The post-thrombotic syndrome (PTS) is the main long-term complication in patients with deep vein thrombosis (DVT). Patients with iliofemoral DVT managed conservatively with anticoagulation therapy, and compression stockings have a high risk of PTS. Less than half of these patients regain iliofemoral patency, which is a main predictor for the development of PTS. By restoring venous patency and preserving valvular function, early thrombus removal strategies, including percutaneous catheter-based techniques and surgical thrombectomy, reduce the risk of PTS. Current consensus guidelines recommend percutaneous catheter-based techniques as first-line therapy for selected patients with iliofemoral DVT.

Catheter-directed thrombolysis (CDT) refers to the infusion of a thrombolytic drug directly into the thrombus through a multi-sidehole catheter placed under fluoroscopic guidance and is the most widely used percutaneous treatment for acute DVT. A higher degree of thrombus load reduction after CDT has been associated with a lower risk of PTS and better quality of life. A further development is ultrasound-assisted catheter-directed thrombolysis (USAT), combining CDT with a catheter system that uses high-frequency, low-power ultrasound. According to in vitro studies, ultrasound causes reversible disaggregation of uncrosslinked fibrin fibers, and ultrasound pressure waves increase thrombus penetration of thrombolytic drugs by acoustic streaming.

It remains controversial whether USAT is superior to conventional CDT. The BERN Ultrasound-Assisted Thrombolysis for Iliofemoral Deep Vein Thrombosis Versus Standard Catheter Directed Thrombolysis (BERNUTFUL) trial investigated whether the addition of intravascular ultrasound did not facilitate thrombus resolution.

Background—For patients with acute iliofemoral deep vein thrombosis, it remains unclear whether the addition of intravascular high-frequency, low-power ultrasound energy facilitates the resolution of thrombosis during catheter-directed thrombolysis.

Methods and Results—In a controlled clinical trial, 48 patients (mean age 50±21 years, 52% women) with acute iliofemoral deep vein thrombosis were randomized to receive ultrasound-assisted catheter-directed thrombolysis (N=24) or conventional catheter-directed thrombolysis (N=24). Thrombolysis regimen (20 mg r-tPA over 15 hours) was identical in all patients. The primary efficacy end point was the percentage of thrombus load reduction from baseline to 15 hours according to the length-adjusted thrombus score, obtained from standardized venograms and evaluated by a core laboratory blinded to group assignment. The percentage of thrombus load reduction was 55%±27% in the ultrasound-assisted catheter-directed thrombolysis group and 54%±27% in the conventional catheter-directed thrombolysis group (P=0.91). Adjunctive angioplasty and stenting was performed in 19 (80%) patients and in 20 (83%) patients, respectively (P>0.99). Treatment-related complications occurred in 3 (12%) and 2 (8%) patients, respectively (P>0.99). At 3-month follow-up, primary venous patency was 100% in the ultrasound-assisted catheter-directed thrombolysis group and 96% in the conventional catheter-directed thrombolysis group (P=0.33), and there was no difference in the severity of the post-thrombotic syndrome (mean Villalta score: 3.0±3.9 [range 0–15] versus 1.9±1.9 [range 0–7]; P=0.21), respectively.

Conclusions—In this randomized controlled clinical trial of patients with acute iliofemoral deep vein thrombosis treated with a fixed-dose catheter thrombolysis regimen, the addition of intravascular ultrasound did not facilitate thrombus resolution.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01482273.

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Key Words: catheter ■ stent ■ thrombolysis ■ thrombosis ■ vein
WHAT IS KNOWN

- Catheter-directed thrombolysis reduces the incidence of the post-thrombotic syndrome in patients with iliofemoral deep vein thrombosis.
- A higher degree of thrombus load reduction after catheter-directed thrombolysis is associated with a lower risk of developing the post-thrombotic syndrome.
- Ultrasound-assisted thrombolysis is thought to improve efficacy of catheter-directed thrombolysis.

WHAT THE STUDY ADDS

- A standardized thrombolysis regimen with 20 mg r-tPA over 15 hours for the treatment of patients with iliofemoral deep vein thrombosis is safe and associated with a high degree of thrombus load reduction.
- In patients with acute iliofemoral deep vein thrombosis, high-frequency (2.2 MHz), low-power (0.5 W) ultrasound-assisted thrombolysis does not improve the degree of thrombus load reduction in comparison to conventional catheter-directed thrombolysis.

percentage of thrombus load reduction compared with conventional CDT using a fixed-dose thrombolysis regimen in patients presenting with acute iliofemoral DVT.

Methods

Patients and Study Design

We performed this pilot study as a parallel group, single center, randomized, open-label, controlled trial at a tertiary teaching hospital in Switzerland. From November 2011 to November 2013, consecutive patients referred to the emergency department or directly to the clinic for angiology with the diagnosis of iliofemoral DVT were screened. Inclusion criteria were the presence of symptomatic proximal DVT involving the iliac or common femoral veins (lower extremity thrombosis classification, LET class IB) with symptom duration of <1 month; life expectancy <24 months or chronic nonambulatory state; intracranial or intraspinal bleed, intracranial neoplasm, vascular malformation, aneurysm; severe hypertension on repeated readings (systolic >180 mm Hg or diastolic >105 mm Hg); pregnancy, lactation, or parturition within the previous 30 days; thrombolytic therapy <1 month; life expectancy <24 months or chronic nonambulatory status. Of the 92 patients fulfilling the inclusion criteria, 44 were excluded because of one or several exclusion criteria (Figure 1). Overall, 48 patients were randomly allocated in a 1 to 1 ratio to receive either a fixed-dose ultrasound-assisted catheter-directed thrombolysis (USAT group) or a fixed-dose conventional catheter-directed thrombolysis (CDT group = control group).

The study was approved by the local ethics committee, and all patients provided written informed consent before enrollment.

Anticoagulation Therapy

At initial presentation, patients received an intravenous bolus of unfractionated heparin (UFH) of 80 U per kg body weight. Initial UFH bolus was omitted in patients already treated with UFH, low molecular weight heparin (LMWH), fondaparinux, or oral anticoagulation before study enrollment. For patients who had received LMWH at a weight-adjusted therapeutic dose, the start of the UFH infusion was delayed until 8 to 12 hours after the last LMWH injection. During catheter thrombolysis, UFH infusion was administered through the venous access sheath and adjusted every 6 hours to achieve and maintain an activated partial thromboplastin time corresponding to therapeutic heparin levels (equivalent to 0.3–0.7 IU/mL by factor Xa inhibition). Initiation of vitamin K antagonist or switch from UFH to rivaroxaban, LMWH, or fondaparinux was allowed after a minimum duration of 24 hours UFH infusion. The minimum duration of anticoagulation therapy after catheter thrombolysis was 3 months.

Standardized Procedure of Ultrasound-Assisted and Conventional Catheter-Directed Thrombolysis

In all randomized patients, EkoSonic MACH4 Endovascular System catheters (EKOS Corporation; Bothell, WA) were placed. The catheter system consists of 3 components: the EkoSonic control unit; an intelligent drug delivery catheter (IDDC); and a removable MicroSonic distal suction device (MSD). The catheter system is inserted under ultrasound guidance with the patient in prone position. In case of isolated iliac vein thrombosis, venous access was obtained at the common femoral vein, with the patient in supine position. A 7-French introducer sheath was chosen to enable ascending venography with the EkoSonic IDDC in place. Following ascending venography, a 0.035 inch hydrophilic guidewire (Terumo Corporation, Tokyo, Japan) and a standard angiographic 4-French diagnostic catheter were used to cross the thrombotic occlusion under fluoroscopy, and selective contrast injections through the diagnostic catheter were performed to define the proximal and distal thrombus extension. The angiographic catheter was then exchanged for the EkoSonic IDDC with a treatment zone corresponding to the length of the thrombotic occlusion. Finally, the guidewire was removed and the MSD inserted into the IDDC.

Once the MSD was in place, standardized baseline ascending digital subtraction venography with 2 frames per second was performed via the access sheath using a 20 mL syringe filled with 15 mL iodinated contrast medium and 5 mL normal saline injected rapidly through the introducer sheath. Thereafter, patients were transferred to the intermediate care unit and CDT was initiated. As previously described, a standardized thrombolysis protocol with 20 mg r-tPA over 15 hours (without bolus) was used in both groups, with a continuous infusion of r-tPA (Actilyse, Boehringer Ingelheim, Germany) at a rate of 2 mg/h for the first 5 hours, then reduced to 1 mg/h for the remaining 10 hours, with normal saline coolant at a rate of 35 mL/h. In case of bilateral catheter insertion, 10 mg of r-tPA over 15 hours were administered per catheter. Intermittent pneumatic compression devices were applied on both legs during catheter thrombolysis. In patients randomized to USAT, high-frequency (2.2 MHz),
low-power (0.5 W) intravascular ultrasound was switched on at the control unit, whereas it remained switched off in patients randomized to the CDT group.

At 15 hours, rt-PA infusion and, in the USAT group, delivery of ultrasound energy were stopped. With the MSD still in place, ascending venography using the same standardized procedure as described earlier was performed. In case of an unsatisfactory venographic result after catheter thrombolysis, additional rheolytic thrombectomy using the AngioJet device (MEDRAD, Minneapolis, MN) with or without PowerPulse thrombolysis or continued USAT for additional 10 to 24 hours was performed at the discretion of the operator. The former was used preferably for short thrombotic obstructions. Adjunctive angioplasty and stenting using self-expandable venous stents (for inferior vena cava, sinus-XL from OptiMed [Ettlingen, Germany]; for iliac veins, Zilver Vena from Cook [Bloomington, Ind] and sinus-Venous from OptiMed; for femoral veins, sinus-SuperFlex from OptiMed) was performed in the presence of residual venous stenosis defined as luminal narrowing ≥50% by quantitative angiography or intravascular ultrasound, or absent antegrade flow, or presence of collateral flow at the site of suspected stenosis. Intravascular ultrasound was occasionally used to identify residual venous stenosis in case of equivocal venographic results.

Length-Adjusted Thrombus Score (LAT Score)
The EkoSonic Catheter system with radio-opaque ultrasound elements provided a unique opportunity for the measurement of the exact intravascular thrombus load because the distance between 2 ultrasound elements (defined as ultrasound segment) was known: 1 cm for a treatment zone of 6 to 30 cm; 1.4 cm for a treatment zone of 40 cm; and 1.7 cm for a treatment zone of 50 cm. A score ranging from 0 to 2 points was assigned to each ultrasound segment: 0 points for segments which were completely or near completely free of filling defects; 1 point for segments which were partially thrombosed with evidence of contrast flow; and 2 points for segments which were completely thrombosed without contrast flow or near completely obstructed, that is, contrast flow only around the indwelling catheter. The total LAT score was calculated by the sum of the ultrasound segment scores multiplied by the length of the ultrasound segment in centimeters (Figure 2). Because the aim of this score was to precisely assess the thrombus load of the treated vein segment before and after catheter thrombolysis, only the veins with the indwelling catheter were considered for analysis.

Outcome Measures
The primary efficacy end point of BERNUTIFUL was the percentage of thrombus load reduction from baseline to 15 hours of catheter thrombolysis according to the LAT score. The percentage of thrombus load reduction was calculated according to the following formula: [(LAT score baseline–LAT score after thrombolysis)/LAT score baseline]×100.

Secondary efficacy end points were the need for additional thrombus removal therapy or adjunctive stenting following catheter thrombolysis. At the predefined follow-up visit at 3 months, a standardized clinical examination was performed to obtain the Villalta score, the Clinical Etiologic Anatomic Pathophysiological score, and the disease-specific quality of life with the Chronic Venous Insufficiency Questionnaire.
Primary treatment success was defined according to the Reporting Standards for Endovascular Treatment of Lower Extremity Deep Vein Thrombosis of the Society of Interventional Radiology as successful restoration of antegrade inline flow in the treated vein with elimination of any underlying obstructive lesion at the end of the final endovascular procedure. Primary patency rate was defined as the percentage of patients with primary treatment success and without the occurrence of either thrombosis of the treated segment or a reintervention to maintain patency of the treated segment, irrespective of any interval therapies. Duplex ultrasound studies using a Siemens S200 (Siemens AG, Medical Solutions, Zurich, Switzerland) were performed at follow-up visits to assess venous patency as previously described.

Early rethrombosis was defined as loss of primary-assisted patency within 30 days after the intervention.

Safety end points were the incidence of bleeding complications and the recurrence of thromboembolic complications during follow-up. Bleeding complications were classified according to the International Society on Thrombosis and Haemostasis.

Randomization and Blinding
A simple randomization sequence without stratification using random block sizes of 4 and 6 was created using Stata 9.1 (StataCorp, College Station, TX) statistical software with a 1:1 allocation for USAT and conventional CDT. Consecutively numbered, sealed envelopes containing the group allocation were stored at the Venous Thromboembolism Research Group office and accessible only to the principal and coinvestigators as well as the dedicated study nurses.

For the primary outcome measure, venograms were assessed by an independent core laboratory (coreLab, Bad Krozingen GmbH, Bad Krozingen, Germany) which was blinded to group assignment. All venograms were also assessed by a coinvestigator (D. Spirk) who was also blinded to the group assignment and assessed the venograms twice with 22 weeks between the readings.

Statistical Analysis

Sample Size Calculation
Sample size assumptions were based on the retrospective analysis of 16 patients previously treated with the EkoSonic Endovascular System by our standardized thrombolysis protocol. The mean percentage of thrombus load reduction in these patients was 64.5% with a standard deviation of ±26.8%. According to in vitro experiments, high-frequency ultrasound significantly increased the thrombolytic effect of r-PA and its uptake into the thrombus by ≥50% in comparison to thrombolysis without ultrasound energy. We therefore assumed that CDT with ultrasound enhancement (EKOS group) should be ≥50% more effective than without ultrasound enhancement (CDT control group) and calculated an expected relative mean thrombus reduction of 43% in the CDT control group. Based on these assumptions, the estimated sample size was 24 patients per study group with a power of 80% and a 2-sided alpha set at 0.05.

Validation of the LAT Score
We calculated the interclass correlation coefficient (ICC) to estimate the inter-rater reliability between the core laboratory and the investigator, as well as the intra-rater reliability (repeated readings by the investigator) for the total LAT scores and the percentage of thrombus reduction based on the LAT scores. We classified inter-rater and intra-rater reliability based on the magnitude of the ICC as follows: <0.40, poor to fair; 0.40 to 0.59, moderate; 0.60 to 0.79, substantial; and 0.80 to 1.0, almost perfect. For the primary end point, only the readings by the core laboratory were considered. Bland–Altman plots were also used to assess the agreement of total LAT scores and the percentage of thrombus reduction between the core laboratory and the investigator.

Data are presented as mean±standard deviations for continuous variables. Categorical variables are presented as absolute numbers and percentages with 95% confidence intervals (95% CI) where appropriate. The primary end point analysis between the study groups was performed using an unpaired \( t \) test. Other \( P \) values for differences between the study groups were calculated from unpaired \( t \)-tests or Wilcoxon rank-sum test where appropriate for continuous variables and Fisher exact test for categorical variables. Univariable regression analysis was performed to investigate whether symptom duration in days and r-PA dose per treatment zone in centimeter were correlates of the primary end point. All statistical analyses were performed using STATA version 9.1 (StataCorp, College Station, TX).

Results

Study Population
Overall, mean age was 50±21 years and 25 (52%) were women (Table). DVT was confined to the left leg in 33
(69%) patients, to the right leg in 12 (25%), and bilateral in 3 (6%) patients. All patients had a thrombotic occlusion of the iliac veins or the common femoral vein, with distal extension to the femoro-popliteal deep veins in 32 (67%) cases, with proximal extension into the inferior vena cava in 2 (4%) cases and both proximal and distal extension in 6 (13%) cases (Table).

Before CDT, 14 (58%) patients in the USAT group and 15 (63%) in the CDT group were pretreated with LMWH, 4 (17%) patients in the USAT group and 9 (38%) in the CDT group were treated with UFH, 4 (17%) patients in the USAT group and 5 (21%) in the CDT group were treated with vitamin K antagonist, and 3 (13%) patient in the USAT group and 2 (8%) in the CDT group were treated with rivaroxaban.

### Treatment Details

Venous access was obtained in the popliteal vein in all but 2 patients where the common femoral vein was used. In 3 (6%) patients, the catheter system was inserted bilaterally, with 2 patients in the USAT group and 1 patient in the CDT group, respectively ($P>0.99$). The mean treatment zone length of the catheter system in the USAT group was 41±11 cm versus 44±8 cm in the CDT group ($P=0.25$). The mean r-tPA dose per treatment zone centimeter was 0.56±0.27 mg/cm in the USAT group and 0.47±0.11 mg/cm in the CDT group ($P=0.26$). Primary treatment success was obtained in all but one patient in the USAT group ($P>0.99$).

### Intra- and Inter-Rater Reliability of the Length-Adjusted Thrombus Score

The intrarater reliability for total LAT score (ICC=0.99) and for the percentage of thrombolysis according to LAT score reduction (ICC=0.98) were near perfect. The inter-rater reliability between the core laboratory and the investigator for total LAT score (ICC=0.98) and for the percentage of thrombolysis according to the LAT score reduction (ICC=0.92)
were near perfect. For the Bland–Altman inter-rater agreement plots, the mean differences in the total LAT score and the percentage of thrombolysis between the core laboratory and the investigator were 0.50±5.4 and 2.0±10.1%, respectively (Figure 3).

Primary Outcome Analysis
The baseline thrombus load according to the LAT score was 59±26 in the USAT group versus 58±22 in the CDT group (P=0.86). After 15 hours of CDT, LAT score was significantly reduced in both groups (P<0.01 for both) without difference between the USAT group (27±24) and the CDT group (25±16, P=0.68). The percentage of thrombus load reduction from baseline to 15 hours was 55±27% in the USAT group and 54±27% in the CDT group (P=0.91). In univariable regression analysis, neither symptom duration in days (P=0.14) nor the r-tPA dose per treatment zone in centimeter (P=0.31) was correlates of the percentage of thrombus load reduction. A thrombus load reduction of ≥50% was obtained in 14 (58%) patients in the USAT group and in 15 (63%) patients in the CDT group (P=0.99).

Adjunctive Interventional Therapies
Adjunctive catheter-based thrombus removal therapy was performed in 7 (29%) patients in the USAT group (5 patients with AngioJet thrombectomy and 2 patients with prolonged USAT for a mean duration of 14±8 hours and an additional r-tPA dose of 18±3 mg) and 11 (46%; P=0.37) patients in the CDT group (7 patients with AngioJet thrombectomy, 2 with prolonged USAT and AngioJet thrombectomy, and 4 with prolonged USAT for a mean duration of 21±2 hours and an additional r-tPA dose of 28±11 mg).

Adjunctive angioplasty and stenting was performed in 19 (80%) patients from the USAT group and in 20 (83%) patients from the CDT group (P=0.99), with a mean of 1.3±1.0 (range 1–3) stents in the USAT group and 1.4±1.1 (range 1–4) stents in the CDT group (P=0.67).

Complications
In total, treatment-related complications occurred in 5 (10.5%; 95% CI, 3.5%–22.7%) patients: 3 (12.5%) in the USAT group and 2 (8.3%) in the CDT group (P=0.99). In the USAT group, 1 major bleeding (4.2%; 95% CI, 0.1%–21.1%) in the form of a retroperitoneal hematoma requiring 4 U of packed blood cells occurred, with no major bleedings in the CDT group (P>0.99). Minor bleeding complications occurred in 3 (6.3%; 95% CI, 1.3%–17.2%) patients, with 1 (4.2%, an access-related hematoma) in the USAT group and 2 (8.3%, an access-related hematoma and a transient asymptomatic hemoglobinuria after additional AngioJet thrombectomy) in the CDT group (P=0.99).

Clinical Outcomes at 3-Month Follow-Up
Mean hospital duration in the USAT group was 2.7±1.4 days versus 2.8±1.3 days in the CDT group (P=0.83). At 3 months, 1 patient in each group did not appear to the follow-up visit, and no bleeding complications were reported. Early rethrombosis at day one occurred in one patient (4.2%; 95% CI, 0.1%–21.1%) in the CDT group for whom venous patency was successfully re-established with additional USAT. Primary patency at 3 months was 100% (95% CI, 85%–100%) in the USAT group and 96% (95% CI, 79%–100%; P=0.33) in the CDT group, secondary patency was 100% in both groups. In one patient of the USAT group, a subsegmental low-risk pulmonary embolism was diagnosed at 1 month.

At 3 months, mean Villalta score (3.0±3.9 [range 0–15] versus 1.9±1.9 [range 0–7]; P=0.21), mean revised venous clinical severity score (3.8±2.3 versus 3.4±1.9; P=0.63), and Clinical Etiologic Anatomic Pathophysiological class (1.2±1.9 versus 1.1±1.2 points; P=0.91) were similar in the USAT and the CDT group, respectively. Disease-specific quality of life according to the Chronic Venous Insufficiency Questionnaire was also similar in both study groups (28±11.6 in the USAT group versus 26.2±7.5 in the CDT group; P=0.55).

Discussion
In the present randomized controlled clinical trial of patients with acute iliofemoral DVT treated with a fixed-dose catheter thrombolysis regimen, the addition of intravascular ultrasound energy did not enhance thrombus resolution. Furthermore, no effect was found for any of the secondary outcomes, including the use of adjunctive thrombus removal procedures, stent implantation, patency rates, and the occurrence of the PTS at 3 months. We therefore conclude that the in vitro effects of high-frequency (2.2 MHz), low-power (0.5 W) ultrasound, that is, fibrin separation and acoustic streaming, cannot be translated to patients with acute iliofemoral DVT. Given the higher costs

Figure 3. Bland–Altman inter-rater agreement plot of total LAT score (A) and percentage of thrombolysis (B) assessed by investigators and core laboratory. LAT score indicates lengths-adjusted thrombus score; and SD, standard deviation.
of the USAT catheter system compared with conventional CDT multisidehole-catheters, our data question the usefulness and particularly the cost-effectiveness of adding intravascular ultrasound for the treatment of acute iliofemoral DVT.

In a retrospective single center study including 10 patients with lower extremity DVT, Motarjeme found a higher rate of complete thrombolysis and a shorter treatment time (mean 21.2 hours; range 6–43) with USAT compared with National Venous Registry as historical CDT control group.\(^3^5\) In another retrospective multicentre study on USAT with various thrombolytic drugs by Parikh et al including 32 patients with lower extremity DVT, median treatment time was up to 41% shorter and total thrombolytic dose up to 68% lower in the subgroup of patients treated with one of the recombinant plasminogen activators than in a contemporary control group treated by conventional CDT.\(^1^6^,^3^3\) More recently, Baker et al published a retrospective analysis of their single center experience in the treatment of patients with iliofemoral DVT, of whom 19 were treated with conventional CDT and 64 with USAT using various thrombolytic drugs.\(^1^7\) Baseline characteristics including DVT extension and duration of symptoms were similar in both groups. They did not find any difference in the treatment duration, the total thrombolytic drug dose, the percentage of thrombus load reduction, or the rate of bleeding complications between the 2 treatment modalities.\(^1^7\) In the aforementioned studies, thrombolytic drug regimens were highly variable and treatment duration was guided by visual assessment of venous flow and thrombus resolution during repetitive venograms. In contrast to previous studies, we used a standardized fixed-dose treatment regimen, which allowed to rigorously assess the value of adding intravascular ultrasound energy to conventional CDT.

Despite encouraging results from in vitro and animal studies,\(^3^4\) it remains unclear why adding ultrasound energy did not result in a better thrombolysis result in our study. Thrombus age is highly variable in patients with acute DVT and might not be comparable to thrombosis generated in vitro or in vivo experiments. Although the ultrasound frequency of 2.2 MHz is certainly appropriate to penetrate thrombus, the low power of 0.5 Watt per ultrasound element might be insufficient to obtain a substantial effect on thrombus resolution.\(^1^2\) Further studies are required to show whether an increase in ultrasound energy may enhance thrombolysis without causing harmful effects, including damage to veins and surrounding tissue from cavitation. It also remains unclear whether an increase in ultrasound energy is feasible at all because end of life of individual ultrasound elements frequently occurs beyond 24 hours with delivery of low-power energy.

Our study population was confined to patients with symptom duration of <2 weeks.\(^1^9\) We have previously shown that the percentage of thrombus load reduction was lower in patients with subacute or acute-on-chronic DVT, using the same standardized USAT treatment regimen as in this study.\(^2^0\) In contrast, Dumantepe et al reported a percentage of thrombus load reduction of ≥50% in 11 out of 12 chronic DVT patients after a mean USAT duration of 26.2±7 hours and a mean r-tPA dose of 42±8 mg (mean symptom duration 92 days; range 34–183).\(^3^5\) It remains to be shown whether USAT has any advantage over conventional CDT in patients with longer symptom duration.

Currently available venographic scoring systems are relatively imprecise to measure thrombus load, particularly for the iliac veins.\(^3^6\) A sensitive, standardized, and reliable thrombus score is required to precisely quantify changes in thrombus load pre- and post-CDT.\(^2^9\) We therefore developed and validated the lengths-adjusted thrombus score (LAT score). The intra- and inter-rater reliability of the LAT score between the core laboratory and the investigator was high both for the measurement of the thrombus load as well as for the percentage of thrombus load reduction, confirming that this score might be useful for future studies. However, as for all available venographic scoring systems, the LAT score does not account for the diameter of the vein segments.

**Limitations**

Our study results are limited to patients with acute iliofemoral DVT and cannot be extrapolated to other vascular beds, including the pulmonary\(^3^7\) or peripheral arteries. A randomized controlled trial comparing USAT with conventional CDT in patients with thrombosed infrapopliteal native arteries or bypass grafts (ISRCTN72676102) is ongoing.\(^3^8\) Based on in vitro data, BERNUTIFUL was powered to show superiority of USAT over conventional CDT with a relative 50% increase in the reduction in thrombus load, and therefore, a relatively small sample size of 48 patients was required. We cannot rule out that a larger sample size would have been more adequate to detect a smaller effect size. However, we think that this is rather unlikely because the reduction in thrombus load was almost identical in both treatment groups. The dose and duration of the standardized thrombolysis protocol used in our study was adopted from a recent randomized trial of patients with intermediate-risk pulmonary embolism where this regimen significantly improved right ventricular enlargement at 24 hours in comparison to treatment with heparin alone, without any major bleeding complications.\(^3^7\) In a recent nonrandomized study of patients with iliofemoral DVT, this treatment regimen was effective and safe in restoring venous patency.\(^2^4\) Finally, the study was not powered to detect a difference in rates of adjunctive catheter-based thrombus removal after our fixed-dose thrombolysis regimen, and it remains unclear whether a larger sample size would have resulted in a significant difference in favor of USAT.

In summary, the BERNUTIFUL trial is the first randomized trial to test the value of adding intravascular ultrasound energy to conventional CDT in patients with acute iliofemoral DVT and proved that high-frequency, low-energy ultrasound did not change the degree of thrombus load reduction.

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