

Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA)

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Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial



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Summary

Background Early thrombus removal might prevent post-thrombotic syndrome by preserving venous function and restoring flow. Previous trials comparing additional catheter-directed thrombolysis to standard treatment showed conflicting outcomes. We aimed to assess the benefit of additional ultrasound-accelerated catheter-directed thrombolysis for the prevention of post-thrombotic syndrome compared with standard therapy in patients with iliofemoral deep-vein thrombosis.

Methods We did a multicentre, randomised, single-blind, allocation-concealed, parallel group, superiority trial in 15 hospitals in the Netherlands. Patients aged 18–85 years with a first-time acute iliofemoral deep-vein thrombosis and symptoms for no more than 14 days were randomly assigned (1:1) to either standard treatment with additional ultrasound-accelerated catheter-directed thrombolysis or standard treatment alone. Randomisation was done with a web-based automatic programme and a random varying block size (2–12), stratified by age and centre. Standard treatment included anticoagulant therapy, compression therapy (knee-high elastic compression stockings; 30–40 mmHg), and early ambulation. Additional ultrasound-accelerated catheter-directed thrombolysis was done with urokinase with a starting bolus of 250 000 international units (IU) in 10 mL NaCl followed by a continuous dose of 100 000 IU/h for a maximum of 96 h through the Ekos Endowave-system. Adjunctive percutaneous transluminal angioplasty, thrombosuction, or stenting was performed at the discretion of the physician who performed the intervention. The primary outcome was the proportion of patients with post-thrombotic syndrome at 12 months diagnosed according to the original Villalta criteria—a Villalta-score of at least 5 on two consecutive occasions at least 3 months apart or the occurrence of venous ulceration—and was assessed in a modified intention-to-treat population of all randomly assigned patients who passed screening and started treatment. The safety analysis was assessed in the same modified intention-to-treat population. This study is complete and is registered at ClinicalTrials.gov, NCT00970619.

Findings Between May 28, 2010, and Sept 18, 2017, 184 patients were randomly assigned to either additional ultrasound-accelerated catheter-directed thrombolysis (n=91) or standard treatment alone (n=93). Exclusion because of screening failure or early withdrawal of informed consent resulted in 77 patients in the intervention group and 75 in the standard treatment group starting allocated treatment. Median follow-up was 12·0 months (IQR 6·0–12·0). 12-month post-thrombotic syndrome occurred in 22 (29%) patients allocated to additional treatment versus 26 (35%) patients receiving standard treatment alone (odds ratio 0·75 [95% CI 0·38 to 1·50]; p=0·42). Major bleeding occurred in four (5%) patients in the intervention group, with associated neuropraxia or the peroneal nerve in one patient, and no events in the standard treatment group. No serious adverse events occurred. None of the four deaths (one [1%] in the intervention group vs three [4%] in the standard treatment group) were treatment related.

Interpretation This study showed that additional ultrasound-accelerated catheter-directed thrombolysis does not change the risk of post-thrombotic syndrome 1 year after acute iliofemoral deep-vein thrombosis compared with standard therapy alone. Although this trial is inconclusive, the outcome suggests the possibility of a moderate beneficial effect with additional ultrasound-accelerated catheter-directed thrombolysis. Further research is therefore warranted to better understand this outcome in the context of previous trials, preferably by combining the available evidence in an individual patient data meta-analysis.

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Research in context

Evidence before this study

We performed a systematic review in January, 2010. Therefore, we searched MEDLINE, PubMed, the ISRCTN controlled trials database, the UK National Health Service Centre for Reviews and Dissemination database, ClinicalTrials.gov, the Health Services Research Projects in progress (HSRProj), and Cordis database for randomised controlled trials referencing “post thrombotic syndrome” OR “post phlebotic syndrome” AND “catheter directed thrombolysis”. We found two publications of small, randomised controlled trials reporting on short-term results after catheter-directed thrombolysis in patients after an event of acute deep-vein thrombosis. One study by Elsharawy and colleagues (35 patients) assessed additional catheter-directed thrombolysis versus standard anticoagulation therapy.

At 6 months, the proportion of patients with patency was 72% (13 of 18) in patients treated with thrombolysis and 12% (two of 17) in those with standard therapy ($p < 0.001$). The other study, by Enden and colleagues, reported on the short-term results for the first 103 patients from the CaVenT trial allocated to either additional catheter-directed thrombolysis or standard treatment alone. At 6 months, the proportion of patients with iliofemoral patency was 64% (32 of 50) in the intervention group versus 36% (19 of 53) in the standard treatment group, corresponding to an absolute risk reduction of 28% (95% CI 9.7–46.7; $p = 0.004$). While our study was ongoing, the CaVenT trial (209 patients) reported its long-term results, and a difference in post-thrombotic syndrome corresponding to an absolute risk reduction of 14.4% (95% CI 0.2–27.9) was observed in patients with iliofemoral deep-vein thrombosis treated with catheter-directed

thrombolysis and adjunctive stenting versus standard anticoagulant treatment alone. More recently, the ATTRACT trial (692 patients) results were published, and no difference was observed in the proportion of patients with post-thrombotic syndrome between treatment groups (157 [47%] of 336 in the thrombolysis group and 171 [48%] of 355 in the control group; with a risk ratio of 0.96 [95% CI 0.82–1.11]; $p = 0.56$).

Added value of this study

Our trial only included patients with iliofemoral thrombosis; patients perceived at the highest risk of post-thrombotic syndrome and anticipated to gain the most from the intervention. Contrary to the expectations, the results of the CAVA trial show that even in the population at highest risk of post-thrombotic syndrome, early reperfusion with catheter-directed thrombolysis did not reduce the incidence of post-thrombotic syndrome. This highlights the need for reconsideration of this strategy, including patient selection, and intervention methods.

Implications of all the available evidence

The overall evidence is heterogeneous due to differences in populations, interventions, and definitions of the outcome and therefore, efforts should be made to match up the underlying risks to facilitate comparisons. Evidence suggests that catheter-directed thrombolysis as it is currently performed is not optimal for the prevention of post-thrombotic syndrome after an acute iliofemoral deep-vein thrombosis. However, individual patient data meta-analysis might provide a better and more accurate estimate of the effectiveness of this treatment.

Introduction

Deep-vein thrombosis is a serious condition with a lifetime incidence of 2.5–5.0%,^{1,2} with persistence of long-term complications known as post-thrombotic syndrome in 40–60% of those affected.^{3,4} Post-thrombotic syndrome negatively impacts quality of life⁵ and is associated with substantial costs.⁶ Standard treatment of deep-vein thrombosis includes immediate anticoagulant therapy to prevent thrombus growth and embolisation, as well as early mobilisation and compression therapy with the potential to reduce residual thrombus burden and the onset of post-thrombotic syndrome.^{7–9} Although effective in most patients, this treatment is not sufficient for those at the highest risk of post-thrombotic syndrome,⁹ in particular those with iliofemoral thrombosis.^{3,10,11} Early removal of the thrombus might improve long-term outcomes in these patients by restoring patency and preserving function of the affected vein segments.^{12,13} Previous trials comparing additional catheter-directed thrombolysis to standard treatment showed conflicting outcomes.^{14–16} Although the CaVenT trial^{14,15} found an absolute risk reduction of 14.4% (95% CI 0.2–27.9) for the development of post-thrombotic syndrome with additional

catheter-directed thrombolysis after iliofemoral deep-vein thrombosis, no difference in risk was observed for the incidence of post-thrombotic syndrome with additional pharmacomechanical thrombolytic treatment in the larger ATTRACT trial.¹⁶ However, a subanalysis of the ATTRACT trial including patients with moderate-to-severe post-thrombotic syndrome did indicate a risk reduction with additional catheter-directed thrombolysis.¹⁷ Because spontaneous resolution of iliofemoral thrombosis is rare, enhancing this natural process through ultrasound-accelerated catheter-directed thrombolysis might be most beneficial in these patients. Here, we present the ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation (CAVA) trial, in which we aimed to assess the efficacy and safety of additional ultrasound-accelerated catheter-directed thrombolysis for the prevention of post-thrombotic syndrome in patients with iliofemoral deep-vein thrombosis.

Methods

Study design and participants

The CAVA trial was a multicentre, randomised, single-blind, allocation-concealed, parallel group, superiority

trial done in 15 hospitals throughout the Netherlands (appendix p 2). Six centres were interventional centres thereby responsible for doing the thrombolysis and eventual adjunctive interventions. Details on the trial design are provided in the protocol (appendix (pp 23–89).

Eligible patients aged 18–85 years had an objectively documented first-time iliofemoral deep-vein thrombosis (ie, complete or partial thrombosis of the common femoral vein or more cranial vein segments) with acute symptoms for no longer than 14 days, a life expectancy of more than 6 months, and no previous thrombus in the affected limb. Exclusion criteria were pre-existent signs of venous insufficiency (CEAP classification C3 or higher);¹⁸ history of gastrointestinal bleeding, cerebrovascular accident, or CNS disease within 1 year; severe hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg); active malignancy (metastatic, progressive, or treated within the previous 6 months); increased alanine transaminase levels (more than three times the upper limit of normal [34 international units (IU)/L for women and 45 IU/L for men]); renal failure (estimated glomerular filtration rate <30 mL/min); major surgery within 6 weeks; pregnancy; or impaired mobility.¹⁸

This trial was approved by the review boards of all participating centres. Patients were recruited at the emergency room or outpatient clinic of the participating centres and written informed consent was obtained before randomisation.

Randomisation and masking

Before study participation, diagnosis of acute iliofemoral deep-vein thrombosis was done in all participating centres by compression ultrasound. After obtaining informed consent, individual patients were randomly allocated in a 1:1 ratio to the intervention group receiving additional ultrasound-accelerated catheter-directed thrombolysis (including standard treatment and adjunctive procedures) or to the standard treatment group. The study coordinator at Maastricht University Medical Centre conducted the randomisation procedure. A web-based randomisation programme (TENALEA, ALEA version release 2.2) was used with a random variable block size (2–12), and randomisation was stratified for participating centre and age in three strata (18–50 years, 51–70 years, and 71–85 years). The allocated treatment was communicated to the patient by the central study coordinator performing the randomisation. Patients received standard treatment for deep-vein thrombosis at their local hospital and were asked not to disclose their allocation during visits with their treating physician or (local) study personnel. Treating physicians were informed of the patient's participation in the study, but not on the treatment allocation.

The coordinating researcher at Maastricht University Medical Centre responsible for collecting, maintaining, and analysing the data was masked to assignment.

Procedures

Patients in both treatment groups received initial and long-term anticoagulation therapy according to international guidelines,⁷ with vitamin K antagonists (acenocoumarol or phenprocoumon), direct oral anticoagulants (rivaroxaban, apixaban, and dabigatran), or low-molecular-weight heparin.

Custom-fitted knee-high elastic compression stockings (30–40 mmHg pressure) initiated within 24 h after deep-vein thrombosis diagnosis with replacement every 6 months were prescribed to all patients. Patients were instructed to use compression stockings during waking hours of every day for a minimum of 24 months after the deep-vein thrombosis.

Thrombolytic intervention had to be started no later than 21 days after the onset of symptoms at one of the six intervention centres. The interventions were performed using urokinase (Medacina, Lampro, Netherlands) in combination with the Ekos Endowave-system (EKOS Corporation, Bothell, WA, USA). This system consists of an intelligent drug delivery catheter with a microsonic core containing multiple high-frequency (2 MHz) ultrasound transducers. A detailed description of the thrombolysis protocol is provided in the appendix (pp 7–9). A total bolus dose of 250 000 IU urokinase in 10 mL NaCl was administered directly after placement of the thrombolysis catheter followed by a total of 100 000 IU/h through continuous infusion during the intervention. Simultaneously, a therapeutic dose of heparin (a total of 1000 IU/h) was administered through the sheath to prevent new thrombus formation. During thrombolysis, which had a maximum duration of 96 h, the patient was confined to bed. During the intervention, standard anticoagulation treatment would be stopped and patients would receive therapeutic doses of low-molecular-weight heparin to prevent further thrombosis. When the intervention was stopped, patients would be restarted on their regular anti-coagulant drugs 1 h after removal of the sheath. Coagulation status was assessed every 6 h to inform decisions on dose adjustment, dose interruption, or treatment termination. Daily venography was performed to assess progress of thrombolysis. Interventions were terminated in the following cases: successful treatment (defined as a regained patency of ≥90%); no change in patency after 48 h; persisting activated partial thromboplastin time longer than 80 s; fibrinogen less than 8 mm in FIBTEM (appendix p 9); plasma fibrinogen less than 1.8 g/L; or when the maximum duration of thrombolytic treatment was reached. Adjunctive procedures (eg, thrombosuction, percutaneous transluminal angioplasty, stenting, endophlebectomy, or creating an arteriovenous fistula, or any combination of these) were at the discretion of the physician performing the intervention; however, they were advocated in the case of compression syndromes or a persistent venous lumen reduction of more than 50%. Stenting, which was done

See Online for appendix

in the intervention group only, was done using dedicated venous stents.

In the case of bilateral deep-vein thrombosis, the leg with the most cranial localisation was considered to be the index leg. In patients with bilateral thrombosis, additional ultrasound-accelerated catheter-directed thrombolysis was performed in both legs.

A detailed overview of study assessments and study visits is provided in the appendix (pp 4–5). Assessment of trial outcomes was stipulated in the outpatient clinic at 3, 6, and 12 months. If venous stenting was done, additional study visits to the intervention centre were planned 2 weeks and 6 weeks after the intervention, solely to assess stent patency. The follow-up visit at baseline and the 12-month follow-up visit were done at one of the six intervention centres nearest to the patients' home to collect additional imaging data (magnetic resonance venography, extended duplex ultrasound, and air plethysmography if available). The lower extremity thrombosis (LET) classification was used to classify the extent of the thrombosis (LET class I defined as isolated calf vein thrombosis; LET class II as femoropopliteal thrombosis; LET class III as common femoral vein or iliac vein thrombosis, or both; and LET class IV as inferior cava vein thrombosis).¹¹

The 3-month and 6-month study visits did not require any advanced imaging assessments or interventions. Therefore, at these visits, assessment of the Villalta score,¹⁹ severity of complaints, the adherence to compression and anticoagulation therapy, and administration of quality-of-life questionnaires could be done at all participating centres.

Textual and full-colour visual aids for standardised scoring of the objective Villalta items were provided to all participating centres.²⁰ The different Villalta items were scored on a 4-point scale (0–3) with a total item score of 33. With higher scores indicating a higher severity of post-thrombotic morbidity, ranging from mild (5–9), moderate (10–14), to severe (≥ 15 or venous ulceration).^{19,20} The severity of post-thrombotic syndrome was also quantified using the venous clinical severity score (0–30),²¹ which was assessed at baseline and 12-month follow-up.

Adherence to compression therapy was based on patient-reported estimates of the number of days per week that compression stockings were used; this information was translated into percentage of adherence.

The occurrence of adverse events (ie, major bleeding, recurrent [non-stent] deep-vein thrombosis, in-stent thrombosis, pulmonary embolism, or death) was recorded when encountered. Serious adverse events, defined as any untoward medical event resulting in death, life-threatening events, (prolonged) hospitalisation, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or any unforeseen adverse outcomes, were also registered and reported to the adjudication committee (appendix p 43).

Quality of life was assessed based on scoring from the general health-related quality of life short form-36 (SF36; version 2),²² and EuroQol5D (EQ5D)²³ questionnaires, the venous disease-specific VEINES-QOL instrument^{24–26} (original relative summary score [T score] and intrinsic score; appendix pp 10–11), and the pain disability index (PDI).²⁷ More details on how quality of life was scored are in the appendix (pp 10–11).

Outcomes

The primary outcome was the proportion of patients with post-thrombotic syndrome at 12 months after the acute event (a Villalta-score of ≥ 5 on two occasions at least 3 months apart with the first assessment at least 3 months after the event or the presence of venous ulceration; appendix p 10).¹⁹

We also assessed the proportion of patients with post-thrombotic syndrome according to the International Society of Thrombosis and Haemostasis (ISTH) consensus scoring method (a Villalta score ≥ 5 or venous ulceration at the 6-month visit or later) was assessed.²⁰ Compared with this method, the original scoring method used for the primary outcome is more conservative in diagnosing post-thrombotic syndrome.

The main safety outcome was major bleeding (appendix p 11), which was defined as a bleeding associated with a fall in haemoglobin of at least 2 g/dL (about 1.24 mmol/L), a need for transfusion of two or more units of packed red blood cells or whole blood, symptomatic in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular), or contributing to the death of the patient.²⁸

Secondary outcomes of recurrent venous thromboembolism (objectified deep-vein thrombosis involving a new venous segment or a previously involved venous segment for which symptomatic and imaging improvement had been obtained in a patient with at least one previous episode of deep-vein thrombosis); pulmonary embolism (spiral CT showing an intravascular migration of a venous thrombus to the pulmonary arterial circulation); in-stent thrombosis (objectified deep-vein thrombosis involving stented vein segments); and death during follow-up were all assessed by an independent adjudication committee. Health-related quality of life was also a secondary outcome.

Data on the proportion of post-thrombotic syndrome during follow-up later than 12 months, data on clot lysis, patency, and valve function, and measurements of markers of coagulation and inflammation will be published in separate manuscripts.

Statistical analysis

The study was designed to show that additional ultrasound-accelerated catheter-directed thrombolysis was superior to standard therapy alone for the prevention of the post-thrombotic syndrome. Given the invasiveness

of the procedure and the associated bleeding risks, we postulated that an outcome reduction of 17% (equivalent to an odds ratio [OR] of 0.26) resulting in a risk of 8% for the incidence of post-thrombotic syndrome in patients receiving additional ultrasound-accelerated catheter-directed thrombolysis instead of the previously reported 25%,^{29,30} would be worth the risk posed by the intervention. 170 patients (85 per treatment group) were required for the trial to have 80% power at a two-sided type 1 error rate of 5%. To compensate for a 5% loss of patients during follow-up, 180 patients were to be included.

A prespecified interim analysis by the data safety monitoring board was planned to consider early termination of the trial for safety reasons at 6 months after the start of the study to compare the occurrence of major bleeding events between the two groups (appendix p 44).

The primary outcome analysis was a modified intention-to-treat analysis including all patients who were randomly assigned, except those who did not pass screening and patients who immediately withdrew consent before start of allocated treatment (appendix p 12). Additionally, a per-protocol analysis was done analysing data of all patients that completed the treatment and follow-up as assigned. For the primary outcome, the proportions of patients with post-thrombotic were compared with χ^2 analysis, and associated ORs and corresponding 95% CIs were calculated using StatPages and Open Source Epidemiologic Statistics for Public Health (OpenEpi). Additionally, we used the Kaplan-Meier method to calculate the cumulative incidence of post-thrombotic syndrome at 12 months adjusted for centre to compare incidences between the two treatment groups. Loss to follow-up, withdrawals, and deaths were censored at the last available date. Hazard ratios (HRs) and their corresponding 95% CIs were calculated using Cox proportional hazard models, stratified for centre and adjusted for age, sex, clinical presentation of the thrombotic event (idiopathic or provoked), and extent of the index thrombosis at ultrasound using the LET classification.^{11,31} Descriptive analyses were used to assess patient characteristics, risk factors for venous thromboembolism, the severity of post-thrombotic syndrome, adherence to therapy, treatment characteristics, the proportion of recurrent venous thromboembolism (deep-vein thrombosis of the leg and pulmonary embolism), in-stent-thrombosis, the proportion of major bleeding, and death. The safety analysis accounted for repeated events but not for differential follow-up. Safety was assessed in the modified intention-to-treat population of all patients who started the intervention. We applied a mixed-design analysis of variance to test for differences between the two treatment groups and to assess changes over time by comparing repeated outcome measures for quality of life scores at different timepoints during follow-up. A significance level of 0.05 (two-sided) or less was considered significant, in the case of multiple testing,

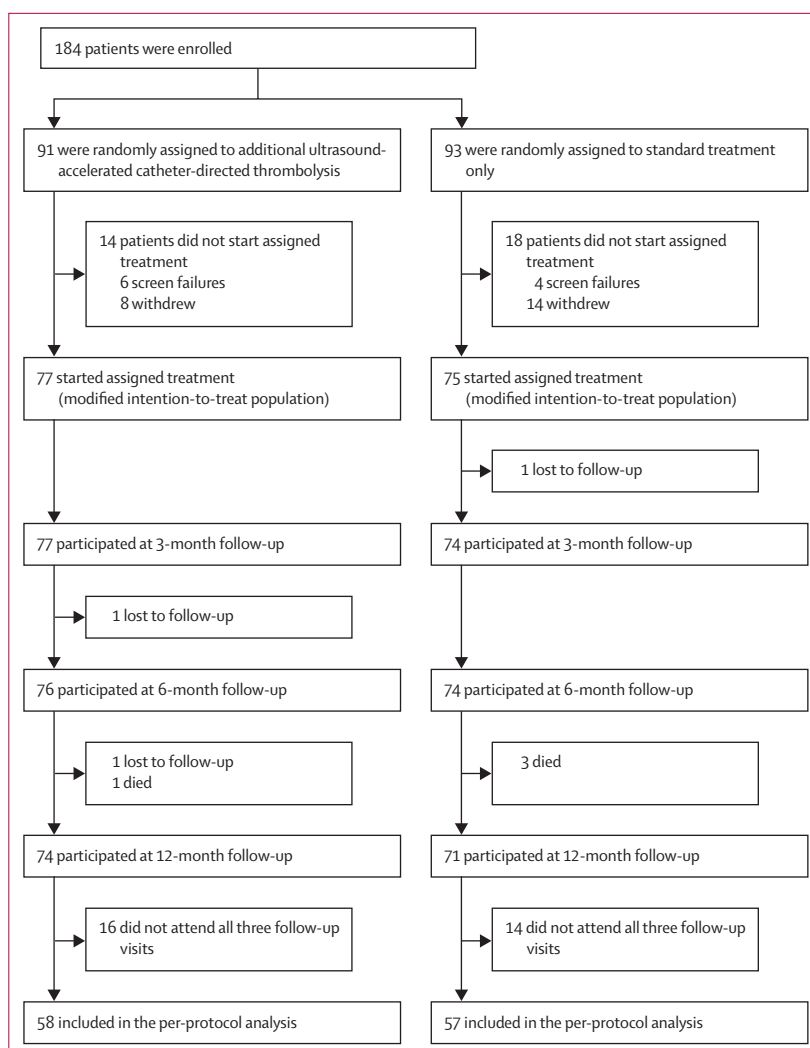


Figure 1: Trial profile

Eight of the screening failures were due to an incorrectly established location of the index thrombus on the diagnostic compression ultrasound. In all analyses, loss to follow-up or deaths were censored when encountered.

adjusted significance levels based on the Bonferroni's correction were used. If 5% or more of data were missing, imputation would be performed.

All analyses were done using SPSS, version 24. The study is registered at ClinicalTrials.gov (NCT00970619).

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Based on the results of the 6-month interim analysis on Nov 1, 2010, the data safety monitoring board recommended that patient recruitment should continue to

	Additional thrombolysis group (n=77)	Standard treatment group (n=75)
Age		
Median, years	49.0 (37.5–67.0)	52.0 (38.0–65.0)
<40 years	23 (30%)	20 (27%)
40–65 years	33 (43%)	38 (51%)
>65 years	21 (27%)	17 (23%)
Sex		
Female	38 (49%)	37 (49%)
Male	39 (51%)	38 (51%)
Body-mass index		
Mean, kg/m ²	28.0 (5.6)	27.4 (4.1)
<25.0 kg/m ²	24 (31%)	22 (29%)
25.0–30.0 kg/m ²	31 (40%)	33 (44%)
≥30.0 kg/m ²	19 (25%)	15 (20%)
Unknown	3 (4%)	5 (7%)
Provoked deep venous thrombosis*	40 (52%)	32 (43%)
Risk factors		
One	32 (42%)	22 (29%)
More than one	8 (10%)	10 (13%)
Surgery in the previous 2 months	9 (12%)	10 (13%)
Trauma in the previous 2 months	4 (5%)	4 (5%)
Pregnancy or childbirth in the previous 3 months	9 (12%)	5 (7%)
Hormone replacement therapy	2 (3%)	0
Oral contraceptives	9 (12%)	13 (17%)
Previous contralateral deep vein thrombosis	9 (12%)	5 (7%)
Previous pulmonary embolism	3 (4%)	5 (7%)
Active malignancy†	4 (5%)	1 (1%)
Thrombus location		
Left	54 (70%)	55 (73%)
Right	21 (27%)	17 (23%)
Bilateral	2 (3%)	3 (4%)
Duration of symptoms at inclusion, days	6.0 (3.0–11.0)	7.0 (3.0–10.0)
Anticoagulant therapy at inclusion		
Vitamin K antagonists	62 (81%)	63 (84%)
Direct oral anticoagulants	12 (16%)	6 (8%)
Low-molecular-weight heparin	1 (1%)	0
Unknown	2 (3%)	6 (8%)

Data are n (%), mean (SD), or median (IQR). *Acute deep-vein thrombosis is considered idiopathic or unprovoked in the absence of the following risk factors: surgery in the previous 2 months, trauma in the previous 2 months, pregnancy or childbirth in the previous 3 months, use of hormone replacement therapy, use of oral contraceptives, and active malignancy. †Active malignancy is defined as a current metastatic or progressive cancer diagnosis or having received cancer treatment within the previous 6 months.

Table 1: Baseline characteristics of the modified intention-to-treat population

complete the originally planned sample size of 180 patients. Between May 28, 2010, and Sept 18, 2017, 184 patients were randomly assigned to standard treatment with additional ultrasound-accelerated catheter-directed

thrombolysis (91 patients), or standard treatment only (93 patients; figure 1). Before start of assigned treatment, ten patients were excluded because they did not meet inclusion criteria (ie, they were misclassified during screening; six in the intervention group and four in the standard treatment group) and 22 patients withdrew informed consent (18 at the day of randomisation, six patients from the intervention group vs 12 from the standard treatment group, and two from each treatment group within 2 days of randomisation; appendix p 12). Despite providing careful and thorough information before inclusion, various reasons led to withdrawal of informed consent directly after randomisation. Ten of the withdrawals in the standard treatment group were because of unwillingness of the patient to participate in additional study assessments while being allocated standard care. Withdrawal of informed consent led to termination of further follow-up. Specification of reasons for exclusion and withdrawal before start of allocated treatment are in the appendix (p 12). The modified intention-to-treat analysis comprised 152 patients. Treatment groups were similar regarding observed baseline characteristics and anticoagulant treatment (table 1). Median age was 52.0 years (IQR 38.0–66.5) with equal representation of both sexes (77 [51%] men and 75 [49%] women) and median symptom duration at inclusion was 6.0 days (3.0–10.3). The prevalence of risk factors was similar between groups.

Median follow-up was 12.0 months (IQR 6.0–12.0). At 12 months, the primary modified intention-to-treat analysis showed that post-thrombotic syndrome occurred in 22 (29%) of 77 patients who received additional ultrasound-accelerated catheter-directed thrombolysis and in 26 (35%) of 75 patients receiving standard treatment (OR 0.75 [95% CI 0.38 to 1.50], $p=0.42$; figure 2, table 2) The absolute difference was –6.1% (95% CI –21.6 to 9.8). The severity of post-thrombotic syndrome in the intervention group compared with the standard treatment group was mild (Villalta score 5–9; ten [13%] in the intervention group vs ten [13%] in the standard treatment group, $p=0.95$), moderate (Villalta score 10–14; 11 [14%] vs 12 [16%], $p=0.77$), or severe (Villalta score ≥15 or venous ulceration; one [1%] vs four [5%], $p=0.21$) and did not differ significantly between treatment groups (table 2). The cumulative incidence of post-thrombotic syndrome at 12 months was 22 (29%) of 77 for additional ultrasound-accelerated catheter-directed thrombolysis and 26 (35%) of 75 for the standard treatment group (hazard ratio [HR] adjusted for centre 0.76 [95% CI 0.43 to 1.35]). Post-thrombotic syndrome was diagnosed at 6 months in 13 (17%) patients in the intervention group and 19 (25%) in the standard treatment group, with another nine (12%) and seven (9%) patients diagnosed at 12-month follow-up. The HRs and 95% CIs stratified for centre and adjusted for age, sex, clinical presentation of the acute thrombosis, and extent of the thrombus for the intervention group versus the

standard treatment group were 0·80 (0·44–1·45) with the original Villalta scoring and 0·93 (0·55–1·56) with the ISTH-consensus scoring method. Similar results were found in the per-protocol analysis (appendix p 16).

Major bleeding occurred solely in the intervention group (in four [5%] of 77 patients), most within 10 days after start of treatment (median 5·5 days [0·8–12·5]). No intracranial or intraspinal bleeds occurred; however, in one patient the major bleeding resulted in neuropraxia of the peroneal nerve. All events were related to the assigned thrombolytic treatment and required additional medical intervention. None of the four deaths, of which one (1%) occurred in the intervention group and three (4%) in the standard treatment group, were related to the instituted treatment or procedure.

During follow-up, a total of 24 thrombotic events occurred in 20 patients: 14 (18%) of 77 patients from the intervention group had a total of 17 events (five recurrent [non-stent] deep-vein thromboses in five [6%] patients and 12 in-stent thromboses in ten [13%] patients) versus six (8%) of 75 patients from the standard treatment group who had seven events (five recurrent [non-stent] deep-vein thromboses in four [5%] patients and two pulmonary emboli in two [3%] patients). All of the thrombotic events (in-stent or non-stent) involved the index leg (table 3, appendix p 15). In the intervention group, all recurrent (non-stent) thrombotic events occurred while patients were on anticoagulant treatment, whereas in the standard treatment group, all patients were off anticoagulant treatment at the time of recurrence. In-stent thrombosis, which occurred solely in the intervention group because patients from the standard treatment group did not undergo venous stenting, occurred 12 times in ten patients (13%). Four of these occurred within 2 weeks after the primary intervention. Repeated thrombolysis was initiated in six (60%) of ten patients and was combined with adjunctive endovascular procedures in two of these patients and hybrid procedures (a combination of surgical and endovascular) in three patients. Two of these patients had a second event of in-stent thrombosis, after which lifelong conservative anticoagulation therapy was initiated. No serious adverse events occurred.

Allocated treatment was monitored and is summarised in the appendix (pp 13–14). Incidences of accidental unmasking were not recorded. In three (4%) of 77 patients assigned to the intervention group, the procedure was not performed. In all other patients in the intervention group, thrombolysis was started at a median of 10·0 days (IQR 6·8–15·0) after onset of symptoms and was continued for a median of 2·0 days (1·0–3·0). Treatment was terminated early in 22 (30%) of the 74 patients who received thrombolytic treatment: in 19 patients because no progress in thrombus resolution was seen, in two patients because of a persisting low fibrinogen level, and

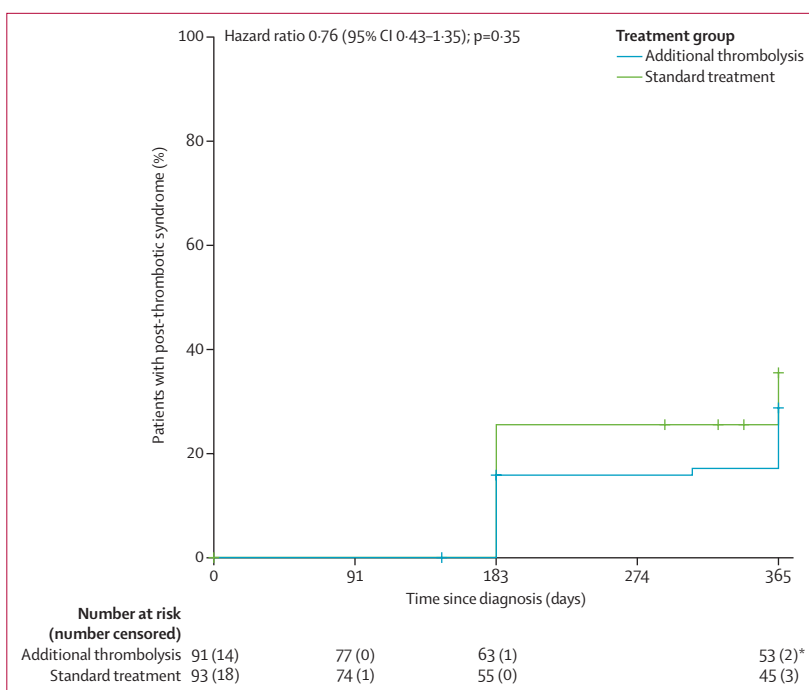


Figure 2: Cumulative incidence of post-thrombotic syndrome

Tick marks show censored patients. *One censored patient (death) had already developed post-thrombotic syndrome and was registered as such.

one patient no longer wished to continue with thrombolysis. Adjunctive procedures were done in 42 (55%) of 77 patients, including venous stenting in 35 patients. Stenting involved the common iliac vein in 29 patients and stenting caudal to the iliofemoral ligament was only done in three patients.

Adherence to compression therapy of more than 80% of days at 12-month follow-up was seen in 49 (66%) of 74 patients in the intervention group and 51 (72%) of 71 patients receiving standard treatment. Few patients refrained from compression therapy: 12 (16%) in the intervention group and 11 (15%) in the standard treatment group. In the intervention group, 63 (82%) of 77 had adherence of more than 80% of days at 3 months and 61 (80%) of 76 had more than 80% adherence at 6 months compared with the control group, in which 60 (81%) of 74 at 3 months and 61 (82%) of 74 at 6 months had more than 80% adherence. In the intervention group, 75 (97%) of 77 patients at 3 months, 73 (96%) of 76 at 6 months, and 36 (49%) of 74 at 12 months were using anticoagulant therapy, compared with 69 (93%) of 74 patients at 3 months, 66 (89%) of 74 at 6 months, and 43 (61%) of 71 patients at 12 months in the standard treatment group.

The complete quality of life data from baseline until month 12 for both treatment groups is in the appendix (p 17). Change between baseline and 12 months in general health-related quality of life measures (SF36 and EQ5D) and disease-specific quality-of-life measures

	Additional thrombolysis group (n=77)	Standard treatment group (n=75)	Difference between treatment groups (95% CI)	Odds ratio (95%CI)
Primary outcome*				
Post-thrombotic syndrome 12 months after deep-vein thrombosis assessed by Villalta's criteria	22 (29%)	26 (35%)	-6.1% (-21.6 to 9.8)	0.75 (0.38 to 1.50)
None (<5)	55 (71%)	49 (65%)	6.0% (-9.8 to 21.6)	1.33 (0.67 to 2.63)
Mild (5-9)	10 (13%)	10 (13%)	-0.3% (-10.8 to 11.5)	0.97 (0.38 to 2.49)
Moderate (10-14)	11 (14%)	12 (16%)	-1.7% (-13.5 to 10.4)	0.88 (0.36 to 2.13)
Severe (≥15)	1 (1%)	4 (5%)	-4.0% (-6.5 to 2.5)	0.23 (0.03 to 2.14)
Additional outcomes*				
Mean Villalta score at 12 months ¹⁹	4.0 (3.2)	4.9 (4.2)	-0.8 (-2.1 to 0.4)	..
Post-thrombotic syndrome according to the ISTH Villalta scoring 12 months after deep-vein thrombosis ²⁰	32 (42%)	33 (44%)	-2.4% (-14.4 to 19.2)	0.91 (0.48 to 1.72)
None (<5)	45 (58%)	42 (56%)	2.4% (-14.4 to 19.2)	1.11 (0.58 to 2.10)
Mild (5-9)	20 (26%)	14 (19%)	7.3% (-20.6 to 7.1)	1.53 (0.71 to 3.31)
Moderate (10-14)	11 (14%)	15 (20%)	-5.7% (-7.3 to 17.6)	0.67 (0.28 to 1.56)
Severe (≥15)	1 (1%)	4 (5%)	-4.0% (-2.5 to 6.5)	0.23 (0.03 to 2.14)
Mean venous clinical severity score at 12 months ²¹	4.2 (2.5)	4.8 (2.7)	-0.7 (-1.6 to 0.2)	..
Ulceration at any follow-up assessment	0	4 (5%)	-5.4% (-1.9 to 7.9)	0.10 (0.01 to 1.94)

Data are n (%) or mean (SD). None of the comparisons in this table showed a statistically significant difference between groups. ISTH=International Society of Thrombosis and Haemostasis. *In the case of bilateral deep-vein thrombosis, the least favourable Villalta scores were used.

Table 2: Efficacy outcomes

	Additional thrombolysis group (n=77)	Standard treatment group (n=75)	Difference between treatment groups (95% CI)	Odds ratio (95% CI)
Primary outcome				
Major bleeding ^{*27}	4 (5%)	0	5.2% (-0.4 to 2.7)	9.25 (0.49 to 174.7)
Secondary outcomes				
Pulmonary embolism	0	2 (3%)	-2.6% (-7.1 to 1.8)	0.19 (0.01 to 4.02)
Recurrent (non-stent) deep-vein thrombosis†	5 (6%)	4 (5%)	1.2% (-6.3 to 8.7)	1.23 (0.32 to 4.78)
In-stent thrombosis‡	10 (13%)
Death	1 (1%)	3 (4%)	-2.7% (-7.8 to 2.4)	0.32 (0.03 to 3.11)

Data are n (%). None of the comparisons in this table showed a statistically significant difference between groups. *Bleeding was associated with neuropraxia of the peroneal nerve. †In the standard treatment group, four patients developed a recurrent deep-vein thrombosis, of which one had two separate events; after the first event, which occurred when the patient had no anticoagulant treatment, treatment was reinstated using direct oral anticoagulants; the second event developed despite anticoagulant treatment; thrombolysis was attempted, however it was unsuccessful; anticoagulant therapy will be continued indefinitely. ‡Of the ten patients who developed an in-stent thrombosis, two patients encountered two separate events; in both cases, the second event was treated conservatively by lifelong continuation of anticoagulant therapy.

Table 3: Safety outcomes

(VEINES-QOL/sym T and intrinsic scores) were similar between treatment groups (appendix p 17). Except for the VEINES-QOL/sym T score ($p=0.71$), all quality of life measurements significantly increased over time ($p<0.04$).

Discussion

Our study did not show a benefit from additional ultrasound-accelerated catheter-directed thrombolysis over standard treatment for the prevention of post-thrombotic syndrome 1 year after acute iliofemoral deep-vein thrombosis. Results were consistent in the modified intention-to-treat and per-protocol analyses and did not depend on predefined patient characteristics.

A non-significant absolute difference of -6.1% was associated with additional ultrasound-accelerated catheter-directed thrombolysis versus standard treatment. This difference is far less than the anticipated -17% difference.

Additionally, our results as presented according to the ISTH definition are in concordance with the main results of the ATTRACT trial,¹⁶ both showing a more modest non-significant risk reduction than our primary analysis using the original Villalta scoring and thus unable to confirm the outcomes of the CaVenT trial,¹⁴ which demonstrated an absolute risk reduction of 14.4% for the development of post-thrombotic syndrome with additional catheter-directed thrombolysis.

We observed a significantly higher incidence of recurrent thrombotic events in the additional ultrasound-accelerated catheter-directed thrombolysis group because of the occurrence of in-stent thromboses. Furthermore, even though without severe consequences, major bleeding occurred solely in the intervention group. Moreover, additional ultrasound-accelerated catheter-directed thrombolysis did not significantly affect quality of life: both the generic as well as disease-specific patient-reported health-related quality of life scores showed a similar improvement in both groups during follow-up.

Outcomes might have been influenced by differences in study design or selected study populations. The number of patients in our trial was lower than in the ATTRACT trial¹⁶ but similar to the number in the CaVenT trial.¹⁴ However, our number of patients with iliofemoral deep-vein thrombosis was about twice as high as in the CaVenT-trial. Thrombus location can influence the risk of developing post-thrombotic syndrome^{10,11} as well as the efficacy of thrombolytic treatment.¹³ The CAVA trial included patients with iliofemoral thrombosis only, providing a more homogeneous study population, which was considered an important advantage over the CaVenT trial. However, contrary to our expectations, this homogeneous selection of high-risk patients did not result in greater benefit for the patients. To that effect, the ATTRACT trial also did not show unequivocally better results in patients with iliofemoral thromboses than those with isolated femoropopliteal thromboses, which are clinically less severe or less therapy resistant. Moreover, a subanalysis involving exclusively patients with iliofemoral thromboses showed no preventive effect of catheter-directed thrombolysis on the development of any (mild to severe) post-thrombotic syndrome. However, the intervention did result in less severe post-thrombotic complaints and higher quality of life after 24 months.¹⁷

Both trials used catheter-directed thrombolysis with a mechanical component, which could potentially have induced vein wall damage, thereby blurring the effects of thrombolysis. However, this confusion is unlikely given the results of a study by Engelberger and colleagues³² that showed no difference in post-thrombotic syndrome incidence whether the mechanical component of the Ekos Endowave-system was activated during thrombolytic treatment or not. Also, the ATTRACT trial,¹⁶ which assessed multiple different thrombolytic treatment strategies, did not report any differential effect on outcomes related to the use of different treatment modalities. In our study, patients who received additional ultrasound-accelerated catheter-directed thrombolysis had treatment according to a single protocol used in all centres. Adjunctive procedures (mainly percutaneous transluminal angioplasty and venous stenting), were complicated by a high proportion of in-stent thromboses. This high proportion might have affected the clinical outcomes because recurrent thrombosis is one of the main risk factors for the development of post-thrombotic syndrome.^{29,33}

The 12-month follow-up of this trial was shorter than the follow-up in the other two trials. Previous studies, including the ATTRACT trial, suggest that although post-thrombotic syndrome can still develop years after the acute event, it usually occurs within the first year.^{10,16,29,33,34} Since the CaVenT trial¹⁴ did not show a difference in incidence of post-thrombotic syndrome until 24 months, a longer follow-up theoretically might have led to different results.⁴

Our study has several limitations. Stringent inclusion criteria were used that resulted in a lengthy period of recruitment and could affect the generalisability of the results. For example, the use of direct oral anticoagulants was introduced during the inclusion period. Multiple patients withdrew informed consent immediately after randomisation because of disappointment when allocated to standard treatment only, which reduced our sample size, and although it did not result in a numerical imbalance between the treatment groups, it might have resulted in imbalance of prognostic factors. The higher-than-expected proportion of patients with post-thrombotic syndrome in the standard treatment group might also have negatively affected the power of the trial. However, in patients that did receive assigned treatment, few were lost to follow-up during the trial. In addition, both treatment groups showed high compliance with compression therapy, maybe because in the Netherlands the use of compression stockings is more commonly accepted and is officially part of treatment than in most other European or North American countries, which might have rendered standard treatment as comparative treatment relatively successful.

The perceived advantage of selecting a homogenous population of patients with iliofemoral thrombosis might have turned out to be a disadvantage for the outcomes of

our study, as these types of thromboses might be more treatment resistant. Whether this treatment resistance is associated with the location of the thrombosis resulting in impaired venous outflow or with characteristics of the clot is uncertain.³⁵ Furthermore, catheter-based intervention protocols encourage physicians to apply additional procedures, including stent placement, introducing an extra risk factor for in-stent-thrombosis. Stents are not sufficiently equipped to reduce clot formation and new generations of stents might be required. Additionally, no robust evidence supports a particular anticoagulant regimen to prevent in-stent-thrombosis.³⁶ Thus, a multidisciplinary approach is probably needed to solve the remaining problems, including better selection of patients, optimisation of treatment protocols, improvement of the quality of the reperfusion process, assessment of the need for stenting, and enhancement of the quality of stent materials as well as optimisation of the (post-interventional) antithrombotic policy. These problems need to be addressed in concert in order to make further steps towards successful reperfusion therapy in venous thrombosis.

In conclusion, this study showed that additional ultrasound-accelerated catheter-directed thrombolysis does not change the risk of post-thrombotic syndrome 1 year after an acute iliofemoral deep-vein thrombosis compared with standard therapy alone. Although this trial is inconclusive, the outcome suggests the possibility of a moderate effect. Further research is therefore warranted to better understand our results in the context of previous trials, preferably by combining the available evidence in an individual patient data meta-analysis.

Contributors

PN contributed to the literature search, data collection, data analysis, data interpretation, composition of figures and tables, and writing of the manuscript. AJtC-H contributed to study concept, study design, funding, literature search, data analysis, data interpretation, composition of figures and tables, and writing of the manuscript. CHAW and HtC contributed to study concept, study design, and writing of the manuscript. All other authors contributed equally to data collection and review of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Data sharing requests should be directed to the first authors PN (pascale.notten@mumc.nl) and AJtC-H (arina.tencate@maastrichtuniversity.nl).

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References

- Browse NL, Burnand KG, Lea Thomas M. Deep vein thrombosis: pathology, diagnosis and treatment. In: Browse NL, Burnand KG, Irvine AT, Wilson NM, eds. *Diseases of the veins*, 2nd edn. London, England: Edward Arnold, 1999: 443–74.
- White RH. The epidemiology of venous thromboembolism. *Circulation* 2003; **107** (suppl 1): 14–8.
- Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med* 2008; **149**: 698–707.
- Schulman S, Lindmarker P, Holmström M, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *J Thromb Haemost* 2006; **4**: 734–42.
- Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. *J Thromb Haemost* 2008; **6**: 1105–12.
- Ten Cate-Hoek AJ, Toll DB, Büller HR, et al. Cost-effectiveness of ruling out deep venous thrombosis in primary care versus care as usual. *J Thromb Haemost* 2009; **7**: 2042–49.
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; **149**: 315–52.
- Appelen D, van Loo E, Prins MH, Neumann MH, Kolbach DN. Compression therapy for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev* 2017; **9**: CD004174.
- Amin EE, Bistervels IM, Meijer K, et al. Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis. *Blood* 2018; **132**: 2298–304.
- Tick LW, Doggen CJ, Rosendaal FR, et al. Predictors of the post-thrombotic syndrome with non-invasive venous examinations in patients 6 weeks after a first episode of deep vein thrombosis. *J Thromb Haemost* 2010; **8**: 2685–92.
- Strijkers RH, Arnoldussen CW, Wittens CH. Validation of the LET classification. *Phlebology* 2015; **30** (suppl): 14–19.
- Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. *Eur J Vasc Endovasc Surg* 2002; **24**: 209–14.
- Comerota AJ, Paolini D. Treatment of acute iliofemoral deep venous thrombosis: a strategy of thrombus removal. *Eur J Vasc Endovasc Surg* 2007; **33**: 351–62.
- Enden T, Haig Y, Kløw NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet* 2012; **379**: 31–38.
- Haig Y, Enden T, Grøtta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. *Lancet Haematol* 2016; **3**: e64–71.
- Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med* 2017; **377**: 2240–52.
- Comerota AJ, Kearon C, Gu CS, et al. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis. *Circulation* 2019; **139**: 1162–73.
- Porter JM, Moneta GL. Reporting standards in venous disease: an update. *J Vasc Surg* 1995; **21**: 635–45.
- Villalta S, Bagatella P, Piccioli A, Lensing AW, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome. *Haemostasis* 1994; **24**: 158a (abstr).
- Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost* 2009; **7**: 879–83.
- Rutherford RB, Padberg FT Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg* 2000; **31**: 1307–12.
- Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. *J Clin Epidemiol* 1998; **51**: 1055–68.
- Brooks R. EuroQol: the current state of play. *Health Policy* 1996; **37**: 53–72.
- van der Velden SK, Biemans AA, Nijsten T, Sommer A. Translation and validation of the Dutch VEINES-QOL/Sym in varicose vein patients. *Phlebology* 2014; **29**: 227–35.
- Lamping DL, Schroter S, Kurz X, Kahn SR, Abenheim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. *J Vasc Surg* 2003; **37**: 410–19.
- Bland JM, Dumville JC, Ashby RL, et al. Validation of the VEINES-QOL quality of life instrument in venous leg ulcers: repeatability and validity study embedded in a randomised clinical trial. *BMC Cardiovasc Disord* 2015; **15**: 85.
- Pollard CA. Preliminary validity study of the pain disability index. *Percept Mot Skills* 1984; **59**: 974.
- Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3**: 692–94.
- Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004; **141**: 249–56.
- Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; **349**: 759–62.
- Arnoldussen CW, Wittens CH. An imaging approach to deep vein thrombosis and the lower extremity thrombosis classification. *Phlebology* 2012; **27** (suppl 1): 143–48.
- Engelberger RP, Spirk D, Willenberg T, et al. Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute iliofemoral deep vein thrombosis. *Circ Cardiovasc Interv* 2015; **8**: e002027.
- Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; **125**: 1–7.
- Prandoni P, Frulla M, Sartor D, Concolato A, Girolami A. Vein abnormalities and the post-thrombotic syndrome. *J Thromb Haemost* 2005; **3**: 401–02.
- Bouman AC, McPherson H, Cheung YW, et al. Clot structure and fibrinolytic potential in patients with post thrombotic syndrome. *Thromb Res* 2016; **137**: 85–91.
- Eijgenraam P, ten Cate H, ten Cate-Hoek AJ. Venous stenting after deep venous thrombosis and antithrombotic therapy: a systematic review. *Rev Vasc Med* 2014; **2**: 88–97.