaar (80)	DVT	SF-36 VT-QOL	Cohort, identified retrospectively	45	24 months	Assessment of QOL should be included in future studies on DVT
2004	Delis (81)	Iliofemoral DVT	SF-36	Cohort, identified retrospectively	39	5 years	QOL was reduced in 5 of 8 domains compared to healthy subjects (age and sex adjusted)
2004	Hedner (82)	Proximal DVT	SF-36 EQ-5D DVTQOL	Validation study	121	Max. 6 months	DVTQOL is user-friendly …with good reliability and validity. Test-retest…and responsiveness…must be explored

Table 9 continued

2002	Kahn (13)	DVT ± PTS	SF-36 VEINES-QOL	Cohort	41	>12 months	PTS has significant impact on disease-specific QOL. QOL measures correlated well with physician-assessed PTS (Villalta scale)
2004	Kahn (83)	Chronic venous disease ± DVT		International cohort study (VEINES Study)	1531	Years	Disease severity is worse and QOL poorer in chronic venous disease with prior VTE compared with other forms of chronic venous disease.
2005	Kahn (84)	DVT		Multicenter, prospective cohort (VETO Study)	359	Visits at 0, 1 and 4 months	QOL improved during first 4 months following DVT. Average QOL remains poorer than population norms at 4 months. Worsening of PTS (Villalta scale) is associated with worsening of QOL.
2006	Kahn (72)	DVT		Valdiation study within a prospective cohort study (VETO Study)			Developed using gold-standard methods... valid and reliable. .. provides a rigorous tool (for) comprehensive evaluation of outcomes in clinical trials and epidemiological studies.
2008	Kahn (74)	DVT 47 % with PTS		Prospective cohort study	387	24 months	Development of PTS is the principal determinant of QOL 2 yrs after DVT.

2. Aims

Properly designed studies with long-term follow up for the evaluation of additional CDT in patients with acute DVT of the lower limb have been in demand for years. Routine diagnostic imaging for detection of acute DVT using ultrasound techniques is not always feasible. The overall objectives of the present work aimed at evaluating and improving diagnostic imaging and therapy of proximal DVT of the lower limb using scientifically sound methods.

The specific aims of the thesis were:

- To design and implement a well designed RCT for the evaluation of safety and efficacy of site-directed thrombolysis in patients with acute iliofemoral DVT receiving CDT in addition to conventional AC and compression therapy (paper I).
- To translate and assess data quality, reliability and validity of a disease-specific questionnaire for the assessment of QOL in patients following DVT of the lower limb (paper II).
- To evaluate whether additional CDT increases venous patency 6 months following acute iliofemoral DVT (paper III).
- To compare a novel MRI sequence with contrast-enhanced MRI in visualisation of the deep veins of the leg and detection of deep vein thrombosis (paper IV).

3. Materials and methods

3.1 Recommendations and permissions

The CaVenT Study and the MRI study were initiated after obtaining recommendations and permissions from Regional Ethics committee, the Data Inspectorate, the Norwegian Directorate for Health, and the Norwegian Medicines Agency. Liability insurance in connection with clinical trials of drugs was established by membership of the Drug Liability Association. The CaVenT Study is internationally registered with number NCT00251771 (www.clinicaltrials.org). Quality assurance of the study protocol has also been secured through acceptance in Lancet's Protocol Reviews following external peer-review (http://www.thelancet.com/journals/lancet/misc/protocol/07PRT-295). (With this the Lancet guarantees to peer review the future manuscript presenting the main results from the CaVenT study).

3.2 Study design

The CaVenT Study is an open, multicenter RCT designed to adhere to established standards for fair testing of treatments and published recommendations for studies on venous disease (54). After obtaining informed, written consent the patients were randomized to receive conventional treatment alone (control group) or CDT in addition to conventional treatment (interventional or CDT group). All patients were called for clinical follow up 6, 24 and 60 months following the thrombotic event. (Data from follow up are still being collected).

The validation study of VEINES-QOL/Sym was implemented as a small cohort study within the initial phase of the CaVenT Study.

The first part of the MRI project was designed as a pilot study with healthy volunteers. The second part was a small cohort study of consecutively recruited patients with acute DVT.

3.2.1 Sample size and power calculations

Sample size of the CaVenT Study was calculated from the *a priori* hypothesis that frequency of PTS after 2 years will be at least 25% in those allocated conventional therapy compared to less than 10% in those given additional CDT. With a significance level of 5% and a statistical power of 80%, sample size calculations indicated that a total of nearly 200 patients (97.4 in each group) were required (62;63). Based on the *a priori* short-term hypothesis that venous patency after 6 months occurs in less than 50% in those allocated conventional treatment compared to at least 80% in those given CDT, it may be shown with the same significance level and statistical power as given above, that 76

patients are required. Reporting of patency after 6 months based on the first approximately 100 patients with 6 months patency data was planned *a priori*. There were no power calculations for the QOL or MRI studies.

3.3 Study participants

The CaVenT Study has been recruiting patients from 22 hospitals within the South-Eastern Norway Regional Health Authority during the time period 2006-2009. Patients who met the inclusion criteria without any exclusion criteria were invited to participate in the studies (table 10). Those who accepted to participate gave written informed consent. Self-reporting QOL questionnaires from the first 74 patients were used in the validation study. For the MRI study 15 healthy volunteers were recruited among staff and medical students at Oslo University Hospital, Ullevål. Six patients with iliofemoral DVT were prospectively recruited from the same hospital.

Table 10 Inclusion and exclusion criteria for the studies

Inclusion criteria for the CaVenT Study and MRI Study
1. Age 18-75 years
2. Onset of symptoms < 21 days
3. Objectively verified proximal DVT, for the CaVenT Study: localised in the upper half of the thigh, the common iliac vein, or the combined iliofemoral segment
4. Written informed consent
Exclusion criteria for MRI Study
1. Any contraindication to MRI (claustrophobia, metal implants) or Vasovist® (hypersensitivity)
Exclusion criteria for the CaVenT Study
1. Anticoagulant therapy before trial entry for > 7 days
2. Contraindications to thrombolytic therapy, including bleeding diathesis
3. Indications for thrombolytic therapy, for example, phlegmasia cerulea dolens or isolated vena cava thrombosis
4. Severe anemia (hemoglobin < 8 g/dL)
5. Thrombocytopenia (platelets < $80 \cdot 10^9$/L)
6. Severe renal failure—creatinine clearance < 30 mL/min*§
7. Severe hypertension, that is, persistent systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg
8. Pregnancy§ and thrombosis ≤7 days postpartum (may be included after 7 days postpartum)
9. Less than 14 days postsurgery or posttrauma (may be included after 14 days)
10. History of subarachnoidal or intracerebral bleeding
11. Disease with life expectancy <24 months
12. Drug abuse or mental disease that may interfere with treatment and follow-up
13. Former ipsilateral proximal DVT
14. Malignant disease requiring chemotherapy
15. Any thrombolytic therapy within 7 days before trial inclusion

*Creatinine clearance will be calculated according to the following formula:

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

b = 1.04 (females); 1.23 (males)

§ Also exclusion criteria for MRI study

3.4 Study procedures

3.4.1 Randomisation

A random block allocation sequence for each hospital was generated by using the web site Randomization.com (http://www.randomization.com), with stratification for involvement of the pelvic veins, as the level of DVT may influence PTS development. Randomization was performed by the local study investigator at the recruiting investigation site by picking the lowest number of sealed numbered envelopes. The different local investigators were not aware of the block size of 6, which was constructed to secure that the centres contributing with few patients allocated patients equally to the two treatment arms. Patients were assigned 1:1 to control or interventional group.

3.4.2 Routine diagnostic imaging of acute deep vein thrombosis

Proximal DVT had to be verified using compression ultrasound, venography, CT- or MRI-venography in line with routines at the different trial investigation sites.

3.4.3 Standard treatment of acute deep vein thrombosis

Antithrombotic therapy with AC was initiated and given in accordance to local routines at the recruiting trial investigation site based on international guidelines (47). AC was given as sc LMWH[7] and simultaneous oral warfarin (Marevan®). LMWH was discontinued when INR had been in therapeutic range (2.0-3.0) for at least 24 hours, but was not to be given for less than a total of 4-5 days. Warfarin was prescribed for at least 6 months.

Patients were advised to wear knee-high, or thigh-high if preferred by the patient, class II (30 mmHg) ECS daily for at least 6 months, as stated in the study protocol. At 6 months follow-up all patients were urgently advised to continue with ECS for another 18 month.

3.4.4 Catheter-directed thrombolysis

Patients allocated to receive CDT were transferred to the nearest of 4 interventional centres offering this procedure (Aker, Ullevål and Rikshospitalet, i.e., Oslo University Hospital, or Østfold Hospital Trust in Fredrikstad). CDT was started on the first following working day. Meanwhile these patients received sc LMWH. Further details of the CDT procedure are described in paper I and III. During thrombolysis any overt bleeding or symptoms suspect of bleeding or pulmonary embolism were dealt with according to local routines. Major bleeding was defined as previously reported (85). AC

[7] Either dalteparin (Fragmin®) 200 U/kg, or enoxaparin (Klexane®) 1.5 mg/kg

was then initiated as previously described in section 3.4.3 within 1 hr following completion of thrombolysis.

3.4.5 Non-invasive assessment of veins at follow-up

Non-invasive assessments of the veins were performed after 6 months ± 2 weeks by an angiologist with no previous contact or knowledge of the patients' treatment allocation or medical history. To further secure an unbiased evaluation of outcomes, the patients were explicitly told not to reveal which treatment they had been given.

The venous system was examined using ultrasound and air-plethysmography. Ultrasound was used for the assessment of postthrombotic wall-thickening, intraluminal hyperechoic structures, flow, compressibility, and incompetence. Venous flow was graded as spontaneous, forced (on peripheral compression), or absent (53). Incompetence was evaluated with the patient in standing position, and reflux was defined as reversal of the velocity curve lasting longer than 0.5 seconds following standardised distal pneumatic decompression (86). Functional obstruction of the veins was assessed by using air plethysmography (87;88). Assessment of venous patency included compressibility, flow, and venous obstruction. Patients having any of the following: incompressibility of the femoral vein, no iliofemoral venous flow and/or functional venous obstruction, were classified as not having regained iliofemoral venous patency. Patients with duplicate femoral veins with normal compressibility and flow in at least one course and without functional obstruction were considered successfully recanalized.

3.4.6 Clinical evaluation of postthrombotic changes

At follow-up, information was obtained regarding comorbidity of the lower limb, recurrent venous thromboembolism or new diagnosis of cancer. Evaluation of development of chronic venous disease and PTS was assessed by CEAP-classification (89) and Villalta score (68), respectively. The CEAP classification includes assessment of Clinical (dermatological) signs, Etiology, Anatomic distribution and Pathophysiologic dysfunction, see table 11 for details.

Table 11 The CEAP classification of chronic venous disorders

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	

The Villalta scale was developed for assessment of PTS and consists of five patient-rated venous symptoms of the affected leg (pain, cramps, heaviness, paresthesia, pruritus) and six clinician-rated signs (pretibial edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, redness). The symptoms and signs are each rated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Points are summed to produce a total score. Patients are classified with PTS if the score is ≥ 5, or if a venous ulcer is present. A score of 5-14 indicates mild/moderate PTS, whereas a score of ≥15 or the presence of a venous ulcer regardless of total score indicates severe PTS.

3.4.7 Assessment of quality of life

Health related quality of life was assessed by the patients completing the self-reporting questionnaires EQ-5D (90) and VEINES-QOL/Sym (72) in a clinical setting at baseline and follow up. The Norwegian versions of the two instruments are presented in the appendix.

3.4.8 MRI

MRI was performed in a 1.5 T whole body scanner (Philips Intera, software release 2, Philips, Best, The Netherlands). The participants were scanned in a supine position with feet first. A 1.5 T body coil (Synergy Body Coil, Philips, Best, The Netherlands) was positioned for imaging at three different positions covering the calves, thighs and pelvis. All images were obtained in the axial plane. Contrast-enhanced images were obtained under conditions corresponding to the non-enhanced sequence. Gadofosveset trisodium (Vasovist®, Bayer Schering Pharma AG, Berlin, Germany) was administered at 0.12 ml/kg (0.03 mmol/kg) body weight and injected by hand through a cannulated cubital vein for

25-30 sec followed by a 25-30 ml saline flush, in accordance to the Norwegian Medical Agency (www.legemiddelverket.no) and previous reports from the manufacturer (91). Scanning was initiated after 3 minutes delay.

3.4.9 Ultrasound in MRI study

Additional and complete compression ultrasound was performed in all patients in the MRI study on both lower extremities' deep veins covering the proximal part of the calves up to the inguinal ligament (18). The examinations were performed on an Acuson Seqoia no. 512® (Siemens, Germany) with linear (5-8 MHz, CD 4-7 MHz), curved (2-4 MHz, CD 1.75-4 MHz), and sector (2.5-4 MHz, CD 2.5-4 MHz) probes. Direct signs of acute DVT were defined as incompressibility of vein, echoic content of vein lumen, and no detection of flow in pelvic veins and ICV. Indirect signs included dilatation of deep veins.

3.4.10 Statistical analyses

Statistical analyses were performed using the statistical package SPSS version 15 (SPSS, Chicago, Illinois, USA). Findings with p-values lower than 0.05 were considered statistically significant. When comparing dichotomous variables in the two treatment groups, a two-sided Chi-square test was used. When comparing continuous variables, a two-sided Mann-Whitney test was used.

The analyses from the validation of VEINES/QOL/Sym included internal consistency assessment using item-total correlation and Cronbach's alpha. Test-retest reliability was assessed by calculation of the intra-class correlation coefficient. Construct validity was assessed as correlation with the EQ-5D, the Villalta score, CEAP classification, and presence of comorbidity of the lower limb. The t-test was used for binary groups and Spearman's correlation for nominal groups.

Statistical differences in vessel visualisation and image quality on MRI were calculated using 2-tailed Wilcoxon signed ranks test. Agreement in vessel visualisation between b-TFE and CE-FFE images was calculated as percent agreement. An inter-observer reliability analysis using the Kappa statistic was performed to determine consistency among the two observers in diagnosing DVT.

4. Summary of results

4.1 Paper I

Catheter-directed Venous Thrombolysis in acute iliofemoral vein thrombosis - the CaVenT Study: Rationale and design of a multicenter, randomized, controlled, clinical trial (NCT00251771)

Properly designed RCTs are needed to evaluate the clinical efficacy and safety of additional CDT compared with conventional treatment with AC and ECS in patients with iliofemoral DVT. Clinical efficacy should be assessed as a functional outcome of the affected limb. Totally 200 patients are required to detect a reduction in PTS from 25% to 10% 2 years following the thrombotic event. The CaVenT Study employs standardized and verifiable methods for outcome assessment including venous patency, incompetence, obstruction, and PTS. Implementation of the CaVenT study will be a substantial contribution towards improved evidence-based practice in the treatment of acute proximal DVT of the leg. Any documentation of improved functional outcome will have a significant impact on clinical practice and may lead to a modification of existing international guidelines.

4.2 Paper II

Assessing burden of illness following acute deep vein thrombosis: data quality, reliability and validity of the Norwegian version of VEINES-QOL/Sym, a disease-specific questionnaire

The data quality, reliability and validity of the Norwegian version of VEINES-QOL/Sym were assessed in 74 patients with deep vein thrombosis (DVT). Items had low levels of missing data, with the great majority being under 3%. Item-total correlations ranged from 0.41 to 0.78 with the exception of 0.29 for the symptom item 'night cramps'. Internal consistency was supported by Cronbach's alpha of 0.88 and 0.94 for VEINES-Sym and VEINES-QOL, respectively. Test–retest reliability assessed for 40 patients gave intra-class correlation coefficients of 0.83 and 0.88 for VEINES-Sym and VEINES-QOL, respectively. VEINES-Sym and VEINES-QOL were strongly correlated with EQ-5D total scores. There were moderate to large correlations with Villalta scores and small to moderate correlations with the CEAP classification. Six months after the thrombotic event, 21 (28.4%) patients had developed PTS according to Villalta score, and this was significantly associated ($p < 0.01$) with a reduction in both VEINES scores. 14 patients reported comorbidity of the lower limb, and this was associated with a reduction in both scores; reduction being significant for VEINES-QOL ($p < 0.05$).

4.3 Paper III

Additional catheter-directed thrombolysis in deep vein thrombosis increased patency - short-term results from the CaVenT Study: an open, randomised controlled trial

In 50 patients who were randomised to additional CDT, grade III (complete) lysis was achieved in 24 and grade II (50-90%) lysis in 20. One patient suffered major bleeding and 3 had clinically relevant bleeding related to the CDT procedure. Patency of the iliofemoral vein after 6 months was found in 32 of 50 patients (64.0%) in CDT group and in 19 of 53 (35.8%) in control group. This corresponds to an absolute risk reduction of 28.2% (95% confidence interval 9.7 to 46.7%, P=0.004). Functional venous obstruction was found in 10 (20.0%) in CDT group and 26 (49.1%) controls. This corresponds to an absolute risk reduction of 29.1% (20.0 to 38.0%, P=0.004). Femoral venous reflux was found in approximately 60% and did not differ significantly between the two groups.

4.4 Paper IV

MRI of veins and thrombosis

Fifteen healthy volunteers underwent MRI without (b-TFE) and with contrast-enhancement (CE-FFE) for imaging of the deep veins of the lower limb. Vena cava inferior (VCI) was only partially visualised in 7 and 4 volunteers on b-TFE and CE-FFE, respectively ($p<0.008$). The great majority of femoral and calf veins and all pelvic and popliteal veins were completely visualised on both sequences. Percent agreement between the two techniques was 50.0 % for VCI, and 90.0-100.0 % for other segments. For both techniques poorest image quality was obtained in the pelvis. Contrast-to-noise ratio was higher on b-TFE compared to CE-FFE; the difference being significant in calf images ($p=0.036$). Sensitivity was 100% for proximal DVT with both MRI methods. Specificity was 70-100% (CE-FFE) and 80-100% (b-TFE) for femoral DVT. Interobserver reliability was Kappa 1.0 (b-TFE) and 0.9 (CE-FFE) for proximal DVT. Results were overall poor for distal DVT.

5. Discussion

5.1 Study design for evaluation of venous thrombolysis

There is no robust evidence on clinical efficacy of additional CDT in iliofemoral DVT as controlled trials with long-term follow-up are completely lacking (14;52). A number of case-series reports on technical success and effective thrombolysis at the cost of a small increase in bleeding complications (see section 5.3 and table 14). The long-term follow-up in these reports has focused on patency rates and the need for re-interventions. Hence, very little is known on clinically relevant efficacy in terms of functional outcome of the affected leg following venous thrombolysis. Properly designed RCTs are required to fill this gap in evidence, otherwise CDT will continue to be a cost demanding, experimental treatment prone to lack support by policy makers and payers, e.g., as in Canada and Netherlands (personal communication Philip Wells and Menno Huismann), and we can "... continue to base our decisions on an endless row of small case series and retrospective reviews of heterogeneous data" (92).

RCTs may be criticized for lacking generalizability due to eligibility criteria that may not resemble the "real clinical world" (93). In the CaVenT study the inclusion and exclusion criteria were aimed at allowing a representative patient population with regards to gender, age and risk factors. This is in contrary to several of the case series on CDT. Patients with an increased risk of bleeding were not recruited. Patients with advanced or chemotherapy demanding cancer or drug abuse were not included because of high risk of rethrombosis and potentially reduced compliance and loss to follow-up. These groups of patients are not likely to be offered CDT in clinical practice due to the same reasons. Rethrombosis has been shown to increase risk of PTS. Hence repeated DVT complicates end-point assessment of PTS and was tried to be avoided by not recruiting patients with previous proximal ipsilateral DVT. Recurrent DVT of the same limb during follow-up was not possible to avoid.

In spite of aiming at a widely representative population in the CaVenT Study, recruitment rates were lower than hoped for during the whole period of 2006-2009 (92). In average only 1 patient has been recruited per week. We are aware of that a number of patients denied participation. Other and probably more important challenges have been of organizational matter as several of the participating centers are not supplied with designated personnel, clinics or wards for patients with VTE, and the patients are often treated in general medicine departments. Finally, the implementation of the CaVenT Study had to take place in between all other daily tasks for the local trial site investigators and their colleagues.

Based on a checklist for critical appraisal of RCTs the CaVenT Study is found to meet accepted standards, as presented in table 12 (www.kunnskapssenteret.no).

A crucial step in RCT design, which is not covered in this check list, is the estimation of the effect size of the therapy being tested. This estimate has to be deduced from previous knowledge about the disease; i.e., DVT and PTS. When planning and designing the CaVenT Study, it was hypothesized that additional CDT reduces the absolute risk of PTS with 15%; from 25% in control group to 10% in the intervention group. As this estimate is associated with uncertainty, the CaVenT Study may be too small to detect the difference, and we may accept a false null hypothesis that there is no reduction in PTS following CDT (i.e., type II error). The risk of doing a type II error was set to 20% (63;94). If reducing this risk to 10%, the sample size would have to increase from 200 to 260 (with a level of significance of 5%), leading to a much greater demand on time and other resources to implement the CaVenT Study. It has been commented that severe PTS may be a much more clinically relevant outcome measure than PTS itself, however, a study demonstrating a reduction of severe PTS in terms of venous ulcers from 6% to 3% would require about 2000 patients, and would be impossible to carry out with the available resources in our region (92).

We hypothesized that CDT reduces PTS from 25% to 10%. In case we detect this difference or even a smaller effect size, i.e., an absolute risk reduction of 5, 10 or 15 %; this would correspond to a number needed to treat of 20, 10 or 6.7, respectively, to avoid one case of PTS. This has to be weighed against the risks and complications adhering to CDT. Whether CDT is a cost-effective intervention will be assessed in a planned health economic evaluation when the future long-term results of the CaVenT Study are available. Finally, how to weigh additional bleeding complications against PTS reduction and improved QOL is not clear.

Table 12 Critical appraisal of randomized controlled trials, here the CaVenT Study:

	Ask	Tip	Yes	No	Comment
1	Is the objective of the study clearly formulated?		X		
2	Is RCT a suitable design for answering the research question?		X		
3	Was the study sample allocated treatment groups by acceptable randomization procedure?	*-Detailed description* *-Consealed allocation (sealed envelopes, computer-programmes, tables, etc.)* *-No differences in baseline characteristics between groups*	X		Use of computer based randomization is preferable to envelopes
4	Where the treatments groups given same management except for the intervention being evaluated?	*-Adherence to study protocol*	X		CDT provided more detailed information on DVT at baseline
5	Were participants, health care personnel, outcome assessors blinded to treatment allocation?	*-Judge whether blinding was possible* *-Subjective measures like pain and function more prone to bias if unblinded* *-Outcome assessor can usually be blinded*	X		Blinding of outcome assessor
6	Were all participants accounted for by the end of study?	*-Was loss to follow-up great; was it equally distributed between the groups?* *-Were reasons for loss to follow-up described?* *-Was loss to follow-up considered in the analyses?* *-Were the participants analyzed in their allocated group?*	NA		"Yes" is the likely answer to these questions when the future data on long-term follow-up are available
7	What are the results?	*-Can the most important findings be summarized in one sentence?* *-What is the effect estimate for the different outcome measures?* *-Is the difference important?*	NA		
8	How precise are the results?	*-was a p-value given?* *-Range of confidence interval related to minimally important effect*	NA		
9	Can the results be transferred to clinical practice?	*-Are the recruited patients representative to the patients I meet?* *-Is the intervention accurately described and possible to implement?* *-Is the intervention likely to influence outcome considered dose or duration?* *-Is the intervention acceptable?*	NA		
10	Were all important outcomes evaluated in the study?	*-Relevance to patients, next of kin, decision makers, experts, or clinicians* *-Were outcomes measured with reliable methods?*	X		
11	Should clinical practice be changed based on the results of the study?	*-Is efficacy of the intervention worth the costs and potential side effects?* *-Are the results supported by a systematic review?*	X		Consider precision of results!

5.2 Postthrombotic syndrome as outcome measure

PTS is recognized as the most common complication following DVT, but existing knowledge about this chronic, clinical entity is limited (8). This can be explained by focus on recurrent VTE as main efficacy outcome of clinical trials on DVT treatment (47). The Cochrane Review from 2004 identified only 2 RCTs that reported on PTS following additional systemic thrombolysis (figure 2) (52). The study of Arnesen and colleagues (95) was considered to be of highest quality. This sparse evidence supports our hypothesis that additional CDT may reduce PTS from 25 % to 10 % compared with standard AC and ECS.

Reported incidence of PTS has been variable, but prospective studies indicate development of PTS in 20-50% following DVT (8). Two open RCTs comparing treatment with additional ECS to AC alone have brought new insight and are often referred to. They both found that 2 years of ECS reduced PTS with nearly 50%; see table 4 (10;11). This indicates that ECS is effective therapy, and compression is consequently recommended for 24 months following proximal DVT (grade 1A recommendations) (47). Unfortunately, there seems to be delay in implementing long-term ECS therapy in postthrombotic care (personal experience).

There is no established definition or gold standard test for PTS, and to infer and compare frequency of PTS across studies is therefore problem-ridden. It is suggested that initial pain and swelling for acute DVT may last for up to 3-6 months, and that PTS should not be diagnosed until after this time (96). There is evidence indicating that the great majority of cases of PTS usually manifest within 2 years after DVT (10;96), but PTS may develop or deteriorate beyond 2 years (97).

A number of PTS definitions based on combinations of various clinical symptoms and signs, possibly combined with functional tests of the veins, have been suggested (97). This is illustrated in table 13 by four trials previously referred to in the thesis, employing four different definitions of PTS. The use of Villalta score is now supported in recent reporting guidelines for endovascular treatment of venous thrombosis from the Society of Interventional Radiology (54) and in recommendations for standardization of the measurement of PTS in clinical studies from the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH, Vienna, July, 2008) (69). The CaVenT Study mainly adhered to these recommendations, though there was no training of trial investigators in use of Villalta score, patients wore ECS when attending follow-up which may mask signs like swelling and vein dilatation, and the end-point evaluator was not blinded to which leg had suffered from DVT.

Table 13 Examples on how PTS has been defined in previous, important studies

Year	1st author	Definition PTS
1982	Arnesen (95)	Subjective complaints and clinical signs; no/moderate/serious, including ulcer
1997	Brandjes (11)	Symptoms and signs scored in a form combining components of earlier scoring systems
1998	Schweizer (98)	Patients described own symptoms; no/slight/moderate/serious, including ulcer
2004	Prandoni (10)	Villalta score

Further, also arguing for the use of Villalta score for measurement of PTS, previous studies reporting on measurement properties of the Villalta score was recently reviewed (99). The available data were found to be "consistent in supporting that Villalta score is a reliable, valid, acceptable and responsive measure of PTS in patients with previous, objectively confirmed DVT", while the reliability of the symptoms components, numeric points for ulcer severity (e.g. no ulcer, healed ulcer, one open ulcer, > 1 open ulcer) to discriminate among severe forms of PTS, and responsiveness to clinical changes need further research.

Based on a number of observational studies, the only risk factor clearly associated with PTS development is repeated ipsilateral DVT, increasing the risk up to six fold (97;100). This was recently shown in a prospective cohort study of 387 patients (14). This study also found that more severe venous symptoms and signs 1 month after DVT, extensive iliofemoral DVT, higher BMI, older age and female sex predicted worse postthrombotic scores over time. Another and similar study of 406 patients found that proximal DVT, male sex, and high D-dimer levels were independently associated with PTS development in patients with a first time DVT (101). The CaVenT study is not powered to detect possible risk factors for PTS, but future data should be analyzed with regards to the above mentioned predictive co-factors.

5.3 Short-term results as surrogate outcome measure

Postthrombotic persistent venous obstruction and/or incompetence have been regarded as the predispositions for PTS development (8). From this follows that regaining patency and/or salvaging valves of the deep veins is likely to be important in preventing PTS and this founded the basis for the short-term hypothesis of the CaVenT Study. The relationship between immediate or mid-term patency and subsequent development of PTS remains unclear as no studies have investigated relationship between patency and long-term clinical outcome (52;102). A SR from 2007 compared pooled data from observational studies on CDT with results from RCTs on systemic venous thrombolysis and found that the pooled CDT data showed higher rates of complete early opening of occluded veins, lower prevalence of PTS, but more often minor bleeding complications (102). The authors concluded that CDT seems more beneficial than systemic administration, and an advantage is the option for adjunctive angioplasty. This conclusion should be interpreted with caution because of heterogeneity and other methodological limitations, i.e., few, small and mainly observational studies.

Following standard treatment of DVT 6 and 12 months patency are reported to be 38-50% (1). Patency following treatment with CDT has been assessed in at least 14 case series, as summarized in table 14. Three of these series reported 6 months patency to be 83%, 85% and 100% (103-105), while the majority of the series assessed patency after 2 years. These studies have a number of methodological weaknesses including lack of representative control groups, substantial loss to follow-up, small samples, high probability of selection bias, non-blinded assessments of outcome at all levels, use of variable thrombolytic and adjunctive procedures, and unclear and variable definitions and methods of assessment of patency, as shown in table 14.

In the CaVenT study additional CDT increased 6 months patency from 38.5% to 64.0% ($p=0.004$). Corresponding numbers in the smaller RCT of Elsharawy was 12% to 72% ($p<0.001$), with “no obstruction or reflux” indicating patency. Based on our study protocol with non-invasive assessment of the deep veins at follow-up, we defined iliofemoral patency as deep vein segments with flow on Doppler, compressibility on ultrasound and no sign of venous obstruction on air-plethysmography. This is likely to be a conservative and strict definition that may contribute to the apparent differences in results compared to other studies. However; this definition is clear, and it is verifiable for subsequent research. Finally, the finding among our controls of 38.5% patency is in line with previous studies (1).

We found that functional venous obstruction was reduced from 49.1% to 20.0% (p=0.004) following additional CDT. In the Elsharawy et al study moderate obstruction was found in more than 20% of patients in both groups (p=0.027), whereas severe obstruction was reduced from 59% to 6% (p=0.001). In the CaVenT study venous incompetence after 6 months was found in approximately 60% of patients in both treatment groups. This is in contrast to previous assumptions of valve salvage from rapid removal of thrombus, and to the findings of Elsharawy et al who found that CDT reduced reflux from 41% to 11% (p=0.042). The results of these two RCTs are not easy to compare, as the relatively small sample sizes and different definitions and measures of postthrombotic venous functions are likely to explain the seeming differences in results.

Another unsettled aspect is how the CDT procedure should be performed with regards to choice and dose of thrombolytic agent and concurrent antithrombotic infusion. In the CaVenT Study patients received a weight adjusted dose of alteplase of 0.01 mg/kg/h and maximum 20 mg/24h. This is slightly lower than in case series describing alteplase infusion in CDT (106-109). Chang et al and the Danish reports of 2005/2009 employed pulse spray technique to shorten overall infusion time, however total dose of alteplase does not seem to have been reduced. Concomitant infusion of heparin was used in most of the series, except in the RCT of Elsharawy and in the American registry study where this was left to the discretion of the operator (53;55). In the CaVenT Study heparin dose was adjusted to keep APTT at 40-60 sec, while others have aimed at 75-100 sec (110), 50-80 sec (111), 60 sec (109), or 50-70 sec (112). Whether the more careful approach of the CaVenT Study with lower thrombolytic and antithrombotic dosage explains the apparent smaller effect in valve salvage and improved patency cannot be ruled out, but future results will indicate whether the approach was a safer one with reduced frequency of bleeding.

The CaVenT patients received CDT at the nearest among four participating intervention centres, all with several years of experience with venous CDT, indicating that beginners' problems in performing the procedure was avoided and did not influence on the results.

There is agreement that deep venous reflux should be assessed by Doppler ultrasound, but plethysmographic technique has also been used as in the study of Elsharawy. Consensus guidelines suggest that both manual and automatic compression and decompression of the calf may be used , and a cut-off of retrograde flow of 0.5 sec following decompression of the calf (86). In the CaVenT Study reflux was assessed in line with consensus guidelines. Reflux may be found in patients with no previous DVT, indicating that other factors than previous thrombosis may also contribute to venous

valve incompetence (113). The time interval from acute onset of venous thrombosis to deterioration or disintegration of valve function remains uncertain.

Studies that have looked into the contribution of venous obstruction and incompetence in PTS development have found indications of incompetence being of lesser importance than obstruction (114;115). This is in keeping with the fact that the valves of the deep veins are mainly located in the paired calf veins, that only one valve may be found in a minority of external iliac veins, and that one popliteal valve and 1-4 femoral valves are normally found (116). Accordingly, CDT is actually directed towards proximal vein segments with very few valves to salvage, suggesting that venous incompetence is not among the important outcomes when assessing efficacy.

Finally, one should keep in mind that the underlying pathophysiological mechanisms for development of PTS are more complex than merely obstruction and/or reflux, and are likely to include endothelial dysfunction, deranged lymphatic function, associated arterial occlusive disease, joint disorders, inflammation and metabolic disturbances (117). Mechanisms remain unclear, but two recent reports indicate that inflammatory mechanisms are involved (118;119). As the CaVenT study was not designed to further elucidate possible underlying mechanisms for PTS development subgroup analyses should be interpreted with caution, but data will be explored when available.

Table 14 Studies reporting on venous patency and incompetence following catheter-directed thrombolysis

Year	1st author	N=	Techn. success (%)*	Angio plasty/ stent	Assessment of patency	Patency (%)¤			Comment	Reflux (%)¤#
						6 m	12 m	24 m		
1997	Verhaeghe (106)	24	79	9	Cumulative patency of reopened veins (life-table method)		78		3 patients also received thrombectomy	
1997	Bjarnason (110)	77	79	52	Primary patency rate (life-table methods); no intervention needed after a technically successful treatment		63 40	60 37 75	-iliac vein -femoral vein -subgroup without malignant disease (N=50)	
1999	Mewissen (53)	287	83	104	Primary patency rate (life-table methods); time uninterrupted by thrombosis, assessed by duplex US at follow-up		60		54 received concomitant systemic thrombolysis 54 had acute on chronic DVT	
2000	Patel (120)	10	100	10	Stent patency assessed by duplex US		90			0
2001	Abu-Rahma (103)	18	89	10	Cumulative primary patency rate (life-table methods); time uninterrupted by thrombosis assessed by duplex US, defining patency as < 30% residual stenosis	83	69	69	(latest results are from 36 m)	
2002	Elsharawy (55)	18	100	1	Assessment by duplex US and plethysmography, and possibly venography	72			RCT§	11
2004	Laiho (107)	16	NA	3	Compression and duplex US			75	Deep vein obstruction in calf veins reported in 2 patients	44
2004	Ly (111)	28	96	8	1) venous obstruction using air-plethysmography 2) normal findings on air-plethysmography and duplex US			89 64		32
2005	Sillesen (108)	45	93	30	Duplex US			93		4
2006	Lin (121)	46	70	36	Not clearly stated; primary patency rate		64			
2007	Protack (104)	57	63	51	Primary patency rate (life-table methods); freedom from re-thrombosis by duplex US	85	83	83	30 received additional pulse-spray	
2007	Casella (109)	18	78	1	Duplex US		56		Average follow-up ≈ 1 year	50

Table 14 continued

2007	Kölbel (112)	37	100	31	Primary patency without any reintervention confirmed by duplex US and venography		77	(At median 16 m follow-up)	
2008	Chang (105)	20	80	3	Duplex US	100			42
2009	Jørgensen (122)	101	100?	56	Duplex US		94	5 years patency 82% Abstract ISTH Boston Probably includes patients of (108)	0

*Different cut-off values were used

m=months

US=ultrasound

¤ Empty cells indicate data not reported

Assessed using duplex US, except (55) using photoplethysmography

§ All other studies are case series with no control group

5.4 Measurement of quality of life after DVT

Previous to the CaVenT Study there was no available disease-specific questionnaire in Norwegian for assessing QOL in patients with chronic venous disease. The frequently used generic instruments SF-36 and EQ-5D were both available in previously validated Norwegian versions (www.euroqol.org) (123). The EQ-5D was chosen because of its smaller size and its utility in cost-effectiveness analysis (124).

The VEINES-QOL/Sym was modelled after SF-36 with regards to "the content and format of questionnaire items and response scales" (125). It is validated in both English and French versions, and its use has been reported in 3 large cohorts with DVT patients (summarized in table 8). Four other disease-specific questionnaires have been validated and/or employed in DVT studies, however, using the terms "venous thrombosis" and "quality of life" combined with these instruments and/or 1st author in a Medline search did not reveal more documentation regarding experience with these instruments in DVT studies than presented in table 8, though existing evidence suggest high quality of a number of these with regard to how they were developed and tested. Hence, none of these instruments were employed in the CaVenT Study because of sparse documentation compared to the VEINES-QOL/Sym questionnaire. Finally, use of VEINES-QOL/Sym and EQ-5D is supported by recent reporting guidelines on endovascular treatment for DVT of the lower limb (54).

Translation of questionnaires should be carried out following the principle of translation-back translation, as described in suggested guidelines (73). The Norwegian translation mainly adhered to these; we used both informed and uninformed translators, including one with English as first-language, followed by synthesis of the translations. No problematic issues arose during this process or when testing the questionnaire on 11 patients with previous DVT in a pilot study.

Sample size of studies validating patient-reported QOL instruments is variable (table 8), and the required sample size of studies assessing measurement properties is not clearly defined (126). Our validation study did not include a sample size calculation, but the sample size was comparable to other studies on translated instruments, and in line with tentative guidelines (73;126). As discussed below, our results were overall consistent and in line with the results of previous psychometric evaluation of VEINES-QOL/Sym (72), supporting that the sample population was adequate.

In our study we obtained good data quality with low levels of missing data indicating acceptability of the Norwegian version. We did not register how many minutes it took the patients to complete the questionnaire. As in the original work of Kahn et al (72) most item-total correlations were > 0.4, all

were >0.2, and levels of Cronbach's α were >0.8, altogether indicating internal consistency reliability of the questionnaire in our study as well. Likewise, test-retest reliability gave satisfactory intra-class correlation coefficients of >0.8. Construct validity in our study was supported by statistically significant moderate to large levels of correlation of VEINES-QOL/Sym scores with EQ-5D scores, both total and individual items, Villalta score, CEAP classification and presence of co-morbidity of the leg 6 months following DVT. In the original work construct validity was indicated by correlations with SF-36 scores (higher levels for physical than mental health scores), low correlations with age and gender, and an expected gradient of lower scores with increasing severity of PTS as assessed with Villalta score. No test for statistical significance was presented for these correlations, and assessment was based on 1 and 4 months follow-up. Evaluation of responsiveness of the Norwegian version of VEINES-QOL/Sym will be assessed when 2 years data from the CaVenT Study are available.

Some patients of the CaVenT Study were confused when completing the baseline questionnaire during the acute phase as most items focus on the previous 4 weeks, and most patients, including all patients of the CaVenT Study, have had shorter duration of symptoms by the time of diagnosis. However, this did not seem to affect the psychometric properties of the instrument in other reports including baseline scores (72), but needs to be kept in mind when assessing change in patient reported QOL in interventional studies on DVT treatment.

The developers of the VEINES-QOL/Sym instrument have previously pointed out that future work should be undertaken to establish population norms for both scores in DVT patients in different countries, to further evaluate the ability of the VEINES-QOL/Sym to detect change and to test the questionnaire in independent patient samples to confirm its psychometric properties (72). Our work contributes to the latter, but we do not know of other recent reports on these issues.

Additionally, to find out what represents important changes to the patients, and not only statistically significant changes, it would be of benefit to perform studies that look more into the meaning of differences in VEINES-QOL and -Sym scores. The SF-36 scores range from 0-100 and a difference of 3–4(5) points in the score for physical health has been suggested to be (clinically) meaningful to patients, though this issue is not straightforward (74;127). Together with previous results in patients with chronic venous disease, Kahn and colleges inferred that the same difference is meaningful for the VEINES-QOL/Sym scores, and employed this when estimating effect size and calculating sample size for their recent study on determinants of QOL following DVT (74). They showed that mean VEINES-QOL/Sym scores increased from baseline with 5.9 and 4.7 points, respectively, in patients with PTS after 2 years compared to 3.6 and 2.0 in patients without PTS. The scores also increased

among categories of severity of PTS. These differences were interpreted to be clinically meaningful. However; to infer that a meaningful difference in SF-36 scores directly applies to the VEINES-QOL/Sym scores may not be correct. As it has been shown that minimal important difference may vary even between sub scales of one instrument (*Kvam AK et al, unpublished results*), meaningful difference is likely to differ between two instruments, and even between the two VEINES-QOL and –Sym scores. In summary, the meaningful interpretation of the two VEINES scores is not clearly established and needs further investigation.

5.5 Detection of DVT with MRI

In clinical practice ultrasound is the method of choice for DVT detection of the lower limb (17). Ultrasound has the advantage of no side-effects, radiation or contrast agent, low costs, and high availability. The method has limitations as it is highly investigator dependent and with relatively low ability to visualize deeper structures compared to the other diagnostic imaging modalities, i.e., venography, CT, and MRI. As some cases are inconclusive, alternative methods of imaging is required. Conventional and CT venography expose the patient to radiation and potentially nephrotoxic contrast agent. Besides the very rare complication nephrogenic systemic fibrosis, which has been reported following injection of MRI contrast agent in patients with severe kidney failure, MRI is without side-effects, and has been shown to perform well in patients with inconclusive results on ultrasound (26). It is therefore reasonable to choose MRI if ultrasound is inconclusive in patients with known or suspected kidney failure.

Our MRI study was performed as a pilot study on healthy volunteers and a small number of patients with verified proximal DVT on ultrasound. We found that image quality and visualisation of the deep veins of the lower limb were mainly adequate and comparable when comparing a novel balanced sequence with contrast enhanced MRI. When applying the same methods on patients with an ultrasound verified proximal DVT we found that calf level imaging was problematic with unreliable inter-observer rating and low sensitivity and specificity. The low inter-observer agreement was achieved in spite of instructions on reading with both observers. More extensive instruction may improve this.

Use of so called blood pool contrast agent has not previously been reported in DVT detection, but is likely to produce comparable or better results than traditional MRI contrast due to its longer intravascular phase. Use of blood pool MRI contrast for DVT detection cannot be supported based on the present study, as the non-enhanced balanced sequence showed comparable inter-observer agreement and diagnostic properties. Our results indicated good diagnostic properties of both MRI methods in proximal DVT, but due to the study's methodological limitations the strength of results is weak. In summary, the MRI study and results are comparable to other studies on MRI in DVT detection (table 3).

6. Conclusions and future perspectives

From the work of this thesis it may be concluded that:

- The CaVenT study is properly designed to demonstrate efficacy of additional CDT in the treatment of iliofemoral DVT.
- A Norwegian version of VEINES-QOL/Sym was a valid and reliable questionnaire for assessment of QOL in patients with previous DVT.
- Additional CDT is effective in regaining patency after 6 months.
- MRI with a novel balanced technique is comparable to contrast enhanced MRI in visualization of the deep veins of the lower extremities.
- Both MR techniques performed well in proximal, but not in distal DVT.

6.1 Future studies on diagnostic imaging of DVT

To confirm the indicative results of our work on balanced and contrast-enhanced MRI in DVT detection, a study adhering to the STARD initiative (www.stard-statement.org) for complete and transparent assessment of clinical, diagnostic accuracy in line with level 2 diagnostic efficacy (see table 4) should be performed. Such a study may also involve D-dimer levels and assessment of clinical probability. It may be of even greater importance to perform outcome studies that evaluate the routine diagnostic methods of ultrasound and CT in VTE diagnostic combined with D-dimer and clinical probability. Finally, further research on MRI for visualisation and characterisation of the thrombus itself may lead to novel insight into e.g. thrombus age and lysability, as so far preliminary reported for the MRDTI technique (25). At the present, we are not planning further MRI evaluations.

6.2 Ongoing and future studies on DVT treatment

Fortunately, at the moment there are a number of ongoing studies that will produce results with major and novel contributions to the knowledge on DVT treatment:

- **The CaVenT Study** (NCT00251771, www.clinicaltrials.gov)

  The completion of the CaVenT Study will give clinically relevant results on efficacy and safety for CDT in iliofemoral DVT. The CaVenT Study will also provide patient-based data for a full economic evaluation (cost-effectiveness study) (128) of CDT, and this has previously not been reported as studies assessing economic burden of VTE and its complications have

employed retrospective observational cohort design and literature-based models only (12;67;129).

- **The ATTRACT Study** (NCT00790335, www.clinicaltrials.gov)

  The upcoming and very similar, but larger American ATTRACT Study will start recruitment in 2009. As with CaVenT, ATTRACT will produce long-term clinically relevant results on PTS development, QOL and cost-effectiveness.

  Both studies may be able to identify predictive factors for the development of PTS, but this is not among their primary aims. Likewise, results on use of adjunctive endovascular procedures like angioplasty, stent, thrombectomy, and cava filters along with different methods of administrating alteplase, e.g., continuous infusion, pulse spray technique, will be available as secondary end-points.

- **The SOX Trial** (NCT00143598, www.clinicaltrials.gov)

  Novel and valuable insight into PTS development will be provided by the ongoing and first ever double blinded placebo controlled study on ECS in proximal DVT; the SOX Trial.

All these studies are depending on high quality implementation and long-term follow-up! When they are completed, analyzed and reported, and if the results indicate need to change current guidelines, they should be followed by studies investigating uptake and implementation of thrombolytic and compression therapy in clinical practice, including evaluation of different implementation approaches. This will in the end secure an improved and evidence-based practice for DVT patients.

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Appendices

a. VEINES QOL/-Sym

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	☐ 4	Moderat
☐ 2	Svært lite	☐ 5	Mye
☐ 3	Lite	☐ 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

b. EQ-5D

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. ☐

c. Collaborators

The following study site investigators and physicians (in alphabetical order) gave essential contributions to the implementation of the CaVenT Study: Jørund Asvall, Gry Kloumann Bekken, Yngve Benestad, Lars Christian Haugli Bråten, Øyvind Bukten, Dag Olav Dahle, Jacob Dalgaard, Seth Donkor, Ola Hagen, Torbjørn Holm, Anne Gro Holtan, Tor Olav Isaksen, Marianne Kalbakken, Lydia Klevstul, Heidi Lona, Erwin Müller, Marius Myrstad, Dag Nilssen, Emil Nyquist, Hege Pihlstrøm, Hilde Risstad, Jürgen Rolke, Nina Hågenrud Schultz, Kari Mørkve Soldal, Cecilie Soma, Vigdis Stenberg, Hoa Tran, Arnljot Tveit, Sara Ulimoen, Per Vandvik, Peter Ysteng, and Willy Åsebø. So did study nurse Siv Foyn. Secretary Marianne Nyberg was essential in organizing follow-up. Radiographer Kent Pettersson contributed to the MRI examinations.

8. Papers I-IV

I

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II

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III

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IV

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