Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial

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Summary

Background **Conventional anticoagulant treatment for acute deep vein thrombosis (DVT) effectively prevents thrombus extension and recurrence, but does not dissolve the clot, and many patients develop post-thrombotic syndrome (PTS). We aimed to examine whether additional treatment with catheter-directed thrombolysis (CDT) using alteplase reduced development of PTS.**

Methods **Participants in this open-label, randomised controlled trial were recruited from 20 hospitals in the Norwegian southeastern health region. Patients aged 18–75 years with a first-time iliofemoral DVT were included within 21 days from symptom onset. Patients were randomly assigned (1:1) by picking lowest number of sealed envelopes to conventional treatment alone or additional CDT. Randomisation was stratified for involvement of the pelvic veins with blocks of six. We assessed two co-primary outcomes: frequency of PTS as assessed by Villalta score at 24 months, and iliofemoral patency after 6 months. Analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00251771.**

Findings **209 patients were randomly assigned to treatment groups (108 control, 101 CDT). At completion of 24 months' follow-up, data for clinical status were available for 189 patients (90%; 99 control, 90 CDT). At 24 months, 37 (41·1%, 95% CI 31·5–51·4) patients allocated additional CDT presented with PTS compared with 55 (55·6%, 95% CI 45·7–65·0) in the control group (p=0·047). The difference in PTS corresponds to an absolute risk reduction of 14·4% (95% CI 0·2–27·9), and the number needed to treat was 7 (95% CI 4–502). Iliofemoral patency after 6 months was reported in 58 patients (65·9%, 95% CI 55·5–75·0) on CDT versus 45 (47·4%, 37·6–57·3) on control (p=0·012). 20 bleeding complications related to CDT included three major and five clinically relevant bleeds.**

Interpretation **Additional CDT should be considered in patients with a high proximal DVT and low risk of bleeding.**

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Introduction

Acute deep vein thrombosis (DVT) of the lower limbs occurs in about 1·0 person per 1000 population per year and is associated with substantial morbidity.[1] International guidelines for antithrombotic therapy form the basis of adequate treatment.[2] Although anticoagulation effectively prevents thrombus extension, pulmonary embolism, death, and recurrence, many patients develop venous dysfunction resulting in post-thrombotic syndrome (PTS). This syndrome is characterised by pain, swelling, a sensation of heaviness, oedema, pigmentation, and deterioration of the skin, including venous ulcers in severe cases.[3] PTS is associated with reduced individual health-related quality of life and a substantially increased economic burden.[4–6]

About 80% of symptomatic DVT of the lower limbs affects the popliteal and more proximal veins.[7] After adequate anticoagulation, nearly half of these patients develop some degree of PTS.[8] Daily use of elastic compression stockings (class II, 30 mm Hg) reduces the risk of PTS by about 50%.[8,9] However, even with recommended treatment, around one in four patients is at risk of a chronically impaired long-term outcome, and improved treatment to reduce PTS development is greatly needed.

PTS probably evolves from venous obstruction, venous incompetence caused by inflammatory destruction of the venous valves in response to the acute thrombotic occlusion, or both.[3] A recent systematic review[10] suggested that accelerated removal of thrombus material by systemic thrombolysis can prevent vein dysfunction and PTS, but such treatment was associated with an unacceptable risk of bleeding. Catheter-directed thrombolysis (CDT) is a novel modality in which a catheter is introduced into the affected vein and advanced through the thrombotic segment. Multiple side-holes enable delivery of a thrombolytic agent directly into the clots, and reduced doses of thrombolytic agents are used. Several case series have shown effective lysis and

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promising results; however, the net clinical effect and safety have not been documented in clinical trials. The Catheter-directed Venous Thrombolysis (CaVenT) study aimed to evaluate whether additional CDT for acute iliofemoral vein thrombosis improved long-term outcomes by reducing the risk of PTS.

Methods

Study design and participants

The CaVenT Study was a Norwegian, multicentre, open-label, randomised controlled trial of the efficacy and safety of additional CDT with alteplase in patients with a first-time acute iliofemoral DVT. Patients aged 18–75 years with an objectively verified DVT above mid-thigh level and symptom duration up to 21 days were eligible for inclusion. Patients were ineligible if an increased risk of bleeding or other exclusion criteria were present (panel 1). The study was approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Medicines Agency. Written informed consent was obtained from all patients. The trial complied with the Declaration of Helsinki and Good Clinical Practice including monitoring of data. The trial protocol was accepted by *The Lancet*.

Randomisation and masking

Patients were randomly assigned to treatment groups at one of the 20 participating hospitals to conventional treatment with initial low molecular weight heparin (LMWH) and warfarin followed by warfarin alone with target intensity international normalised ratio (INR) of 2·0–3·0, or to CDT in addition to conventional treatment. A random block allocation sequence for each trial site with stratification for involvement of the pelvic veins and block size of six was generated with the website Randomization.com. Local trial investigators were unaware of the block size and undertook enrolment and treatment assignment by picking the lowest number of sealed, opaque, numbered envelopes.

Panel 1: Inclusion and exclusion criteria

Inclusion criteria

- Age 18–75 years
- Onset of symptoms within the past 21 days
- Objectively verified (by diagnostic imaging) deep vein thrombosis localised in the upper half of the thigh, the common iliac vein, or the combined iliofemoral segment
- Informed consent

Exclusion criteria

- Anticoagulant treatment before trial entry for more than the past 7 days
- Contraindications to thrombolytic treatment, including bleeding diathesis
- Indications for thrombolytic treatment—eg, phlegmasia caerulea dolens or isolated vena cava thrombosis
- Severe anaemia (haemoglobin <80 g/L)
- Thrombocytopenia (platelets <80·10⁹/L)
- Severe renal failure (estimated creatinine clearance <30 mL/min)
- Severe hypertension—ie, persistent systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 100 mm Hg
- Pregnancy or thrombosis within 7 days postpartum
- Less than 14 days postsurgery or post-trauma
- History of subarachnoid or intracerebral bleeding
- Disease with life expectancy less than 24 months
- Drug misuse or mental disease that could interfere with treatment and follow-up
- Former ipsilateral proximal deep vein thrombosis
- Malignant disease needing chemotherapy
- Any thrombolytic treatment within 7 days before trial inclusion

Procedures

DVT of the lower limb was verified by routine ultrasound, or by venography or CT if ultrasound was inconclusive. In all patients, anticoagulation was started with subcutaneous LMWH, either with dalteparin (Fragmin, Pfizer, New York, NY, USA) or enoxaparin (Klexane, Sanofi, Paris, France), for at least 5 days according to the guidelines.[2] Patients allocated CDT did not receive warfarin initially and were transferred to one of the four participating interventional centres at Aker, Rikshospitalet, or Ullevål University Hospitals in Oslo, or the Østfold Hospital Trust in Fredrikstad. LMWH was discontinued for at least 8 h before CDT, and was reintroduced in combination with warfarin (with target INR 2·0–3·0) 1 h after completion of the procedure. All patients in both groups were advised to use knee-high elastic compression stockings (class II) daily for 24 months.

Details of the CDT procedure have been reported elsewhere.[11] A venography done at the start of the procedure established the topography of the thrombus. After local anaesthesia, an infusion catheter with multiple side-holes (Uni*Fuse Infusion Catheter, Angiodynamics, Latham, NY, USA), or a similar catheter, covering the thrombosed segments was introduced under ultrasonographic guidance, preferentially into the popliteal vein. 20 mg alteplase (Actilyse, Boehringer-Ingelheim, Ingelheim am Rhein, Germany) diluted in 500 mL 0·9% NaCl was given at 0·01 mg/kg per h for maximum 96 h, and the maximum dose was 20 mg/24 h. Unfractionated heparin was given simultaneously as a continuous intravenous infusion and the dose was adjusted to keep activated partial thromboplastin time (Cephotest, Axis-Shield, Oslo, Norway) at 1·2–1·7 times higher than the upper normal limit. Additional antiplatelet treatment was not given.

Clot burden at start of CDT and during thrombolysis was assessed daily by venography and graded with a scoring system.[12] Use of adjunctive angioplasty and stents to establish flow and obtain less than 50% residual stenosis were left to the discretion of the operator. On the basis of clinical observation and laboratory monitoring, all adverse events during hospital stay or shortly after discharge were recorded. Major bleeding was defined as previously reported.[13]

There were two co-primary effect variables: iliofemoral patency after 6 months and frequency of PTS after

24 months. Short-term patency results have previously been published in the first 100 patients.[14] Secondary effect variables included frequency of clinically relevant bleeding related to CDT, recurrent venous thromboembolism (VTE) during follow-up, PTS at 6 months, and whether PTS at 24 months was related to immediate thrombolysis in the CDT group. Recurrent VTE was registered if objectively verified with routine imaging at local trial site. Frequency of PTS in patients with iliofemoral patency after 6 months was a post-hoc secondary endpoint.

Clinical visits at 6 months (within 2 weeks) and 24 months (within 4 weeks) were done by a surgeon and vascular physiologist (C-ES) with no knowledge of the patients' medical history or treatment allocation. The patients were explicitly told not to reveal treatment allocation. PTS was diagnosed with the Villalta scale and patients were classified with PTS if the score was 5 or more, or if a venous ulcer was present (panel 2).[15,16] All patients were screened for thrombophilia before or after anticoagulation treatment.

Statistical analysis

On the basis of existing documentation, we assumed that the prevalence of PTS after 2 years would be at least 25% in patients allocated conventional treatment as compared with less than 10% in those allocated additional CDT.[11] At a significance level of 5% and a statistical power of 80% or greater, 200 patients had to be included in the study. Statistical analyses were by intention to treat[17] after exclusion of ineligible patients who had been included by mistake. On the basis of previous reports stating that PTS should be diagnosed no earlier than 24 months (chronic phase), Villalta score from the 6-month clinical visit (subacute phase) was not carried forward for any missing 24-month outcome data.[18] Missing outcome data because of withdrawal of consent or death from cancer or other causes not related to CDT or anticoagulation were assumed to be missing independently of treatment received and were not included in the analyses. When comparing dichotomous variables in the two treatment groups, we used a two-sided uncorrected χ^2 test. When comparing continuous variables, we used a two-sided *t* test, provided that the distributions were sufficiently close to the normal distribution. Otherwise, a two-sided Mann-Whitney test was used. SPSS (version 19) was used for all analyses. Findings with p values less than 0·05 were deemed statistically significant. Complications were presented as percentages.

This trial is registered at ClinicalTrials.gov, NCT00251771, and the EudraCT number is 2005-004486-42.

Role of the funding sources

The trial was an investigator-initiated trial and a major collaborative effort among the hospitals of the Norwegian southeastern health region. The funding bodies had no role in data collection, analysis, or interpretation of the data, the writing of the report, or the decision to submit for publication. NEK, PMS, TE, and YH had complete access to the data and had full responsibility for the decision to submit the report.

Results

During January, 2006, to December, 2009, 209 patients were recruited from 20 centres within eight hospital

***Panel 2*: Villalta scale for assessment of post-thrombotic syndrome (PTS)[15,16]**

Five patient-rated venous symptoms

- Pain
- Cramps
- Heaviness
- Paraesthesia
- Pruritus

Six clinician-rated signs

- Pretibial oedema
- Skin induration
- Hyperpigmentation
- Pain during calf compression
- Venous ectasia
- Redness

Scoring

Each sign or symptom is rated as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), and summed to produce a total score. A total score of less than 5 indicates no PTS, of 5–14 indicates mild or moderate PTS, and of 15 or more (or presence of venous ulcer) indicates severe PTS.

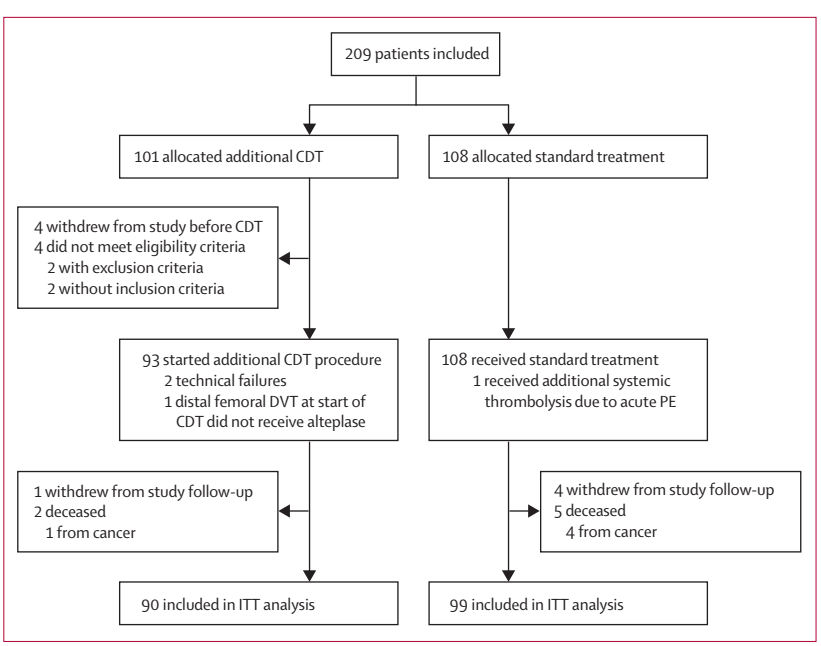

***Figure*: Trial profile**

CDT=catheter-directed thrombolysis. DVT=deep vein thrombosis. PE=pulmonary embolism. ITT=intention-to-treat.

trusts of the South-Eastern Norway Regional Health Authority (figure). During the trial, screening logs were recorded for 613 patients admitted with VTE at two of the main study sites, which contributed 61 (29%) of all 209 trial patients (Fredrikstad and Ullevål). The main reasons for exclusion were DVT below mid-thigh (n=209) or in other locations (n=77), age older than 75 years (n=78) or younger than 18 years (n=2), advanced cancer (n=45), previous ipsilateral proximal DVT (n=25), substance misuse (n=22), symptom duration greater than 21 days (n=21), unwillingness to participate (n=15), anticoagulation for longer than 7 days (n=7), bleeding tendency (n=4), and other causes including pregnancy, psychiatric problems, Down's syndrome, or other serious illnesses (n=53). Table 1 shows the demographic and clinical characteristics of the 189 patients included in the present analysis. Mean age was 51·5 years (SD 15·8) and 70 (37%) participants were female. Mean duration of symptoms was 6·6 days (SD 4·6). Most baseline demographic and clinical characteristics were fairly equally distributed between the groups.

	Additional catheter-directed thrombolysis (n=90)	Standard treatment only (n=99)
Baseline		
Age (years)	53·3 (15·7)	50·0 (15·8)
Women	32 (36%)	38 (38%)
Duration of symptoms (days)	6·4 (4·4)	6·8 (4·8)
Isolated pelvic deep vein thrombosis*	3 (3%)	2 (2%)
Iliofemoral deep vein thrombosis*	38 (42%)	34 (34%)
Femoral deep vein thrombosis*	45 (50%)	58 (59%)
Left-sided deep vein thrombosis	54 (60%)	61 (62%)
No risk factor for venous thrombosis	31 (34%)	26 (26%)
Transient risk factors for venous thrombosis†		
Surgery, previous 3 months	15 (17%)	13 (13%)
Trauma, previous 3 months	10 (11%)	15 (15%)
Short-term immobility	20 (22%)	19 (19%)
Infection, previous 6 weeks	6 (7%)	9 (9%)
Pregnancy, previous 3 months†	5 (6%)	3 (3%)
Hormone replacement therapy	4 (4%)	6 (6%)
Oral contraceptive pill	3 (3%)	11 (11%)
Permanent risk factors for venous thrombosis		
Previous venous thrombosis†	9 (10%)	9 (9%)
Cancer†	3 (3%)	1 (1%)
Obesity	9 (10%)	11 (11%)
Inflammatory bowel disease	0	3 (3%)
First-degree relative with venous thrombosis	9 (10%)	13 (13%)
Two risk factors for venous thrombosis	26 (29%)	18 (18%)
Three risk factors for venous thrombosis	10 (11%)	14 (14%)
Thrombophilia		
Heterozygous F5 rs6025 polymorphism	23 (26%)	22 (22%)
Homozygous F5 rs6025 polymorphism	1 (1%)	4 (4%)
F2 rs1799963 polymorphism	6 (7%)	0
Protein C deficiency	0	1 (1%)
Protein S deficiency	5 (6%)	4 (4%)
Lupus anticoagulant	0	4 (4%)
Combined thrombophilia	4 (4%)‡	4 (4%)§
At 24 months		
Daily wear of compression stockings, class II	57 (63%)	51 (52%)
Recurrent venous thromboembolism	10 (11%)	18 (18%)
Cancer diagnosis	4 (4%)	7 (7%)

Data are mean (SD) or n (%). *Based on routine diagnostic imaging before recruitment (missing n=9). †Any condition related to increased risk of bleeding, previous ipsilateral proximal deep vein thrombosis, advanced cancer, and being pregnant are exclusion criteria. ‡One double heterozygous for the F5 rs6025 (factor V Leiden) and F2 rs1799963 (prothrombin gene 20210G→A) polymorphisms, one combined homozygous F5 rs6025 and heterozygous F2 rs1799963, one combined homozygous F2 rs1799963 and protein S deficiency, and one combined heterozygous F5 rs6025 and lupus anticoagulant. §One combined heterozygous F5 rs6025 and protein C deficiency, one combined heterozygous F5 rs6025 and protein S deficiency, two combined heterozygous F2 rs1799963 and protein S deficiency.

Table 1: **Demographic and clinical characteristics**

Compliance with trial treatment was assessed. One patient in the control group received additional systemic thrombolysis on the day after recruitment because of concomitant severe pulmonary embolism. One patient allocated CDT did not receive thrombolysis at the operator's discretion because venography at initiation of the procedure showed acute DVT only in the distal femoral vein. Two patients received CDT for 6 days at the operators' discretion; both resulted in complete lysis without complications. At 6 months' follow-up, the proportion of patients still on oral anticoagulation with INR within the therapeutic range (2·0–3·0) was 61·1% (95% CI 50·0–71·5) in the CDT group and 52·6% (95% CI 41·6–63·5) in the control group (n=148). Correspondingly, at 24 months (n=52), 65·4% (95% CI 46·2–80·6) in the CDT group were within therapeutic range versus 50·0% (95% CI 32·1–67·9) of those on control. At 6 months' follow-up, 70 of 89 patients (78·7%, 95% CI 69·1–85·9) in the CDT group reported daily use of elastic compression stockings compared with 68 of 99 patients (68·7%, 95% CI 59·0–77·0) in the control group; at 24 months, these proportions were 57 of 90 patients (63·3%, 95% CI 53·3–72·6) versus 51 of 99 patients (51·5%, 95% CI 41·2–61·2).

Mean duration of CDT was 2·4 days (SD 1·1). 43 patients had complete thrombolysis with CDT, and 37 had successful partial (50–99%) lysis. Ten patients had unsuccessful (<50%) lysis including two technical failures and two ended early because of bleeding complications. Adjunctive endovascular treatment was given in 39 patients; 23 received balloon angioplasty, 15 received venous stents, and thrombus aspiration (AngioJet, MEDRAD, Warrendale, PA, USA) combined with vena cava filter was used in one patient with thrombus up to the renal veins judged as potentially life-threatening.

Table 2 shows the long-term and short-term primary outcomes. The absolute risk reduction of the long-term endpoint PTS at 24 months' follow-up in the patients allocated CDT compared with the control group was 14·4% (95% CI 0·2–27·9), and the number needed to treat was 7 (95% CI 4–502). Severe PTS was detected in one patient on control treatment, and none of the patients presented with venous ulcers. The absolute gain in the short-term endpoint iliofemoral patency after 6 months

(n=183) was 18·5% (95% CI 4·2–31·8) in the CDT group compared with control.

At 6 months' follow-up there was no difference in PTS as assessed with the Villalta scale between the two treatment groups (table 2). In patients with iliofemoral patency at 6 months (both treatment groups), the frequency of PTS after 24 months was 38 of 103 patients (36·9%, 95% CI 28·2–46·5) compared with 49 of 80 patients with insufficient recanalisation (61·3%, 95% CI 50·3–71·2), corresponding to an absolute risk reduction of 24·4% (95% CI 9·8–37·6; p=0·001). In the CDT group, the frequency of PTS did not differ between unsuccessful, partial, or complete lysis, and the distribution of percent lysis was the same in patients with and without PTS (data not shown). A per-protocol analysis, excluding three patients in the CDT group who did not receive alteplase and one patient allocated control who received systemic alteplase, resulted in an absolute risk reduction of 17·0% (95% CI 2·6–30·5, p=0·021), with a number needed to treat of 6.

20 bleeding complications related to CDT were reported; three were classified as major and five as clinically relevant. The major bleeding events included one abdominal wall haematoma necessitating blood transfusion, one compartment syndrome of the calf needing surgery, and one inguinal puncture site haematoma. There were no deaths, pulmonary embolisms, or cerebral haemorrhages related to CDT. Four patients had non-bleeding complications related to CDT including two patients with transient peripheral neurological deficits of the treated limb, one patient with local infection at the puncture site, and one patient who had recently undergone abdominal surgery complicated with ileus, intestinal resection, and septicaemia, who developed possible vertebral osteomyelitis shortly after discharge. There were no bleeding complications in patients allocated control during the same period. During follow-up, 28 patients had recurrent VTE and 11 were diagnosed with cancer; there was no difference between the groups (p>0·05; table 1).

	Additional catheter-directed thrombolysis (n=90)		Standard treatment only (n=99)		p value*
	n	% (95% CI)	n	% (95% CI)	
Post-thrombotic syndrome at 24 months†	37	41·1% (31·5–51·4)	55	55·6% (45·7–65·0)	0·047
Iliofemoral patency at 6 months†‡	58	65·9% (55·5–75·0)	45	47·4% (37·6–57·3)	0·012
Post-thrombotic syndrome at 6 months§	27	30·3% (21·8–40·5)	32	32·2% (23·9–42·1)	0·77

Post-thrombotic syndrome defined as Villalta score of 5 points or higher. *χ^2 test. †Co-primary outcomes. ‡Five patients had inconclusive patency assessments and one was lost to follow-up at 6 months. §Secondary outcome.

Table 2: **Short-term and long-term outcomes**

Discussion

This randomised trial was the first to show a clinically significant reduction in PTS after additional CDT compared with conventional treatment alone. The absolute risk reduction was 14·4% and treatment of seven patients was needed to prevent one PTS, but CDT entailed a small additional risk of bleeding. We believe that this effect is clinically relevant and is a significant improvement in the prevention of PTS after severe DVT (panel 3).

The frequency of PTS in our study was slightly higher than in some reports, and this finding might relate to several aspects.[8,9,19] Unlike studies that enrolled patients with any proximal DVT, patients in this trial all had a high proximal DVT. More proximal thrombus extension is associated with worse Villalta score over time and higher risk of developing PTS.[20,21] However, since PTS can occur after popliteal and distal femoral DVT, all proximal DVT might benefit from additional CDT, but this notion needs further investigation.[8,9] The duration of the thrombotic occlusion is likely to play a part in valve destruction and the recanalisation process, and thereby in the development of PTS. Although up to 21 days of symptoms was allowed before treatment in this trial, the mean symptom duration of 6·6 days (SD 4·6) was well within the 14 days used in other studies. Patients in both groups reported decreasing use of compression treatment during follow-up. This factor might have contributed to development of PTS.[8,9] Finally, several previous studies used non-standardised clinical scales for the assessment of PTS, thus making comparisons less feasible.[9,22,23]

More standardised measures are likely in future studies because the Villalta scale has recently been further validated and generally recommended.[16,24,25] These recommendations were published after the implementation of our study, and the standardised approach for assessment was not included in the original validation of the scale. The CaVenT study mainly adhered to these recent recommendations. However, the endpoint evaluator was not masked to in which leg the DVT had occurred, the clinical visits took place during normal work hours and not only in the afternoon, and the patients wore elastic compression stockings when attending the clinical visit. The timing of the visits and the use of stockings might have reduced swelling and vein dilatation.[16] Finally, although the Villalta scale is apparently becoming a reference standard for assessment of PTS, areas identified within the scale's reliability and responsiveness need further research.[25] Despite the fairly high frequency of PTS overall, severe PTS occurred in only one patient. Hence, the effect of CDT on severe PTS remains unclear.

We undertook a per-protocol analysis excluding patients in the CDT group who did not receive alteplase and a patient allocated control who received systemic alteplase. The absolute risk reduction was 17·0%, with a number needed to treat of 6. This analysis excluded two patients with technical failures and is probably a less representative sample than that in the intention-to-treat analysis, since some anatomical and pathophysiological variations will

Panel 3: **Research in context**

Systematic review

A Cochrane review published in 2004 concluded that "Thrombolysis appears to offer advantages in terms of reducing post-thrombotic syndrome and maintaining venous patency after deep vein thrombosis".[10] The systematic search was repeated in November, 2007, but no other studies were added, and the meta-analysis and conclusion remained unchanged. Among the 12 studies included, two reported long-term outcomes—ie, post-thrombotic syndrome. Both trials used systemic thrombolysis and there was no validated assessment of outcome.[22,23] One study using catheter-directed thrombolysis did not include evaluation of clinically relevant outcomes.[28] We did a Medline search of publications up to October, 2011, with no language restrictions, using the search terms "venous thrombosis", "thrombolytic therapy", and "randomised controlled trial". Trials examining thrombolysis versus anticoagulation for acute deep vein thrombosis with assessment of long-term clinically relevant outcomes—ie, the post-thrombotic syndrome after 24 months—were considered. No recent trials fulfilling these criteria were found.

Interpretation

This randomised controlled trial was the first to evaluate the clinically relevant efficacy of additional catheter-directed thrombolysis in patients with iliofemoral deep vein thrombosis. Additional thrombolytic treatment reduced post-thrombotic syndrome compared with anticoagulation alone, but was associated with a small additional risk of bleeding. By contrast with systemic thrombolytic treatment, this bleeding risk seems acceptable, and the effect size was in line with results for systemic treatment. Our findings support recent guidelines and catheter-directed thrombolysis should be considered in patients with high proximal deep vein thrombosis and low risk of bleeding.[2] The completion of an ongoing trial (NCT00790335) will give further evidence.

not be feasible for CDT; in our case, one patient with agenesis of the inferior caval vein.

The inherent possibilities of bias from an open-label design cannot be excluded. The patients' expectations might have affected their compliance and reporting of symptoms. Since some of the items of the Villalta scale are patient-reported symptoms, reporting bias cannot be ruled out. Although apparently slightly better in the CDT group than in the control group, compliance for use of neither anticoagulation nor elastic compression stockings differed significantly between the treatment groups. In our view, a masked study is not an option because placebo-control of this invasive procedure would be unethical and highly resource-demanding. Two other aspects distinguishing the CDT group from control and possibly leading to a selection bias were identified during implementation of the study. First, routine questioning after randomisation in the angiography laboratory revealed four patients who were not eligible for study participation, suggesting suboptimum quality of study enrolment that was not likely to be detected in the control group. Second, four patients withdrew consent while waiting for initiation of thrombolysis, suggesting reluctance towards invasive treatment and extended hospital stay and emphasising the importance of valid and sufficient patient information. Finally, risk of selection bias could have been further reduced by randomisation of block size rather than a constant length of six.

Patency, often assessed within the first 6 months of follow-up, has been used as a surrogate outcome in studies of venous thrombolysis despite no clear-cut definition or convincing documentation as a predictor of long-term outcome.[10] We have previously reported an effect of CDT on patency using a rigorous definition of iliofemoral venous patency.[14] The present findings with PTS less frequently encountered in patients who had regained iliofemoral patency after 6 months compared with patients with insufficient recanalisation support a relation between this surrogate outcome and a clinical endpoint. However, venous patency after 6 months cannot replace a clinically relevant outcome measure and trials should aim for long-term clinical follow-up.[11,24] This was also demonstrated by the Villalta scores at 6 months, in which roughly 30% of patients in both treatment groups scored 5 or more, suggesting persistent subacute post-thrombotic symptoms preceding a stable clinical phase when PTS can finally be assessed.[18]

When bleeding events without clinical relevance were excluded, our bleeding complication rate of 9% was similar to previous reports.[10,12,26] Most of the relevant bleeding events were related to the puncture site and are likely to have been caused by multiple punctures during establishment of popliteal vein access. This finding emphasises the importance of securing one venous puncture only. No bleeding complications led to a permanently impaired outcome, supporting the previous suggestion that complication rates are acceptable and less frequent with newer CDT approaches compared with early reports.[2,10] Our results give further support to this suggestion, but the bleeding risk should still be kept in mind during selection of patients for CDT.

A Cochrane review including 12 studies of variable quality and only one of CDT has concluded that venous thrombolysis "appears to offer advantages".[10] For two more recent randomised trials only 6 months' follow-up has been reported, and these results have so far contributed the only existing evidence from randomised trials for the efficacy of CDT (panel 3).[14,27,28] Among the 11 studies of systemic thrombolysis only two reported long-term PTS, and this outcome was assessed with two different non-validated clinical scales. The combined total population was only 101 patients. PTS occurred in 29 of 61 patients in the thrombolysis group versus 26 of 40 patients in the control group, which is in line with our results. Additionally, several case series of variable sizes suggest that additional CDT is feasible, safe, and efficient for clot removal.[12,28–30] However, to compare the efficacy of CDT across these studies, most of which have no control group, is problematic. Follow-up has been variable and outcomes including patency and PTS have been assessed with various methods and definitions. Case series suggesting very efficient CDT are likely to represent highly selected patient populations—eg, low age and exclusion of patients with occluded popliteal vein.[30] However, technical differences including administration

and dosing of the thrombolytic agent might also contribute to differences across studies.

We regard our study population to be representative and the CDT procedure to be applicable in a clinical setting for three reasons: (1) patients were recruited in a routine clinical setting; (2) trial sites consisted of local, regional, and university hospitals; and (3) almost all the exclusion criteria were related to potentially increased complication risks. Finally, on the basis of screening logs from two main trial sites, 10% of patients presenting with acute VTE were recruited with few eligible patients declining to participate.

With respect to technical procedural aspects, more aggressive endovascular treatment, including adjunctive pharmacomechanical techniques and higher doses of thrombolytic agent and heparin, is likely to accelerate and increase lysis and to reduce treatment time. These changes could lead to additional improvements in patency and long-term clinical outcome, but might also carry increased risks. Results of the ongoing ATTRACT study (NCT00790335) will add to evidence by assessing three pharmacomechanical approaches, including increased alteplase doses. However, reduced treatment time with CDT techniques similar to ours has been reported.[31] To restore continuous venous flow, the use of a stent or stents in iliac vein and balloon angioplasty in the femoropopliteal vein segment has been suggested.[32] This proposal is based on scarce documentation, and adjunctive endovascular treatment (and stents in particular) was not aggressively used in our study and might have modified the outcome in the CDT group.[33,34]

Because extensive DVT is associated with increased risk of PTS development, comparison of patients with and without pelvic vein involvement would have been interesting. However, venography done during the CDT procedure revealed pelvic DVT in some patients in whom routine ultrasound imaging at baseline had shown only femoral DVT, suggesting that the diagnostic quality for thrombus extension was poor (data not shown). Only patients in the CDT group received venography, hence the baseline imaging of patients in the control group could not be reassessed.

The absolute reduction in PTS of 14·4% in our study corresponded with the 15% estimate used in the sample size calculation in our protocol. We eventually reached the target sample size, but because of loss to follow-up and handling of missing data as described, the final study population was closer to the critical limit for detection of a clinical effect, and the effect estimate was imprecise. This issue emphasises the need for additional and more robust evidence in upcoming trials. Another limitation of our study is possible local differences, since four interventional centres did the intervention. Although CDT was established as a treatment option in all the centres before trial initiation, one regional centre with accordingly more procedures might have done better overall.

In conclusion, additional CDT improved the clinically relevant long-term outcome after iliofemoral DVT by reducing PTS compared with conventional treatment with anticoagulation and elastic compression stockings alone. This improvement was at a cost of a small additional risk of bleeding, emphasising the importance of patient selection and securely performed invasive procedures. Our findings are promising and supplement the scarce and weak documentation on prevention of PTS. We believe that our result is an important contribution to the evidence base for treatment of severe DVT and should be taken into account when clinical guidelines are revised.

Contributors

All authors contributed to the design and implementation of the study, the collection of data (except LS), and critical review of the report. TE was trial manager, analysed the data, wrote the first draft, and coordinated the writing of the report. YH analysed the data, co-managed the trial, and co-wrote the initial drafts. N-EK and PMS had the original idea and design of the study and obtained the main funding. LS was trial statistician.

Conflicts of interest

We declare that we have no conflicts of interest.

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