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Interim outcomes of mechanical thrombectomy for deep vein thrombosis from the All-Comer CLOUT Registry

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ABSTRACT

Objectives: The multicenter, prospective, single arm CLOUT registry assesses the safety and effectiveness of the Clot-Triever System (Inari Medical, Irvine, CA) for the treatment of acute and nonacute lower extremity deep vein thrombosis (DVT) in all-comer patients. Reported here are the outcomes of the first 250 patients.

Methods: All-comer patients with lower extremity DVT were enrolled, including those with bilateral DVT, those with previously failed DVT treatment, and regardless of symptom duration. The primary effectiveness end point is complete or near-complete ($\geq 75\%$) thrombus removal determined by independent core laboratory-adjudicated Marder scores. Safety outcomes include serious adverse events through 30 days and clinical outcomes include post-thrombotic syndrome severity, symptoms, pain, and quality of life through 6 months.

Results: The median age was 62 years and 40% of patients had contraindications to thrombolytics. A range of thrombus chronicity (33% acute, 35% subacute, 32% chronic) was observed. No patients received thrombolytics and 99.6% were treated in a single session. The median thrombectomy time was 28 minutes. The primary effectiveness end point was achieved in 86% of limbs. Through 30 days, one device-related serious adverse event occurred. At 6 months, 24% of patients had post-thrombotic syndrome. Significant and sustained improvements were observed in all clinical outcomes, including the Revised Venous Clinical Severity Score, the numeric pain rating scale, and the EuroQol Group 5-Dimension Self-Report Questionnaire.

Conclusions: The 6-month outcomes from the all-comer CLOUT registry with a range of thrombus chronicities demonstrate favorable effectiveness, safety, and sustained clinical improvements. (*J Vasc Surg Venous Lymphat Disord* 2022;10:832-40.)

Keywords: Deep vein thrombosis; Mechanical thrombectomy; Post-thrombotic syndrome

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Venous thromboembolism (VTE) represents a major cause of morbidity and mortality in the United States, affecting an estimated 478 of 100,000 people per year. The number of VTE cases is projected to more than double by 2050.¹ Deep vein thrombosis (DVT), which makes up 45% to 66% of VTE diagnoses,² often causes functional obstruction of lower extremity venous outflow, leading to acute and long-term reduction in quality of life.³ Furthermore, DVT carries the risk of pulmonary embolism (PE), which can be fatal.

Most DVTs are treated conservatively with anticoagulation alone, although long-term complications, including post-thrombotic syndrome (PTS), occur among 40% to 50% of patients after a first episode of symptomatic DVT.⁴⁻⁸ PTS describes a range of clinical symptoms, including minor to severe leg pain, intractable edema, irreversible skin changes, and ulceration.⁷ The clinical manifestations of PTS are costly to treat and result in a significant decrease in quality of life.^{4,9} Restoring venous patency after DVT may help to decrease the onset of PTS.⁶ Unfortunately, interventions using catheter-directed thrombolysis for DVT treatment have shown mixed efficacy in reducing long-term PTS rates and introduce a significant bleeding risk.^{6,10-13} There continues to be high clinical interest to identify therapies and devices that can successfully and safely remove thrombus without the use of thrombolytics.

The ClotTriever System (Inari Medical, Irvine, CA) is a mechanical thrombectomy system 510(k) cleared for the nonsurgical removal of thrombi and emboli from peripheral blood vessels and for the treatment of DVT. The ClotTriever System is designed to rapidly extract thrombus in a single session without the need for thrombolytics. The multicenter, prospective, single arm ClotTriever Outcomes (CLOUT) registry was designed to assess the safety and effectiveness of the ClotTriever System for the treatment of acute and nonacute lower extremity DVT in an all-comer patient population. We report herein the interim results of the CLOUT registry for the first time.

METHODS

The CLOUT registry. The CLOUT registry is a prospective, multicenter study designed to evaluate all-comer outcomes after use of the ClotTriever System for the treatment of lower extremity DVT. The registry is anticipated to enroll up to 500 patients among up to 50 US clinical sites. The CLOUT registry is registered at clinicaltrials.gov under identifier NCT03575364. The registry was conducted in conformity with the ethical principles set forth by the Declaration of Helsinki, Good Clinical Practice principles, and in accordance with ISO 14155:2011. All patients provided informed written consent and investigators obtained institutional review board approval at each site before enrolling patients. Investigators had

ARTICLE HIGHLIGHTS

- **Type of Research:** Prospective, multicenter, all-comer registry
- **Key Findings:** Two hundred fifty patients were treated with the ClotTriever System to treat lower extremity deep vein thrombosis. No patients received thrombolytics and 99.6% were treated in a single session. Complete or near-complete ($\geq 75\%$) thrombus removal was achieved in 86% of limbs. At 6 months, 24% of patients had post-thrombotic syndrome.
- **Take Home Message:** The ClotTriever System showed excellent thrombus removal results that translate into significant improvements in post-thrombotic syndrome, symptoms, pain, and quality of life through 6 months.

adequate experience with the ClotTriever System before enrolling patients.

Patient population. The inclusion criteria consist of patients being at least 18 years old and having a documented lower extremity DVT involving the femoral, common femoral, or iliac veins, or inferior vena cava (IVC), alone or in combination. Patients were also included irrespective of symptom duration, bilateral disease, recent unsuccessful treatment of their DVT, contraindication to thrombolytics, or coronavirus disease 2019 (COVID-19) status. Unsuccessful prior treatment was defined as anticoagulation for at least 1 week or an unsuccessful intervention, including mechanical, pharmacological, or pharmacomechanical treatments. Patients were excluded if they had a prior venous stent in a target vessel segment, an IVC filter in place at time of thrombectomy, IVC aplasia, or other congenital anatomic anomaly of the IVC or iliac veins, contraindication to anticoagulation, a life expectancy of less than 1 year, chronic nonambulatory status, known hypercoagulable state that could not be medically managed through the study period, or unavailability of a lower extremity venous access site.

Device and procedural characteristics. The ClotTriever System includes two components: (1) a 13F or 16F sheath for access of the treatment site with expandable funnel to facilitate catheter and thrombus removal (Supplementary Fig 1, A, online only) and (2) an over-the-wire thrombectomy catheter consisting of a coring element and integrated collapsible nitinol collection bag for distal protection (Supplementary Fig 1, B, online only). The catheter is inserted through the sheath over an 0.035" guidewire, advanced beyond the thrombus, and deployed. It is then slowly pulled back through the target thrombus towards the sheath, collecting thrombus in the collection bag. The device can be cleaned and

reinserted for additional passes, the number of which was left to physician discretion.

Patient and procedural characteristics, including demographics and comorbidities, were collected at the time of DVT diagnosis and during the thrombectomy procedure. COVID-19 status was collected at enrollment beginning in October 2020. Marder scores were calculated and adjudicated by an independent core laboratory (Syntactx, New York, NY) from intraprocedural venograms.¹⁴ Each vessel, including the common iliac, external iliac, common femoral, cranial femoral, caudal femoral, and popliteal veins, was scored based on the amount of thrombus as either 0% (no occlusion), 25%, 50%, 75%, or 100% (fully occluded) and weighted based on the size of the vessel. The maximum Marder score was 24. Marder scores were calculated from venograms collected before and after treatment after any adjunctive therapy, including stenting. The percent decrease in Marder score was calculated as $\frac{(\text{pre-treatment} - \text{post-treatment})}{\text{pre-treatment}} \times 100$. In addition to core laboratory-adjudicated Marder scores, physicians subjectively noted post-thrombectomy and post-adjunctive therapy occlusion rates (increments of 10% from 0% to 100%) during the procedure.

Thrombus age was approximated by the treating physician based on the appearance and texture of extracted thrombus, along with patient medical history and any relevant imaging. Thrombus was categorized as acute (<2 weeks; soft, jelly-like thrombus), subacute (2-6 weeks; firmer thrombus than acute), or chronic (>6 weeks; firm, highly organized thrombus). If the extracted thrombus had features discordant to the symptom duration alone, the chronicity assessed by visual inspection was used. Thrombus chronicity was determined as the oldest thrombus in each treated limb.

The use of intravascular ultrasound imaging was strongly encouraged before and after thrombectomy. Balloon venoplasty and stenting were permitted at the treating physician's discretion. The need for adjunctive thrombectomy techniques after treatment with the ClotTriever System, including thrombolytic therapy or further mechanical thrombectomy via a different device, was left to the physician's discretion and noted. The anti-coagulation regimen following thrombectomy was at the physician's discretion.

Intensive care unit (ICU) and hospital post-procedure lengths of stay were recorded, with 1 day defined as 1 overnight stay.

Clinical outcomes. Clinical outcomes in the CLOUT registry are assessed before discharge and at 30 days, 6 months, 1 year, and 2 years, with data through 6 months presented here. The primary effectiveness end point is complete or near-complete ($\geq 75\%$) thrombus removal as determined by an independent core laboratory-adjudicated Marder score. Safety outcomes include

serious adverse events (SAEs) through 30 days adjudicated by an independent medical monitor as device related or not and defined as events that are fatal or life threatening, result in persistent or significant disability or incapacity, result in permanent impairment of a body function or permanent damage to a body structure, or result in hospitalization or prolongs a hospitalization and necessitates medical or surgical intervention. Deep vein thromboses found incidentally at follow-up were recorded as SAEs if they met the SAE definition, regardless of whether they were symptomatic, and included those that may have been due to residual thrombus from the index procedure. All-cause mortality and hospital readmissions were also recorded through 30 days.

Duplex ultrasound examination was performed in the treated limbs at baseline, 30 days, and 6 months to assess the presence of flow and compressibility. Flow was assessed in each treated limb as present, absent, or not evaluable, and compressibility was assessed in each treated limb as normal, partial, incompressible, or not evaluable. The Villalta score was assessed at baseline, 30 days, and 6 months. The Villalta score assesses five patient symptoms and six physician-assessed clinical signs, each on a scale of 0 to 3, for a final combined score range of 0 to 33. PTS was defined as a Villalta score of greater than 4, and PTS severity was categorized based on Villalta scores as mild (5-9), moderate (10-14), or severe (>14).¹⁵

Immediate and sustained symptom relief was captured via pain and edema measurements at baseline, discharge, 30 days, and 6 months. Pain was assessed via the numeric pain rating scale (NPRS), with a patient's verbal self-assessment scored between 0 and 10.¹⁶ Edema was assessed by circumference measurement of the treated limb at the ankle, mid-calf, and mid-thigh.

Other disease progression and quality-of-life measures were collected at baseline, 30 days, and 6 months including the Revised Venous Clinical Severity Score (rVCSS) and the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D). The rVCSS assessed venous-specific disease severity by measuring 10 factors such as pain, venous edema, and varicose veins, each graded on a scale of 0 to 3, resulting in an overall score from 0 to 30.¹⁷ The EQ-5D determined the general health-related quality of life with typical scores ranging from 0.00 (equivalent to death) to 1.00 (perfect health).¹⁸

Statistical analysis. This interim analysis included the first 250 patients enrolled in the registry and was not powered for any primary or secondary outcome measures. Categorical variables are expressed using counts and percentages and are compared using McNemar's test. Quantitative variables are expressed using medians and interquartile ranges (IQR) and are compared using the Wilcoxon signed-rank test. Box and whisker plots present the median value as the bold line in the box,

Table I. Baseline and procedural characteristics

Characteristics	
Baseline	
Age, years	62.3 [47.1-70.6]
Male sex	131 (52.4)
Bilateral DVT	10 (4.0)
Provoked DVT	88 (35.1)
Contraindicated to thrombolytics	99 (39.8)
Prior history of DVT	59 (23.6)
Previous treatment of current DVT	60 (23.5)
Thrombus location	
Isolated iliac or iliofemoral	23 (9.3)
Isolated femoral-popliteal	45 (18.3)
Iliofemoral and femoral-popliteal	178 (72.4)
Thrombus location by segment	
Common iliac	121 (57.3)
External iliac	143 (63.3)
Common femoral	177 (77.6)
Cranial femoral	211 (89.0)
Caudal femoral	193 (83.9)
Popliteal	91 (75.5)
Thrombus chronicity	
Acute	83 (32.7)
Subacute	90 (35.4)
Chronic	81 (31.9)
Villalta score	
0-4	32 (13.9)
5-9	82 (35.7)
10-14	50 (21.7)
≥15	66 (28.7)
rVCSS	6.0 [4.0-9.0]
EQ-5D score	0.688 [0.425-0.820]
Procedural	
Single session	249 (99.6)
No. of device passes	4.0 [3.0-6.0]
Thrombectomy procedure time, minutes	28.0 [20.0-44.0]
Estimated blood loss, mL	50.0 [20.0-65.0]
Use of thrombolytics	0 (0.0)
Use of additional thrombectomy device	1 (0.4)
Stent placed	121 (46.5)
Venoplasty	194 (74.6)
Hospital length of stay (no. of post-procedure overnights)	1.0 [1.0-2.0]
ICU stay (no. of patients admitted post-procedure)	6 (2.4)
<p><i>DVT</i>, Deep vein thrombosis; <i>EQ-5D</i>, EuroQol group 5-dimension self-report questionnaire; <i>ICU</i>, intensive care unit; <i>IQR</i>, interquartile range; <i>IVC</i>, inferior vena cava; <i>rVCSS</i>, Revised Venous Clinical Severity Score.</p> <p>Values are median [IQR] or number (%). Denominators vary from 212 to 250 patients or 119 to 260 treated limbs for the different variables.</p>	

with the box bounded by the IQR, and the whiskers representing $1.5 \times$ IQR. A *P* value of less than .05 was considered significant for hypothesis testing, using available pairwise values.

RESULTS

From September 2018 through May 2021, 250 patients with 260 treated limbs were enrolled in the CLOUT registry across 24 sites.

Baseline characteristics

Baseline characteristics of the enrolled patients are shown in Table I. The median age was 62.3 years (IQR, 47.1-70.6), 52.4% were male, 23.6% had a history of prior DVT, and 39.8% of the treated patients had a relative or absolute contraindication to thrombolytic therapy. Four patients were confirmed COVID-19 positive at enrollment.

Nearly one quarter of treated limbs (23.5%) had unsuccessful prior treatment for the current DVT, which led physicians to escalate to mechanical thrombectomy. The majority of these (96.7%) were treated with anticoagulation for at least one week before mechanical thrombectomy with the ClotTriever System. Additionally, one patient failed thrombolytic therapy and three patients failed mechanical thrombectomy before inclusion in the registry. The majority of patients (96.0%) had unilateral DVT, with 10 patients treated for bilateral disease. Thrombus chronicity was determined to be acute (<2 weeks) in 32.7% of treated limbs, subacute (2-6 weeks) in 35.4% of treated limbs, and chronic (>6 weeks) in 31.9% of treated limbs.

Procedural characteristics

The procedural characteristics are shown in Table I. All but 1 (99.6%) of the 250 patients were treated in a single session, with 1 patient returning to undergo stenting as preplanned by the treating physician. The ClotTriever catheter was used for a median of 4.0 passes (IQR, 3.0-6.0 passes) per treated limb with a median thrombectomy time of 28.0 minutes (IQR, 20.0-44.0 minutes). No thrombolytics were used during any of the procedures. The median estimated blood loss was 50.0 mL (IQR, 20.0-65.0 mL). Stents were placed in 46.5% of treated limbs. Intravascular ultrasound examination was used before thrombectomy, after thrombectomy, or both in 239 (91.9%) procedures. Only six patients (2.4%) were referred to the ICU after treatment. The median post-procedure hospital length of stay was 1.0 day (IQR, 1.0-2.0 days).

An example of a successful ClotTriever mechanical thrombectomy procedure extracting thrombus is shown in Supplementary Fig 2 (online only).

Effectiveness outcomes

The Marder scores from the core laboratory were available for 241 treated limbs in 233 patients. The primary

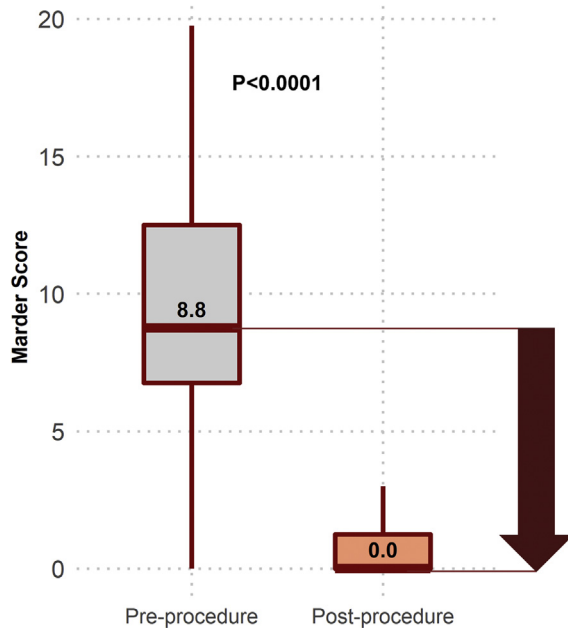


Fig 1. Marder Score Change. Box-and-whisker plots showing the pre-treatment and post-treatment Marder scores, calculated and adjudicated by a core laboratory using the pre-treatment and post-treatment venograms. Boxes represent interquartile range (IQR) [Q1, Q3] with bars representing median values. Whiskers represent $1.5 \times [Q1, Q3]$ ($n = 241$).

effectiveness end point of complete or near-complete ($\geq 75\%$) thrombus removal was achieved in 85.8% of treated limbs. Limbs with isolated iliofemoral thrombus, isolated femoral-popliteal thrombus, and a combination of iliofemoral and femoral-popliteal thrombus showed no significant difference in complete or near-complete thrombus removal ($P = .7887$).

Overall, the Marder scores were reduced by a median of 100% (IQR, 82.1%-100%) from a baseline score of 8.8 (IQR, 6.8-12.5) to a post-procedural score of 0.0 (IQR, 0.0-1.3; $P < .0001$) (Fig 1). The majority of patients (51.9%) had 100% thrombus removal by Marder score. Of the 29 (2.5%) segments with 50% or more thrombus remaining post-thrombectomy, the most common segment was the caudal femoral vein (31.0%).

The post-thrombectomy thrombus load as assessed by the physicians was most frequently 0-10%, occurring in 190/249 limbs (76.3%). In limbs with adjuvant stents, 37/45 (82.2%) saw no change in occlusion rates evaluated post-thrombectomy and post-stent placement.

Safety outcomes

There were 18 SAEs through 30 days (Table II), one of which was adjudicated to be device related. Of the 18 SAEs, 10 were DVT events, 5 of which were attributed to patients who were stented at the rethrombosis event, and one of which was attributed to patient noncompliance with compression therapy. The device-related event

occurred in a patient who developed a fatal PE during the procedure when the operator entangled the ClotTriever catheter with another device, resulting in embolization of the IVC thrombus to the lungs. No SAEs related to acute renal injury or vessel or valve damage were reported.

All-cause mortality through 30 days occurred in three patients. One death occurred in the device-related PE event as described. Two deaths occurred owing to the progression of underlying conditions in one patient with stage IV non-small cell lung cancer and one patient with spinal cord infection owing to a recent spinal surgery. A total of 17 patients (7.3%) were readmitted to the hospital through 30 days. Of these readmissions, seven (3.0%) were procedure related, including five for rethrombosis, 1 for a PE and rethrombosis, and 1 for a stent occlusion.

Clinical outcomes

Flow and compressibility. At baseline, 23.0% of treated limbs had flow present on duplex ultrasound examination, which improved significantly to 85.2% at 30 days ($P < .0001$) with continued improvement to 90.1% at 6 months ($P < .0001$) (Fig 2, A). Normal or partial compressibility on duplex ultrasound examination improved significantly from 24.3% of treated limbs at baseline to 86.0% at 30 days ($P < .0001$) with continued improvement to 88.7% at 6 months ($P < .0001$) (Fig 2, B).

Pain and edema. The median NPRS score at baseline was 5.0 (IQR, 2.0-8.0), which significantly improved at discharge (2.0; IQR, 0.0-5.0; $P < .0001$). The improvement in NPRS score was sustained out to 30 days (0.0; IQR, 0.0-3.0; $P < .0001$) and 6 months (0.0; IQR, 0.0-2.0; $P < .0001$) compared with baseline (Fig 3, A). Of the patients with an NPRS score of greater than 0 at baseline, 132/149 (88.6%) improved by at least 1 point at 30 days and 112/120 (93.3%) improved at 6 months. The median calf circumference at baseline was 39.4 cm (IQR, 35.3-42.9), which significantly improved at discharge (38.0 cm; IQR, 34.0-41.0; $P < .0001$). The improvement in calf circumference was sustained out to 30 days (37.0 cm; IQR, 33.5-41.0; $P < .0001$) and 6 months (37.6 cm; IQR, 33.5-40.0; $P < .0001$) compared with baseline (Fig 3, B). Comparing the calf measurements in treated versus untreated limbs in unilateral patients, the treated limb was 9% larger at baseline, which significantly improved to 1% at 6 months ($P < .0001$). The median thigh circumference significantly improved from 55.0 cm (IQR, 49.3-61.0 cm) at baseline to 53.0 cm (IQR, 48.5-57.5; $P < .0001$ cm) at discharge, with sustained improvement out to 30 days (52.5 cm; IQR, 47.0-57.5 cm; $P < .0001$) and 6 months (52.0 cm; IQR, 46.5-56.3 cm; $P < .0001$) compared with baseline. The ankle circumference also significantly improved from 24.5 cm (IQR, 23.0-26.5) at baseline to 23.9 cm (IQR, 22.0-25.5 cm; $P = .0009$) at discharge, with sustained improvement out to 30 days (23.5 cm; IQR, 22.0-26.0;

Table II. Adjudicated serious adverse events (SAEs) through 30 days

SAE	Total	Device-related
DVT ^a	10 (4.5%)	0 (0)
PE	4 (1.8)	1 (0.4)
Hemoglobin decreased	1 (0.4)	0 (0)
Non-small cell lung cancer stage IV	1 (0.4)	0 (0)
Pulseless electrical activity	1 (0.4)	0 (0)
Spinal cord infection	1 (0.4)	0 (0)
Acute renal injury	0 (0)	0 (0)
Vessel/valve damage	0 (0)	0 (0)

DVT, Deep vein thrombosis; PE, pulmonary embolism. Values are number (%). Serious adverse events (SAEs) through 30 days were adjudicated by an independent medical safety monitor. SAEs are defined as events that are fatal or life-threatening, result in persistent or significant disability or incapacity, result in permanent impairment of a body function or permanent damage to a body structure, result in hospitalization or prolongs a hospitalization and necessitates medical or surgical intervention.
^aDeep vein thromboses found incidentally at follow-up were recorded as SAEs if they met the SAE definition, regardless of whether they were symptomatic, and may have included those due to residual thrombus from the index procedure. The denominator is 223.

$P = .012$) and 6 months (23.5 cm; IQR, 22.0-26.0; $P = .0006$) compared with baseline.

Other clinical outcomes through 6 months. The median Villalta score at baseline was 10.0 (IQR, 6.0-15.0) which improved significantly to 3.0 (IQR, 1.0-5.0) at 30 days ($P < .0001$) and further improved to 1.5 (IQR, 0.0-4.0) at 6 months ($P < .0001$). Of the patients with a Villalta score greater than 0 at baseline and paired data available at follow-up timepoints, 158/176 (89.8%) improved by at least 1 point at 30 days and 129/142 (90.8%) improved by at least 1 point at 6 months.

At baseline, 86.1% of treated limbs had Villalta scores ≥ 5 . At 30 days, 30.5% had Villalta scores ≥ 5 , which further decreased to 24.4% at 6 months, both significant differences compared with baseline ($P < .0001$) (Fig 4, A). The percentage of treated limbs with Villalta scores ≥ 10 significantly decreased compared with baseline from 50.4% to 12.2% at 30 days ($P < .0001$) and to 8.8% at 6 months ($P < .0001$). The PTS rate at 30 days was 30.5% which further improved at 6 months to 24.4%. Limbs with isolated iliofemoral thrombus, isolated femoral-popliteal thrombus, and a combination of iliofemoral and femoral-popliteal thrombus showed no significant difference in PTS rates at 6 months ($P = .5527$). Additionally, the percentage of limbs with PTS at 6 months in those with $\geq 75\%$ or $< 75\%$ thrombus removal was similar (23% vs 24%; $P = NS$), and the percentage of limbs with moderate to severe PTS for these two groups was also similar (5.6% vs 12%; $P = .3725$).

The median rVCSS score at baseline was 6.0 (IQR, 4.0-9.0), which showed significant improvements at

30 days (3.0; IQR, 2.0-6.0; $P < .0001$) and 6 months (3.0; IQR, 1.0-5.0; $P < .0001$) compared with baseline (Fig 4, B). Of the patients with an rVCSS score of greater than 0 at baseline, 123/168 (73.2%) improved by at least 1 point at 30 days and 106/140 (75.7%) at 6 months.

Finally, for the EQ-5D general health-related quality of life index, in which higher scores indicate better health with a maximum score of 1, the median score at baseline was 0.69 (IQR, 0.43-0.82), which improved significantly at 30 days (0.88; IQR, 0.80-1.00; $P < .0001$) and 6 months (1.00; IQR, 0.80-1.00; $P < .0001$) (Fig 4, C). Of the patients with an EQ-5D score of less than 1 at baseline, 146/161 (90.7%) improved at 30 days and 115/131 (87.8%) improved at 6 months.

DISCUSSION

Results from the first 250 patients enrolled in the CLOUT registry demonstrate that mechanical thrombectomy with the ClotTrier System improves disease severity and quality of life in all-comer patients with lower extremity DVT. Although many treated patients had failed prior therapies for their current DVT, the majority had 100% thrombus removal, with more than 85% having complete or near-complete thrombus removal. The outcomes of the CLOUT registry suggest that mechanical thrombectomy with the ClotTrier System is a safe procedure with a low 0.4% rate of device-related SAEs through 30 days. Clinical outcomes, including pain and edema, showed immediate and sustained improvement out to 6 months. Other clinical outcomes including Villalta scores and duplex ultrasound flow and compressibility showed 30-day improvement, which was sustained to 6 months.

Immediate symptom improvements. The in-hospital outcomes from the CLOUT registry show drastic and immediate improvements in pain and edema. Anticoagulation therapy for a minimum of three months is recommended by guidelines as standard of care for DVT.^{19,20} Immediate and in-hospital symptom relief with anticoagulation for DVT have been scarcely reported. In the ATTRACT trial, in patients treated with anticoagulation therapy, although pain severity was improved at 10 days, index leg circumference actually increased in this time frame.¹⁰ Similarly in another prospective study, pain decreased while leg circumference was increased at 14 days.²¹ In contrast, in the CLOUT registry, both pain and edema decreased significantly at discharge (median length of stay of 1 day) compared with baseline.

Six-month outcomes. In the CLOUT registry, mechanical thrombectomy with the ClotTrier System resulted in clinically and statistically significant improvements in outcome measures ranging from substantially improved measures of disease severity to enhanced quality of life through 6 months. Importantly, only 24.4% of treated

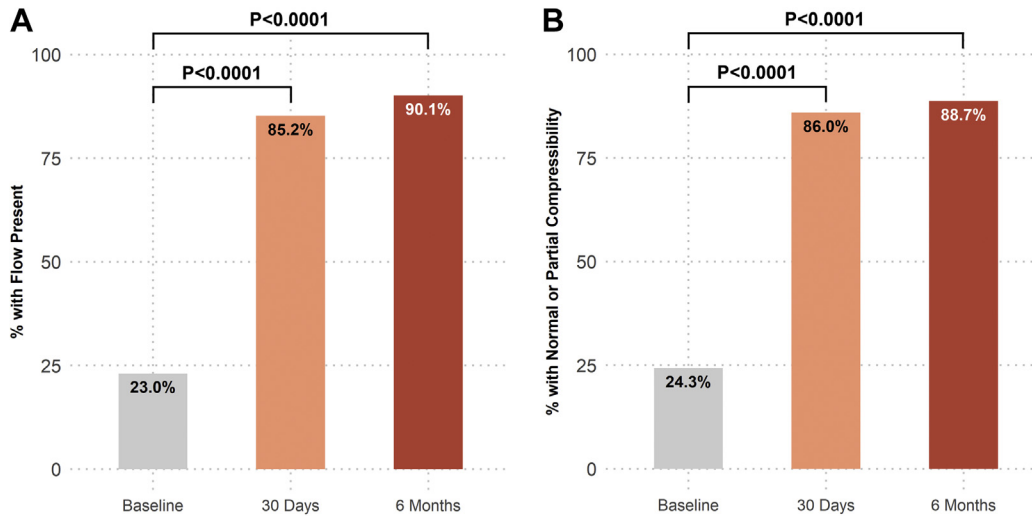


Fig 2. Duplex ultrasound flow and compressibility. Percentage of treated limbs with flow present (A) and normal or partial compressibility (B) assessed by duplex ultrasound examination at baseline, 30 days, and 6 months after the procedure (n = 142-239).

limbs had PTS at 6 months, with moderate to severe PTS seen in less than 9%. Similar results were observed in treated limbs with isolated iliofemoral, isolated femoral-popliteal, and both iliofemoral and femoral-popliteal thrombus. With the available small sample of limbs with $\geq 50\%$ or greater % thrombus remaining, we cannot directly correlate the presence of venous occlusion with worsened PTS. The open vein hypothesis should be further evaluated to determine any benefit to prevent or decrease PTS.

Although comparing PTS rates across studies is difficult, studies with only acute DVT reported that 32.2% to 40.0% of patients had PTS at 6 months in the anticoagulation arm,^{6,10} with moderate to severe PTS seen in 24.0% of treated patients.¹⁰ Additionally, in ATTRACT, the femoral-popliteal subgroup had a PTS rate of 33.0%, with 10.0% having moderate to severe PTS at 6 months. These clinical trials have shown that 27.0% to 30.3% of patients had PTS at 6 months in the interventional catheter-directed therapies (CDT) arms.^{6,10} The CAVENT trial concluded that CDT

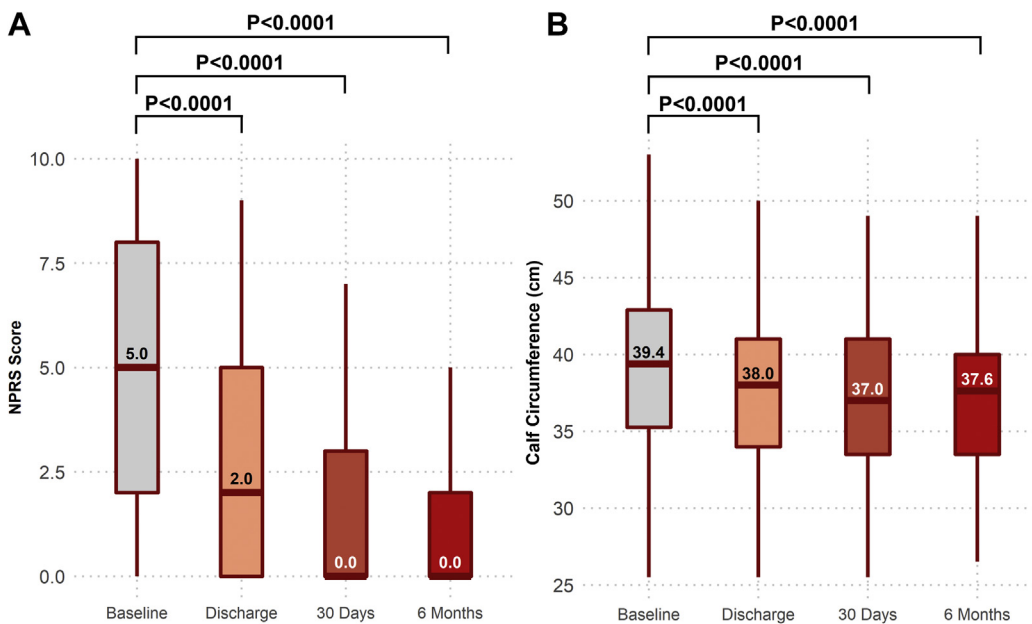


Fig 3. Immediate and sustained improvements in pain and edema. Box-and-whisker plots showing symptoms assessed at baseline, discharge, 30 days, and 6 months after the procedure. (A) National Pain Rating Scale (NPRS) and (B) calf circumference (n = 138-220 limbs and 150-223 patients).

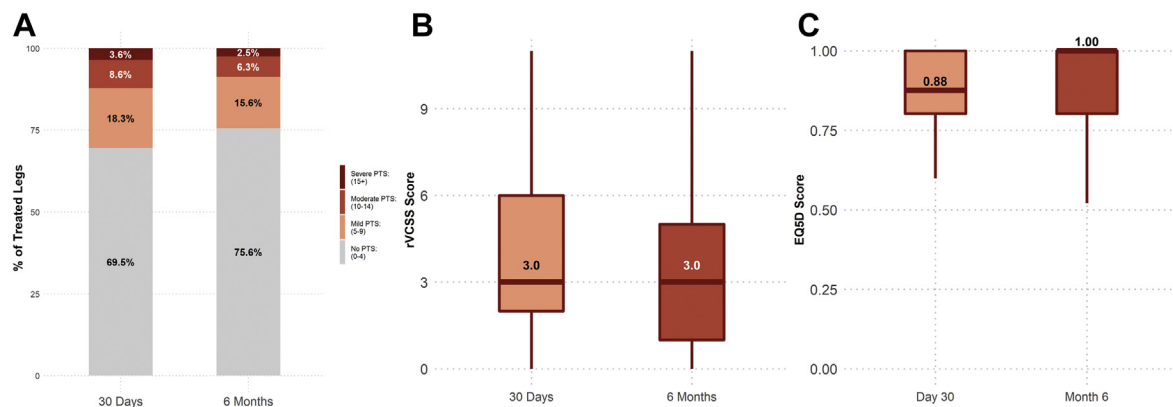


Fig 4. Other clinical outcomes through 6 months. Percentage of treated limbs categorized using Villalta scores at 30 days and 6 months after the procedure. Villalta score categories: no post-thrombotic syndrome (PTS); Villalta of <5; mild PTS, Villalta of 5-9; moderate PTS, Villalta of 10-14; and severe PTS, Villalta of ≥ 15 . **(A)** Box-and-whisker plots showing Revised Venous Clinical Severity Score (rVCSS) **(B)**, and EuroQol group 5-dimension self-report questionnaire (EQ-5D) Quality of life score **(C)** (n = 159-197 limbs and 157-196 patients).

decreases the risk of PTS at 2 and 5 years, whereas the ATTRACT and CAVA trials did not confirm this finding.^{6,11} However, the ATTRACT trial showed signs of improvement in PTS severity in the iliofemoral DVT subgroup, but not the femoral-popliteal DVT subgroup, treated with CDT.^{10,12,22,23} In the CLOUT registry, patient follow-up will continue out to 2 years to further examine the long-term clinical outcomes after mechanical thrombus removal with the ClotTrievers System.

Mechanism of action. The purely mechanical mechanism of action of the ClotTrievers System along with the absence of thrombolytics in any patient contributed to the overall safety of the procedure by eliminating the associated bleeding risks and potential for acute renal injuries.^{13,24} In addition, the mechanism of action of the ClotTrievers System enabled the removal of thrombus with a negligible amount of blood loss during the procedure. ICU stays were prevented in the vast majority of patients owing to the avoidance of thrombolytics, which require close monitoring as standard of care.²⁵ Single-session treatments were performed in all but one patient in the CLOUT registry, in contrast with patients undergoing CDT, who may require multiple sessions.^{6,10,12}

Thrombus chronicity. To enroll as close to an all-comer patient population as possible in the CLOUT registry, patients were included regardless of unilateral or bilateral disease, recent failed treatment of their DVT, duration of their symptoms, or contraindication to thrombolytics. As a result, in the CLOUT registry, the enrolled patients had a range of thrombus chronicity including approximately one-third of treated limbs in each category: acute, subacute, and chronic.

In contrast, previous studies limited enrollment to patients with acute DVT (<3 weeks duration of symptoms in CAVENT and <2 weeks duration of symptoms in

ATTRACT and CAVA) and did not study patients with subacute or chronic DVT.^{6,10-12} This entry criterion was likely set owing to the mechanism of thrombolytic therapy, which has low efficacy on subacute and chronic thrombus as fibrin levels decrease and thrombi become more collagenic over time.²⁶ Owing to the nature of DVT, patient symptoms may be delayed until sufficient venous obstruction occurs. Even after symptoms are noticeable, patients may delay seeking treatment. Further, after seeking care for DVT, many patients are trialed on anticoagulation before they are referred for interventional therapy. Not restricted to only acute thrombus removal, in the CLOUT registry, the ClotTrievers System shows effectiveness in a broad patient population with a range of thrombus chronicity.

The limitations of this registry include the observational nature of the data collection, the lack of a control arm, and the possibility for selection bias and loss-to-follow-up bias. The method for estimating thrombus chronicity was not standardized and relied on the treating physician's subjective evaluation. Duplex ultrasound compressibility assessments can be challenging in proximal segments and in patients with a higher body mass index, which is a known limitation that may result in undetected DVTs at follow-up. Distal DVT was not evaluated and may have impacted patient outcomes. The four patients confirmed as COVID-19 positive at enrollment is likely an underestimation since the collection was added partway through the study. In addition, this is an interim dataset including the first 250 patients enrolled in the registry. Follow-up data were only available out to 6 months, so although these clinical outcomes were encouraging and short-term clinical outcomes have been shown to predict PTS rates out to 2 years,²⁷ the long-term clinical benefits of acute thrombus removal are yet to be fully understood.

CONCLUSIONS

In this interim analysis from the CLOUT registry, the ClotTrier System demonstrated successful treatment of a range of thrombus chronicities within an all-comer DVT patient population with a favorable effectiveness and safety profile. Further registry enrollment and analysis will improve understanding of the long-term clinical impact of ClotTrier treatment in DVT and provide insights for future definitive studies in the field of DVT.

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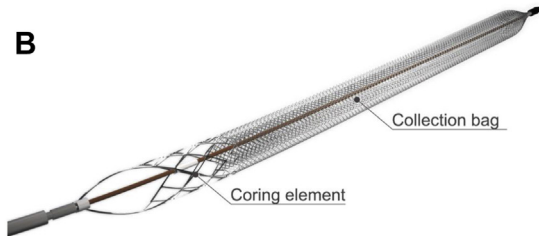
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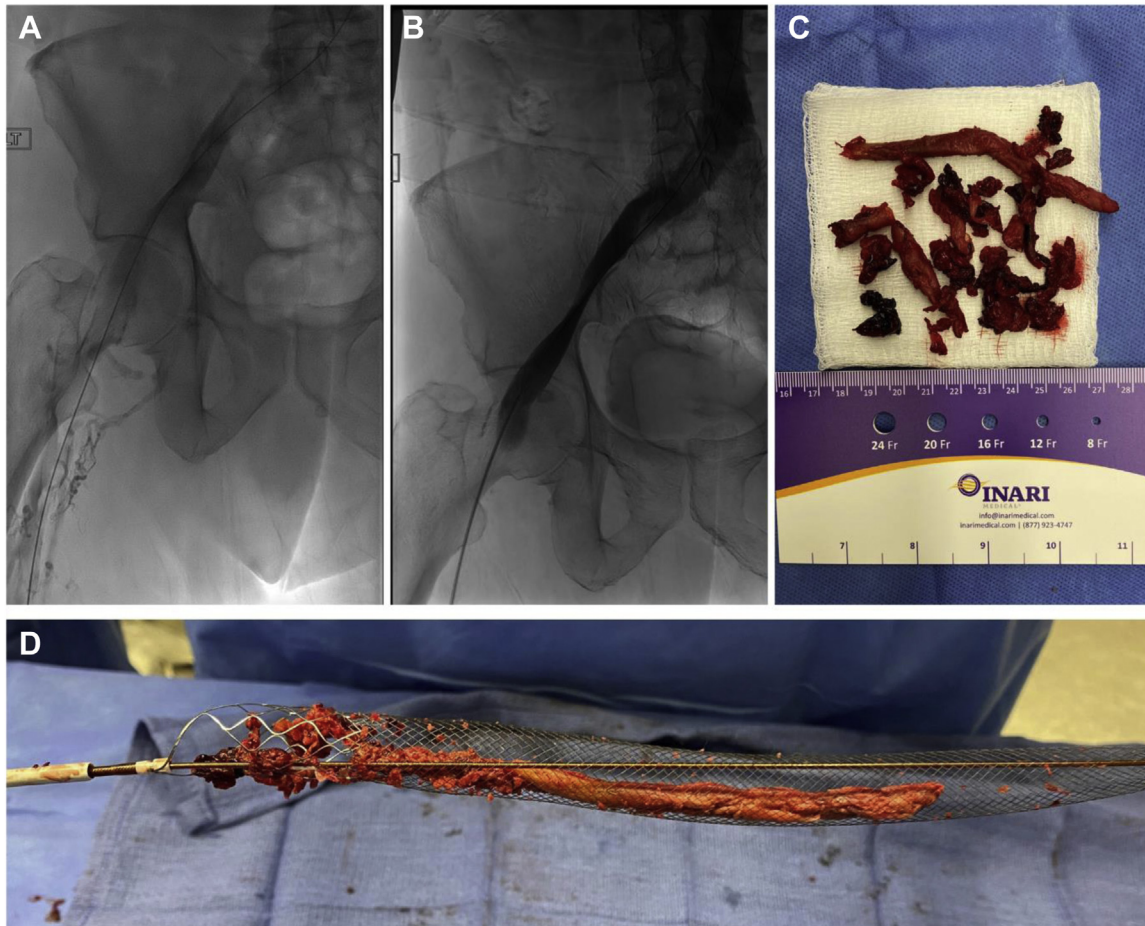
A



B



Supplementary Fig 1 (online only). Mechanical thrombectomy device. The ClotTriever System components, showing the ClotTriever sheath (top) with expandable funnel and the ClotTriever catheter (bottom) with nitinol coring element and integrated collection bag. Images courtesy of Inari Medical.



Supplementary Fig 2 (online only). CLOUT case example. Representative CLOUT case treated with the ClotTriever System. A 58-year-old man with active cancer, type II diabetes, and a recent pulmonary embolism (PE) presented with unilateral deep vein thrombosis (DVT) of the left lower extremity with complete occlusion of the external iliac and common femoral veins. Six passes with the ClotTriever catheter were performed along with percutaneous transluminal angioplasty between passes, resulting in 100% thrombus removal with an estimated blood loss of 10 mL. The patient avoided the intensive care unit (ICU) and was discharged after 48 hours. Venograms (A) before and (B) after thrombectomy show restoration of flow with the extracted thrombus (C and D). Case images courtesy of Dr Hamid Mojibian (Yale University School of Medicine, New Haven, CT).