Fixed low-dose ultrasound-assisted catheter-directed thrombolysis followed by routine stenting of residual stenosis for acute ilio-femoral deep-vein thrombosis

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Summary
Patients with ilio-femoral deep-vein thrombosis (DVT) are at high risk of developing the post-thrombotic syndrome (PTS). In comparison to anticoagulation therapy alone, extended venography-guided catheter-directed thrombolysis without routine stenting of venous stenosis in patients with ilio-femoral DVT is associated with an increased risk of bleeding and a moderate reduction of PTS. We performed a prospective single-centre study to investigate safety, patency and incidence of PTS in patients with acute ilio-femoral DVT treated with fixed-dose ultrasound-assisted catheter-directed thrombolysis (USAT; 20 mg rt-PA during 15 hours) followed by routing stenting of venous stenosis, defined as residual luminal narrowing ≥50%, absent antegrade flow, or presence of collateral flow at the site of suspected stenosis. A total of 87 patients (age 46 ± 21 years, 60% women) were included. At 15 hours, thrombolysis success ≥50% was achieved in 67 (77%) patients. Venous stenting (mean 1.9 ± 1.3 stents) was performed in 70 (80%) patients, with the common iliac vein as the most frequent stenting site (83%). One major (1%; 95% CI, 0–6%) and 6 minor bleedings (7%; 95%CI, 3–14%) occurred. Primary and secondary patency rates at 1 year were 87% (95% CI, 74–94%) and 96% (95% CI, 88–99%), respectively. At three months, 88% (95% CI, 78–94%) of patients were free from PTS according to the Villalta scale, with a similar rate at one year (94%, 95% CI, 81–99%). In conclusion, a fixed-dose USAT regimen followed by routine stenting of underlying venous stenosis in patients with ilio-femoral DVT was associated with a low bleeding rate, high patency rates, and a low incidence of PTS.

Keywords
Haemorrhage, mechanical thrombolysis, post-thrombotic syndrome, vascular patency, venous thrombosis

Introduction
Approximately half of patients with acute deep-vein thrombosis of the common femoral or iliac veins (ilio-femoral DVT) develop clinical signs or symptoms of the post-thrombotic syndrome (PTS) whereas the risk is substantially lower in patients without involvement of these venous segments (1). Despite standard anticoagulation therapy, less than half of patients with ilio-femoral DVT regain venous patency (2). Residual venous obstruction and valve insufficiency are the two main pathophysiological mechanisms of the PTS (3, 4).

The main goals of early thrombus removal are to alleviate acute DVT signs and symptoms and to prevent PTS by restoring venous patency and preserve valve function (5, 6). Early thrombus removal strategies include systemic thrombolysis, surgical thrombectomy and catheter-based therapies (5). Current international consensus guidelines recommend catheter-directed thrombolysis (CDT) as first-line treatment for selected patients with acute ilio-femoral DVT (5-8).

Ultrasound-assisted catheter-directed thrombolysis (USAT) combines conventional CDT with a catheter system that uses high-frequency, low-power ultrasound (9). While ultrasound energy itself cannot dissolve thrombus, it causes reversible disaggregation of uncrosslinked fibrin fibers which increases the thrombus permeability for thrombolytic drugs. In addition, the penetration of thrombolytic drugs into the thrombus is enhanced by ultrasound pressure waves (10, 11). The dose and duration of the thrombolytic infusion is usually guided by visual assessment of venous flow and thrombus resolution during repetitive venograms. Venogram-guided CDT often exceeds 48 hours (h) and may be associated with an increased risk of bleeding and infections (12-16). Moreover, the value of repetitive venograms for guiding CDT dose and duration is debatable, because the majority of patients with ilio-femoral DVT have an underlying venous stenosis compromising venous flow (14, 17). To date, no standardised fixed-dose CDT regimen exists for the treatment of acute ilio-femoral DVT. Aim of the present study was to assess venous patency and clinical outcomes in patients with acute ilio-femoral DVT with or without
proximal or distal thrombus extension treated with a fixed USAT regimen followed by routine stenting of residual venous stenosis.

**Methods**

**Study design and patients**

We performed a prospective data collection on consecutive patients with acute ilio-femoral DVT treated from January 2010 to October 2013 with USAT followed by routine stenting of underlying venous stenosis after a standardised treatment protocol was established in our institution. All follow-up assessments were part of our routine institutional protocol. All patients signed informed consent for the procedure and the anonymous data collection and formal ethics committee approval was waived. Patients were eligible if they had leg pain or swelling ≤ 28 days and thrombus in the iliac or common femoral vein (lower extremity thrombosis classification, LET class III) (18), or in the inferior vena cava (LET class IV) objectively confirmed by duplex sonography or contrast-enhanced computed tomography (CT), irrespective if the pathogenesis was supposed to be ascending or descending thrombosis. Patients with femoro-popliteal DVT without involvement of the common femoral or iliac veins were not treated. During the study period, 11 patients who presented to our hospital with ilio-femoral DVT were not treated with ultrasound-assisted thrombolysis: seven patients were treated conservatively with anticoagulation therapy alone due to high risk of bleeding, five patients who had leg pain or swelling ≤ 28 days and thrombus in the iliac or common femoral vein (lower extremity thrombosis classification, LET class III) (18), or in the inferior vena cava (LET class IV) objectively confirmed by duplex sonography or contrast-enhanced computed tomography (CT), irrespective if the pathogenesis was supposed to be ascending or descending thrombosis. Patients with femoro-popliteal DVT without involvement of the common femoral or iliac veins were not treated.

**Acute DVT** was defined according to the "Reporting Standards for Endovascular Treatment of Lower Extremity Deep Vein Thrombosis" of the Society of Interventional Radiology as thrombosis for which symptoms were present for 14 days or less; **subacute DVT** as thrombosis for which symptoms were present for 15 to 28 days; and **acute-on-chronic DVT** as thrombosis that has both chronic (≥ 28 days) and acute (≤ 14 days) components, as indicated by symptom history (19). **DVT** was classified as **provoked** in the presence of recent immobilitation (bed ridden for > 72 h, plaster cast, or long-distance travel of > 6 h), postoperative, trauma, hormone therapy (oral contraceptives, postmenopausal hormonal replacement, tamoxifen use), active cancer, pregnancy or postpartal period, or after acute medical illness (e.g. pneumonia, congestive heart failure); all other forms of DVT were classified as **unprovoked DVT** (20).

**Anticoagulation therapy**

Patients received an intravenous bolus of unfractionated heparin (UFH) of 80 units per kg body weight at initial presentation. For patients already receiving UFH, fondaparinux, oral anticoagulation or low-molecular-weight heparin (LMWH) before USAT, the initial UFH bolus was omitted. Patients who had received LMWH at a weight-adjusted therapeutic dose, the start of the UFH infusion was delayed until 8–12 h after the last LMWH injection. The UFH infusion was administered through the venous access sheath and adjusted every six hours in order to achieve and maintain aPTT corresponding to therapeutic heparin levels (equivalent to 0.3 to 0.7 IU/ml by factor Xa inhibition). The minimum duration of the UFH infusion was 24 h. Initiation of vitamin K antagonist or switch from UFH to rivaroxaban, LMWH, or fondaparinux was allowed thereafter. The minimum duration of anticoagulation therapy was three months (7). We did not prescribe any platelet aggregation inhibitors after venous stenting unless indicated for other cardiovascular diseases.

**Standardised procedure of ultrasound-assisted catheter-directed thrombolysis**

USAT was performed using the EkoSonic MACH4 Endovascular Systems (EKOS Corporation; Bothell, WA, USA). The EkoSonic Endovascular System consists of three components: the EkoSonic control unit; an Intelligent Drug Delivery Catheter (IDDC); and a removable MicroSonic Device (MSD) containing multiple small ultrasound transducers distributed along the treatment zone (12 to 50 cm) (21). The MSD is placed within the central lumen of the IDDC to deliver high-frequency (2.2 GHz) and low-energy (0.5 Watt per transducer) ultrasound. The EkoSonic control unit provides power to the system and continuously adjusts the administered ultrasound energy according to the temperature at the treatment zone measured by the thermocouples within the IDDC. The insertion of the catheter system was performed at the angiographic suite with continuous haemodynamic monitoring. In 78 (90%) patients, venous access was obtained at the popliteal vein of the affected leg, regardless if thrombosed or patent, under ultrasound guidance with the patient in prone position using a 7-French introducer sheath. In nine (10%) patients with 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. Once the guidewire crossed the thrombotic occlusion, the angiographic catheter was 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. After catheter placement, patients were transferred to the intermediate care unit for monitoring. A continuous infusion of rt-PA at 2 mg/h and of saline coolant at 35 ml/h per catheter, and intravascular ultrasound delivery were initiated once the patient arrived in the intermediate care unit. After 5 h of treatment, the infusion rate of rt-PA was reduced to 1 mg/h per catheter for the remaining 10 h. The suggested total rt-PA dose was 20 mg. Because no standardised thrombolysis regimen exists for the treatment of DVT, we used the thrombolysis protocol (20 mg rt-PA over 15 h) from the ULTIMA Trial, a randomised controlled trial comparing standard therapy with intravenous heparin versus additional USAT for patients with submassive pulmonary embol-
mal or no thrombolysis (grade I, <50% thrombus removal) using removal), partial (grade II, 50–95% of thrombus removal) and mini-
tative score (25) and the revised venous clinical severity score
classification score (25) and the revised venous clinical severity score
mild if the Villalta scale was 5–9 points, moderate if the Villalta scale
compared to the baseline venogram, irrespective of any interval therapy to restore or maintain flow within the treated segment. Secondary patency rate was defined as the percent-age of patients with primary treatment success and without the occurrence of permanent loss of flow in the treated segment, irrespective of any interval therapies. Early rethrombosis referred to loss of primary assisted patency within 30 days after the intervention, late rethrombosis referred to loss of primary assisted patency more than 30 days after the intervention (19). Primary sustained clinical success was defined as the absence of PTS (Villalta score 0–4 points) without the need for repeated interval therapy assessed at the latest follow-up visit, while secondary sustained clinical success allowed the need for interval therapy (28).

Bleding complications were classified according to the Interna-tional Society on Thrombosis and Haemostasis, where major bleedings are either 1) fatal bleeding, 2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or 3) bleeding causing a drop in haemoglobin level of ≥ 2 g/dl, or leading to transfusion of two or more units of whole blood or red cells (29). Minor bleedings are less severe bleedings not included in the definition of major bleedings (29).

Statistical analysis

Data are presented as means ± standard deviations or absolute numbers and percentages for continuous and categorical variables, respectively. Categorical outcomes are presented as percentage with 95% confidence intervals (95% CI). Patency and clinical suc-

Results

Study population

A total of 87 patients with a mean age of 46 ± 21 years (range 16 to 89 years) were treated (Table 1). All patients presented with leg swelling and all but one (99%) with pain in the leg or groin. Symptom duration was acute in 57 (66%), subacute in nine (10%) and acute-on-chronic in 21 (24%) patients. DVT was provoked in 68 (78%) and unprovoked in 19 (22%) patients (Table 1). DVT was confined to the left leg in 58 (67%) cases, to the right leg in 21

Follow-up

Routine follow-up visits were performed at the vascular outpatient clinic by vascular specialists at three, six and 12 months, with yearly visits thereafter. At each visit, signs and symptoms of the PTS were assessed using the Villalta scale, consisting of five patient-rated leg symptoms (pain, cramps, heaviness, paraesthesia, and pruritus) and six physician-rated clinical signs (pretibial oede-ma, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression) (23, 24). For each item, a score of 0 (none) to 3 (severe) points was given and points were summed into a total score (range 0 to 33). PTS was defined by a total score of ≥ 5 points or the presence of a venous ulcer, and classified as mild if the Villalta scale was 5–9 points, moderate if the Villalta scale was 10–14 points, or severe in case of ≥ 15 points or the presence of a venous ulcer (23). At each visit, we also obtained the Clinical Etiological Anatomical Pathophysiological (CEAP) classification score (25) and the revised venous clinical severity score (26).

Duplex ultrasound studies using a Siemens S 2000 (Siemens AG, Medical Solutions, Zurich, Switzerland) were performed at each visit. With the subject in supine position, venous patency of the inferior vena cava, the common and external iliac, the com-
mon femoral, the femoral and the popliteal veins were examined. Patency was defined as spontaneous orthograde venous flow with respiratory variability in the treated vein segment.

Endpoints and definitions

According to the "Reporting Standards for Endovascular Treat-
ment of Lower Extremity Deep Vein Thrombosis" of the Society of Interventional Radiology (19), primary treatment success was de-

Primary patency rate

was defined as the percentage of patients with primary treatment success and was assessed after 15 h of USAT in comparison to the baseline venogram, prior to additional 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 re-intervention to maintain patency of the treated segment. Primary assisted patency rate was defined as the percentage of patients with primary treatment success and without the occurrence of permanent loss of flow in the treated segment, irrespective of any interval therapies. Early rethrombosis referred to loss of primary assisted patency within 30 days after the intervention, late rethrombosis referred to loss of primary assisted patency more than 30 days after the intervention (19). Primary sustained clinical success was defined as the absence of PTS (Villalta score 0–4 points) without the need for repeated interval therapy assessed at the latest follow-up visit, while secondary sustained clinical success allowed the need for interval therapy (28).

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cases, with proximal extension into the inferior vena cava in 10 (11%) cases (▶ Table 1).

Treatment details and success

In eight (9%) patients, USAT devices were inserted bilaterally, the remainder underwent unilateral catheter placement. Mean treatment duration of USAT was 15.1 ± 0.8 h with a total rt-PA dose of 20.0 ± 3.0 mg. The degree of thrombolysis after 15 h of USAT was grade III in 14 (16%; 95% CI, 9–26%) patients, and grade II in 53 (61%; 95% CI, 50–71%) patients. In 18 (21%; 95% CI, 13–31%) patients thrombus removal was less than 50% and in two (2%; 95% CI, 0–8%) no thrombolysis was observed (grade I). The rate of grade II or III thrombolysis was significantly higher in patients with acute DVT (89%; 95% CI, 78–96%) than in patients with subacute (56%; 95% CI, 21–86%) or acute-on-chronic DVT (57%; 95% CI, 34–78%) (p = 0.002). Prolonged USAT for residual thrombosis was performed in six (7%) patients for a mean additional duration of 18.7 ± 5.5 h (range 8 to 24) and a total rt-PA dose of 21.7 ± 10.1 mg (range 10 to 40 mg). Overall, primary treatment success was obtained in 85 (98%; 95% CI, 92–100%) patients. The remaining two patients both had insufficient thrombolysis results, and no further revascularisation therapy was attempted. Mean duration of hospital stay was 2.8 ± 1.3 days (range 1 to 24).

Adjunctive angioplasty and stenting was performed in 70 (80%) patients, with similar rates in patients with acute, subacute and acute-on-chronic symptom onset (80% vs 89% vs 76%; p = 0.72). The stenting rate did not differ in patients with grade II or III thrombolysis compared to patients with grade I lysis (81% vs 79%; p = 0.85). In patients treated with stenting, a mean of 1.9 ± 1.3 (range 1 to 7) stents were used, and stenting of the inferior vena cava was performed in four (6%), of the common iliac vein in 58 (83%), of the external iliac vein in 50 (71%), of the common femoral vein in 21 (30%) and the proximal femoral vein in five (7%) patients.

Prior to USAT, 31 (36%) patients were pre-treated with LWMH, 12 (14%) patients with UFH, three (3%) patients with fondaparinux, six (7%) patients with vitamin K antagonists, and two (2%) patients with rivaroxaban. Oral anticoagulation therapy was initiated the day after the procedure and performed with rivaroxaban (15 mg twice daily for three weeks followed by 20 mg per day) or with vitamin K antagonists (target INR 2–3). In cancer patients, UFH was switched to LMWH. The minimum duration of anticoagulation therapy was three months. In the 72 patients with a minimal follow-up duration of three months, anticoagulation therapy was stopped after a treatment duration of three months in 22 (31%) patients, after six months in 11 (15%) patients, and after 12 months in eight (11%) patients. In 31 (43%) patients, indefinite-duration anticoagulation therapy was established. In 10 (11%) patients pre-treated with platelet aggregation inhibitors prescribed for other cardiovascular diseases, these drugs were continued during USAT and throughout the follow-up period.

Table 1: Patient characteristics, comorbidities, venous thromboembolism risk factors and thrombus extension (n = 87).

<table>
<thead>
<tr>
<th>Demographics</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>46.3 ± 20.8</td>
</tr>
<tr>
<td>Women</td>
<td>52 (60)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 5.0</td>
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<table>
<thead>
<tr>
<th>Risk factors and comorbidities</th>
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<tbody>
<tr>
<td>Immobilisation* (&lt; 3 months)</td>
<td>34 (39)</td>
</tr>
<tr>
<td>Hormone therapy **</td>
<td>27 (31)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Recent hospitalisation (&lt; 3 months)</td>
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<tr>
<td>Arterial hypertension</td>
<td>21 (24)</td>
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<tr>
<td>Obesity</td>
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<td>Known previous VTE</td>
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<td>Varicose veins (including reticular veins)</td>
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<tr>
<td>Severe infection or sepsis (&lt; 3 months)</td>
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<tr>
<td>Dyslipidaemia</td>
<td>10 (11)</td>
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<tr>
<td>Recent surgery (&lt; 4 weeks)</td>
<td>9 (10)</td>
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<tr>
<td>Chronic pulmonary disease</td>
<td>8 (9)</td>
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<td>Peripheral artery disease</td>
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<tr>
<td>Known hereditary thrombophilia</td>
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<td>Diabetes</td>
<td>7 (8)</td>
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<td>Active cancer or treatment (&lt; 6 months)</td>
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<td>Recent trauma (&lt; 4 weeks)</td>
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<td>Pregnancy or postpartum</td>
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<td>Chronic renal failure</td>
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<td>Coronary artery disease</td>
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<td>Acute rheumatic disease (&lt; 3 months)</td>
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</tr>
<tr>
<td>Congestive heart failure</td>
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<td>Cerebrovascular artery disease</td>
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<table>
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<tr>
<th>Thrombus extension/involved vein segments</th>
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<tr>
<td>Inferior vena cava</td>
<td>13 (15)</td>
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<tr>
<td>Common iliac vein</td>
<td>67 (77)</td>
</tr>
<tr>
<td>External iliac vein</td>
<td>83 (95)</td>
</tr>
<tr>
<td>Common femoral vein</td>
<td>79 (91)</td>
</tr>
<tr>
<td>Femoral vein</td>
<td>67 (77)</td>
</tr>
<tr>
<td>Popliteal vein</td>
<td>30 (34)</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD or number (%). * defined as bed ridden for > 72h, plaster cast, or long-distance travel of > 6h; ** oral contraceptive pill, hormone replacement therapy or Tamoxifen use.
Complications

Treatment-related complications occurred in 10 (11%; 95% CI, 6-20%) patients. No symptomatic pulmonary embolism was noted during hospital stay. One major bleeding (1%; 95% CI, 0-6%) occurred (retroperitoneal hematoma requiring 4 units of packed blood cells, most likely due to a wire perforation). Minor bleedings occurred in six (7%; 95% CI, 3-14%) patients, four of which had access-related haematoma. An access-related popliteal haematoma was associated with a transient foot drop in one patient. Two patients had transient asymptomatic haemoglobinuria. Two patients had transient fever of unknown origin with negative blood cultures. There was no local infection at the puncture site. One patient with severe phlegmasia coerulea dolens due to extensive inferior vena cava and bilateral iliac vein thrombosis required fasciotomy of the left lower leg because of compartment syndrome.

Patency rates and clinical outcome

Mean follow-up duration was 273 ± 201 days (range: 1 to 819 days). Early rethrombosis within five days occurred in five (6%; 95% CI, 2-13%) patients. In three of these patients, re-intervention was attempted, and venous patency was successfully re-established with USAT and additional stenting. Late rethrombosis occurred in three (3%; 95% CI, 1-10%) patients of whom two underwent successful re-intervention: one patient with hypoplasia of the inferior vena cava had rethrombosis after 111 days which was successfully treated with USAT and stent prolongation, and one patient had rethrombosis after 333 days due to stent kinking which was successfully treated with catheter thrombectomy and additional stent placement. Two additional symptomatic venous thromboembolic events occurred during follow up; in one patient subsegmental pulmonary embolism was diagnosed 34 days after USAT, and one patient had a recurrent DVT at another venous site at six months.

Primary patency, primary assisted patency and secondary patency at one year were 87% (95% CI, 74-94%), 90% (95% CI, 78-95%), and 96% (95% CI, 88–99%), respectively (Figure 1). In the univariate Cox regression analysis, acute-on-chronic symptom onset (hazard ratio [HR] 4.6, 95% CI, 1.2-17.2; p = 0.024, vs acute or subacute presentation) and stenting of the femoral vein (HR 5.3, 95% CI, 1.1–25.7; p = 0.039, vs other stenting sites) were associated with impaired primary patency.

At three months, 88% (95% CI, 78–94%) of patients were free from PTS according to the Villalta scale, with similar rates after six months (92%; 95% CI, 82-98%) and one year (94%, 95% CI, 81-99%) (Table 2). Overall, primary and secondary sustained clinical success rates at one year were 78% (95% CI, 64-88%) and 90% (95% CI, 80–96%), respectively. In the univariate Cox regression analysis, increasing age was the only factor associated with PTS (HR 1.06, 95% CI, 1.01-1.11, p = 0.020).

Discussion

In the present study of patients with acute ilio-femoral DVT, fixed low-dose ultrasound-assisted catheter-directed thrombolysis followed by routine stenting of underlying venous obstruction was associated with high primary and secondary patency rates and a low incidence of PTS. The combination of fixed low-dose USAT and routine stenting allows to keep total treatment time and hospital stay short.
In the Catheter-directed Venous Thrombolysis (CaVenT) trial, the largest randomised controlled trial including 209 patients with acute ilio-femoral DVT, the PTS rate at 24 months was lower in the CDT group than in the group treated with anticoagulation alone (41.1% vs 55.6%; p = 0.047) (12). The mean treatment duration in the CaVenT trial was nearly four times longer than in our study (2.4 ± 1.1 days vs 15.1 ± 0.8 h) with a higher total rt-PA dose (maximum dose of 20 mg rt-PA per 24 h in the CaVenT trial vs 20 mg in total in our study). This might explain the slightly higher major bleeding rate in the CaVenT trial (3% vs 1% in our study). The only major bleeding complication from a wire perforation in our series could potentially have been prevented by the use of a non-hydrophilic guide wire. In contrast, the occurrence of PTS was lower in our study with a cumulative incidence after 12 months of less than 10%. At first glance, these results are surprising because the immediate treatment success with a degree of thrombolysis of at least 50% (grade II or III lysis) was somewhat higher in the CaVenT trial than in our study (88% vs 77%). In the study by Grewal et al., thrombolysis success of more than 50% reduced the risk of the PTS (30). However, other authors did not find an association between the degree of thrombolysis and the occurrence of PTS (31). The most likely explanation for the favourable results in our study is the higher percentage of patients treated with stenting of the underlying venous obstruction (80% vs 17% in CaVenT) (12). Interestingly, Chung et al found in a retrospective study that 45 of 56 patients with acute ilio-femoral DVT had underlying anatomic abnormalities central to the thrombosed deep vein assessed by spiral CT venography (17). The stenting rate in our study was also higher than in other studies, ranging from 22 to 56% (14, 15, 32-35). In line with this concept, a recently published case series of 37 DVT patients treated by USAT reported early rethrombosis in almost one third (14). The authors considered that delay in stent placement was the likely reason for early rethrombosis. Improved patency rates were also observed in limbs treated with adjunctive stenting after CDT in the National Multicentre Registry including 303 limbs treated with CDT (27). In the CaVenT study, ilio-femoral patency at six months was associated with a significantly reduced risk of PTS at 24 months in comparison to insufficient recanalisation (12). Venous stenting seems to reduce the incidence of the PTS by improving long-term patency rates, but further research is necessary to define the criteria for stent placement in patients with ilio-femoral DVT. The non-significant decrease in the mean Villalta score and the prevalence of PTS over time in our study corresponds well with the large cohort study by Kahn et al. who found a progressive decrease in the Villalta score during the first year (1).

In our study, symptom duration was predictive of the thrombolytic success, with higher degree of thrombolysis in patients with acute onset of symptoms than in patients with subacute or acute-on-chronic onset. This observation is in line with data from the National Multicentre Registry (27). However, age of the thrombus is difficult to predict on the basis of symptom duration alone. Even in patients with acute symptoms, older thrombus may be present (27). Interestingly, the stenting rate in our study did not differ between the different grades of thrombolysis or the symptom duration, suggesting that the presence of underlying vein lesions is

<table>
<thead>
<tr>
<th>Villalta PTS scale</th>
<th>3 months (n=72)</th>
<th>6 months (n=53)</th>
<th>12 months (n=36)</th>
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<tr>
<td>Mean score</td>
<td>2.2 ± 2.2</td>
<td>1.7 ± 1.9</td>
<td>1.7 ± 1.5</td>
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<tr>
<td>No PTS (0–4 points)</td>
<td>63 (88)</td>
<td>49 (92)</td>
<td>34 (94)</td>
</tr>
<tr>
<td>Mild PTS (5–9 points)</td>
<td>7 (10)</td>
<td>4 (8)</td>
<td>2 (6)</td>
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<tr>
<td>Moderate PTS (10–14 points)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Severe PTS (≥15 points or venous ulcer)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**CEAP classification for CVD**

- C0 (No visible or palpable signs of venous disease) 37 (51) 28 (53) 22 (61)
- C1 (Telangiectasies or reticular veins) 16 (22) 13 (25) 8 (22)
- C2 (Varicose veins only) 3 (4) 3 (6) 1 (3)
- C3 (Edema with or without varicose veins) 9 (13) 2 (4) 2 (6)
- C4 (Changes in skin and subcutaneous tissue secondary to CVD) 5 (7) 5 (9) 3 (8)
- C5 (Healed venous ulcer) 2 (3) 2 (4) 0 (0)
- C6 (Active venous ulcer) 0 (0) 0 (0) 0 (0)

<table>
<thead>
<tr>
<th>Venous clinical severity score</th>
<th>Mean score</th>
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<tr>
<td></td>
<td>3.2 ± 2.1</td>
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<tr>
<td>6 months (n = 53)</td>
<td>2.4 ± 2.1</td>
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<tr>
<td>12 months (n = 36)</td>
<td>2.1 ± 1.8</td>
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Data presented as mean ± SD or number (%). CEAP, Clinical Etiological Anatomical Pathophysiological; CVD, chronic venous disease; PTS, post-thrombotic syndrome.
Data on feasibility and safety of USAT for the treatment of DVT has previously been published (14, 32, 33, 36, 37). None of these studies used a fixed-dose treatment regimen but adapted the treatment duration according to venographic results, with mean treatment durations ranging from 21.2 to 47 h and various thrombolytic drug regimens. An argument against extended CDT according to venographic results is that thrombolytic success might be underestimated because of venous outflow obstruction due to underlying chronic compressive or obstructive vein lesions (17, 38). The latter cannot be sufficiently treated by prolonged USAT but requires adjunctive angioplasty and stenting to obtain satisfactory venous outflow. The combination of fixed low-dose USAT and additional stenting if necessary allows keeping total treatment time and hospital stay short (2.8 days in our study). It is currently not known if single-session procedures with percutaneous pharmaco-mechanical thrombectomy systems, including the AngloJet or Trellis devices are superior to USAT or standard CDT and reduce the duration of hospital stay (39-42). In comparison to pharmaco-mechanical thrombolysis, USAT or standard CDT requires less operator experience; however, prolonged thrombolysis infusion necessitates monitoring on intermediate or intensive care units. Single-session procedures may be preferable for institutions with limited access to monitoring units.

Primary patency was lower in patients with acute-on-chronic symptom onset and in patients requiring stenting of the femoral vein. Both factors might be indirect indicators of more diffuse chronic venous disease with extension into the leg veins even though not all of these patients were aware of any previous venous thrombo-embolic events (27). Stenting across the inguinal ligament into the common femoral vein was performed in 30% of our patients due to residual stenosis; it was not associated with reduced primary patency, as also previously shown by Neglen et al. (43).

Our study has several limitations. The study design does not allow a direct comparison with other treatment modalities, and a randomised controlled trial would be required to investigate whether fixed-dose CDT with routine stenting of venous obstruction is superior to extended venography-guided CDT without routine stenting. The question remains if the use of ultrasound adds clinical benefit to the standard CDT procedure. While two retrospective case series suggested greater thrombolysis success and shorter treatment times with USAT (36, 37), another retrospective study showed similar efficacy and safety of USAT in comparison to standard CDT (33). An ongoing randomised controlled trial in patients with ilio-femoral DVT aims to quantify the effect of adding ultrasound to fixed low-dose CDT by using the venographic reduction in thrombus burden from baseline to 15 h (NCT01482273). The majority of our patients had descending DVT because popliteal veins were thrombosed in only 34% of patients. Therefore, our data do not allow conclusions on the efficacy and safety of USAT in patients with ascending ilio-femoral DVT.

What is known about this topic?
- Approximately half of patients with acute ilio-femoral deep-vein thrombosis (DVT) develop a post-thrombotic syndrome (PTS).
- In case of ilio-femoral DVT, catheter-directed thrombolysis reduces the risk of PTS. Most centres guide the duration of thrombolysis according to follow-up venograms. A fixed dose treatment regimen might help to simplify the treatment and allow a better comparison of different studies.
- Most patients with ilio-femoral DVT have underlying venous stenosis. The indication for stent placement after catheter-directed thrombolysis remains controversial, and the stenting rate varies widely between different studies.

What does this paper add?
- A fixed-dose ultrasound-assisted catheter-directed thrombolysis regimen over 15 hours is associated with a low bleeding risk and high patency rates.
- Routine stenting of underlying venous stenosis might be the key to improve long-term patency rates and to reduce the incidence of the PTS.

In conclusion, a standardised fixed low-dose USAT regimen followed if necessary by routine stenting of underlying venous obstruction was associated with a low bleeding rate, high venous patency rates and freedom from PTS of approximately 90%.

Conflicts of interest
Dr. Kucher is a consultant for EKOS Corp. All other authors report no conflict interest.

References

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