3-2024

Safety and efficacy of mechanical aspiration thrombectomy for patients with acute lower extremity ischemia

Alex Powell
Miami Cardiac & Vascular Institute, alexp@baptisthealth.net

Citation
Journal of Vascular Surgery (2024) 79(3):584-592.e5

Safety and efficacy of mechanical aspiration thrombectomy for patients with acute lower extremity ischemia

Thomas S. Maldonado, MD,[a] Alex Powell, MD,[b] Heiko Wendorff, MD,[c] Jarrad Rowse, MD,[d] Khanjan H. Nagarsheth, MD,[e] David J. Dexter, MD,[f] Alan M. Dietzek, MD,[g] Patrick E. Muck, MD,[h] Frank R. Arko, MD,[i] *and* Jayer Chung, MD,[j] for the STRIDE study group, *New York, NY; Miami, FL; Munich, Germany; Birmingham, AL; Baltimore, MD; Norfolk, VA; Danbury, CT; Cincinnati, OH; Charlotte, NC; and Houston, TX*

ABSTRACT

Objective: Acute limb ischemia (ALI) is associated with high rates of amputation and consequent morbidity and mortality. The objective of this study is to report on the safety and efficacy of aspiration thrombectomy using the Indigo Aspiration System in patients with lower extremity (LE) ALI.

Methods: The STRIDE study was an international, multicenter, prospective, study that enrolled 119 participants presenting with LE-ALI. Patients were treated firstline with mechanical thrombectomy using the Indigo Aspiration System, before stenting or angioplasty, or other therapies as determined by treating physician. The primary end point was target limb salvage at 30 days after the procedure. Secondary end points within 30 days included technical success, defined as core laboratory-adjudicated Thrombolysis in Myocardial Infarction (TIMI) 2/3 flow rate immediately after the procedure, changes in modified Society for Vascular Surgery runoff score, improvement of Rutherford classification compared with before the procedure, patency, rate of device-related serious adverse events, and major periprocedural bleeding. Secondary end points that will be evaluated at 12 months include target limb salvage and mortality.

Results: Of the 119 participants enrolled at 16 sites, the mean age was 66.3 years (46.2% female). At baseline (n = 119), ischemic severity was classified as Rutherford I in 10.9%, Rutherford IIa in 54.6%, and Rutherford IIb in 34.5%. The mean target thrombus length was 125.7 ± 124.7 mm. Before the procedure, 93.0% (of patients 107/115) had no flow (TIMI 0) through the target lesion. The target limb salvage rate at 30 days was 98.2% (109/111). The rate of periprocedural major bleed was 4.2% (5/119) and device-related serious adverse events was 0.8% (1/119). Restoration of flow (TIMI 2/3) was achieved in 96.3% of patients (105/109) immediately after the procedure. The median improvement in the modified Society for Vascular Surgery runoff score (before vs after the procedure) was 6.0 (interquartile range, 0.0-11.0). Rutherford classifications also improved after discharge in 86.5% of patients (83/96), as compared with preprocedural scores. Patency at 30 days was achieved in 89.4% of patients (101/113).

Conclusions: In the STRIDE (A Study of Patients with Lower Extremity Acute Limb Ischemia to Remove Thrombus with the Indigo Aspiration System) study, aspiration thrombectomy with the Indigo System provided a safe and effective endovascular treatment for patients with LE-ALI, resulting in a high rate (98.2%) of successful limb salvage at 30 days, with few periprocedural complications. (J Vasc Surg 2024;79:584-92.)

Keywords: Acute limb-threatening ischemia; Acute lower limb ischemia; Aspiration thrombectomy; Endovascular; Peripheral arterial disease

Acute limb ischemia (ALI), characterized by a sudden loss in arterial perfusion to the limbs (<14 days of symptom onset),[1] is a vascular emergency necessitating urgent evaluation and management. The European Society for Vascular Surgery[2] practice guidelines recommend prompt diagnosis and rapid revascularization to decrease the risk of limb loss or death, either by means of catheter-based thrombolysis, thromboaspiration, or open surgery.

Given the paucity of data and heterogeneous presentation, the true incidence of ALI remains uncertain.[2]

From the NYU Langone Medical Center, New York[a]; the Baptist Hospital of Miami, Miami[b]; the Klinikum rechts der Isar, Munich[c]; the University of Alabama at Birmingham, Birmingham[d]; the University of Maryland School of Medicine, Baltimore[e]; the Sentara Norfolk General Hospital, Norfolk[f]; the Danbury Hospital, Danbury[g]; TriHealth, Cincinnati[h]; the Sanger Heart and Vascular Institute, Charlotte[i]; and the Division of Vascular Surgery & Endovascular Therapy, Baylor College of Medicine, Houston.[j]

This study was funded by Penumbra Inc. (Alameda).

ClinicalTrials.gov: NCT04144959.

Presented at the Forty-fifth Annual Charing Cross Symposium (CX), London, UK, April 25-27, 2023.

Additional material for this article may be found online at www.jvascsurg.org.

Correspondence: Thomas S. Maldonado, MD, NYU Langone Vascular & Endovascular Surgery Associates, ,530 First Ave, 11th Floor, New York, NY 10016 (e-mail: thomas.maldonado@nyumc.org).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2023.10.062

However, estimates from the United States[3] suggest a prevalence of 26 patients/100,000 persons/year, and an estimate of approximately 10 patients/100,000 persons/year in the UK.[4]

ALI is associated with high morbidity and mortality rates, with reported mortality at 1 year estimated from 15.0%[1] to 42.5%[2,3] and limb loss at 1 year between 11.0% and 14.8%.[2,3] Optimal clinical outcomes, therefore, necessitate rapid recognition of the condition and prompt restoration of arterial blood flow, to avoid irreversible ischemia and to support limb salvage.[5,6]

Contemporary revascularization guidelines for ALI include, but are not limited to, catheter-directed thrombolysis (CDT), percutaneous thromboaspiration, bypass graft, and surgical thromboembolectomy.[5,6] Over the past decades, the surgical management of ALI has evolved to include endovascular approaches,[3,7] especially after the publication of three randomized, multicenter trials establishing the efficacy of CDT as compared with surgical revascularization.[8-10] CDT,[11] along with newer endovascular approaches including aspiration thrombectomy, have become routine for restoring perfusion in patients with ALI in the Rutherford ALI classification I and II categories.[3,5,8] Nevertheless, the cost of ALI-related complications and mortality remains high, and CDT carries additional risk of vascular complications.[12,13] This factor has led to a strong interest in assessing the efficacy of different revascularization devices and procedures, especially those that may not require thrombolytics.[14] Furthermore, interventional outcomes for patients with ALI remain uncertain, and, despite recent improvements in therapeutic technique and decreases in 1-year amputation rates, there have been no significant improvements in 1-year amputation-free survival, which remains unchanged at 52.3%.[3]

The STRIDE (A Study of Patients with Lower Extremity Acute Limb Ischemia to Remove Thrombus with the Indigo Aspiration System) study was a multicenter, prospective study designed to collect essential, contemporary data on the treatment of ALI, and to assess the safety and efficacy of aspiration thrombectomy using the Indigo Aspiration System (Penumbra Inc, Alameda, CA). Patients presenting with ALI with a vascular severity of Rutherford I to IIb, and treated firstline with the Indigo Aspiration System were considered for enrollment.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter prospective nonrandomized cohort study
- **Key Findings:** Aspiration thrombectomy in 119 participants with lower-extremity acute limb ischemia, resulted in 30-day target limb salvage rates of 98.2%. Rates of periprocedural major bleed was 4.2% and device-related serious adverse events was 0.8%. Immediately after the procedure, flow (Thrombolysis in Myocardial Infarction 2/3) was restored in 96.3% of patients.
- **Take Home Message:** Mechanical aspiration thrombectomy may provide a beneficial treatment option for patients with lower-extremity acute limb ischemia, with high rates of safety and efficacy.

METHODS

Design

The STRIDE study was a prospective, multicenter, observational study to evaluate the safety and efficacy of firstline aspiration thrombectomy (before stenting, angioplasty, and/or other adjunctive procedures) for patients with lower extremity (LE)-ALI (ClinicalTrials.gov Identifier: NCT04144959). This study enrolled 119 participants from 16 sites (13 United States, 3 Europe). The enrollment period was December 17, 2019, to December 5, 2022, with 30-day follow-up completed in January 2023.

Eligibility criteria

Patients (aged ≥18) presenting with acute (≤14 days) occlusion of the lower limb artery(ies) and treated firstline with Indigo Aspiration System (Penumbra Inc.), were eligible. Additional inclusion criteria were patients with a Rutherford Category I, IIa, or IIb score, as well as informed consent obtained from either the patient or legally authorized representative. Arteries below the inguinal ligament were considered arteries of the lower limb. Thrombus extension into the iliac artery was allowed, as long as target thrombus was present below the inguinal ligament as well. Study exclusion criteria are provided in Appendix 1.

Informed consent was obtained using approved institutional review board/ethics committee consent forms, in accordance with local and international ethical guidelines, and per site routine clinical practice. Screening and enrollment logs of eligible participants with LE-ALI as determined by investigators per routine clinical evaluation were maintained at participating hospitals with exclusion reason(s) documented. Participants were considered enrolled when informed consent was obtained and the study device was inserted into the body. At sites in the United States, patients who were identified for participation and met eligibility criteria could be consented up to 2 calendar days after firstline treatment with the Indigo Aspiration System, but before discharge. For sites in Europe, the informed consent process was applied per local ethics committee approvals. Participants who provided consent outside of the protocol-specified window, for example, owing to delays caused by the coronavirus disease 2019 pandemic, required a protocol deviation for

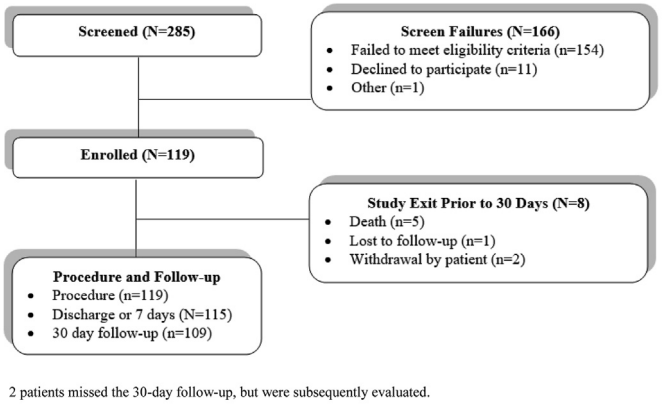

Fig. Flow diagram. Note that two patients missed the 30-day follow-up, but were subsequently evaluated.

delayed consent. A study flow diagram of screening and enrollment is provided in the Figure.

Procedures

All patients underwent noninvasive testing (duplex ultrasound [DUS] examination, computed tomography angiography [CTA], or magnetic resonance angiography [MRA]) of the affected limb for the initial LE-ALI diagnosis and assessment of target lesion. Firstline treatment was aspiration thrombectomy with the Indigo System: thrombus was aspirated using a continuous aspiration source (ENGINE Pump or Pump MAX) designed to maintain consistent vacuum (98.9 kPa or −29.2 in Hg for ENGINE), in conjunction with an aspiration catheter. The most common aspiration catheters were CAT 8 (8F) and Lightning 7 (7F; CE Mark approval in April 2022), used in 35.3% (42/119) and 31.1% (37/119) of patients, respectively. A list of all catheters used is provided in the Appendix 2. The aspiration catheter was introduced through a guide or introducer sheath into the peripheral vasculature and taken over a guidewire to the site of primary occlusion. Additional aspiration catheters with 5F to 12F compatibility were used as determined by target vessel size and at investigator discretion. If needed, an Indigo Separator was used in accordance with the instructions for use to facilitate clearing of thrombus from the catheter lumen. The pump canister and integrated clot catcher (part of the ENGINE Pump) provided live procedural feedback during thrombus engagement and removal. The aspiration system was designed to engage clot while minimizing blood loss, in some cases by using an electronic system (Lightning Aspiration Tubing). Per physician preference, adjunctive treatment could be administered after firstline therapy, and included intra-arterial tissue plasminogen activator. After satisfactory removal of thrombus, balloon angioplasty and stent implantation could be performed.

Follow-up visits for imaging, assessments, documentation of adverse events (AEs), and quality of life metrics occurred at discharge or 7 days (whichever occurred first), and at 30 ± 14 days after the procedure. Patient assessments collected at 30-day follow-up included vital signs, Rutherford classification, ankle-brachial index, degree of stenosis based on imaging (DUS examination/CTA/MRA), medication review, and AE review. Additional follow-up visits at 6 and 12 months will assess all of the outcomes listed. In addition, 12-month limb salvage rate and 12-month mortality will be assessed.

Imaging core laboratory

Images (DUS examination, CTA, or MRA) were deidentified with respect to participant, physician, and study site before upload for review and adjudication by an independent core laboratory. The imaging core laboratory comprised independent medical doctor(s) who did not participate in the study and reviewed images to adjudicate intraprocedural angiograms.

Primary and secondary end points

The primary end point was target limb salvage rate at 30 days after the procedure. Secondary end points included technical success defined as core laboratory-adjudicated reperfusion (Thrombolysis in Myocardial Infarction [TIMI] 2/3) rate immediately after the procedure, change in modified Society for Vascular Surgery (SVS) runoff score (calculated using the degree of stenosis/occlusion in the popliteal artery and three tibial vessels) compared with baseline, improvement of Rutherford classification compared with before the procedure, 30-day patency (assessed as target lesion without hemodynamically significant stenosis/reocclusion on duplex ultrasound examination [>50%], and without target lesion reintervention), rates of device-related serious AEs (SAEs), and periprocedural major bleed.

Definitions

ALI. Levels of severity for ALI are stratified by Rutherford categories I (viable), IIa (marginally threatened), IIb (immediately threatened), and III (irreversible).[15] Additional details provided in the Appendix 3.

AEs. An AE was defined as any undesirable clinical event occurring in a patient during a clinical trial, whether or not it is considered related to the study device or whether anticipated or unanticipated. This includes a change in a patient's condition or laboratory results that have or could have a deleterious effect on the patient's health or well-being, or an untoward clinical sign in users or other persons related to use of medical device.

SAEs. An SAE was defined as event that led to death or an event that led to serious deterioration in the health of the patient that resulted in life-threatening illness or injury, chronic disease, or permanent impairment of a body structure or a body function; or that required inpatient hospitalization or prolongation of existing

hospitalization; or that resulted in medical or surgical intervention to arrest permanent impairment to body structure or a body function.

Distal embolization. A distal embolization was clot that migrated during aspiration or that was not present at baseline imaging, as determined by the investigator. Distal embolization to a new territory requiring intervention following the index procedure is reportable as an AE.

Minor amputation. A minor amputation was defined as the surgical removal of a portion or segment of the LE distal to or through the tarsometatarsal joints.

Major amputation. A major amputation was defined as complete or partial removal of the limb that occurs proximal to the tarsometatarsal joints.

Limb salvage. Limb salvage was defined as condition of the extremity with potential to secure viability and preserve motor function to the weight-bearing portion of the foot if treated. A limb is considered salvageable if amputation is performed at or distal to tarsometatarsal joint.

Major bleeding. Major bleeding was considered as fatal bleeding or bleeding leading to a decrease in hemoglobin of ≥5 g/dL, or significant hypotension with the need for inotropes or requiring surgery (other than vascular site repair), or symptomatic intracranial hemorrhage or requiring transfusion of ≥2 U packed red blood cells (PRBC) or equivalent whole blood.

Minor bleeding. Minor bleeding results in a decrease in hemoglobin of 3 to <5 g/dL and/or requires a blood transfusion of 1 U PRBC or equivalent whole blood.

Modified SVS runoff score. The modified SVS runoff score was calculated using the angiogram by assessing the patency and degree of stenosis/occlusion in the popliteal artery and the three tibial vessels.[16]

Patency. Patency was defined as a target lesion without a hemodynamically significant stenosis/reocclusion on duplex ultrasound examination (>50%) and without target lesion reintervention.

TIMI, adapted. We used the following TIMI classifications: grade 0, no perfusion; grade 1, perfusion after initial occlusion but no distal branch filling; grade 2, perfusion with incomplete or slow distal branch filling; and grade 3, full perfusion with filling of all distal branches.

Tandem lesion. A tandem lesion was defined as two or more significant stenoses of ≥50% that are separated by an angiographically normal segment of fewer than three reference vessel diameters.

Statistical analyses

Data were summarized using standard descriptive statistics (number of observations, mean, median, standard deviation, interquartile range, and minimum and maximum for continuous variables; counts and percentages for discrete variables). Confidence intervals (CIs) were provided as exact CI unless otherwise noted. As part of the primary analysis, all performance and safety outcomes were analyzed under the intent-to-treat principle, which included all enrolled patients. Analyses were conducted using SAS version 9.4 or higher (SAS Institute, Cary, NC).

The primary end point was the target limb salvage rate at 30 days after the procedure. The limb was considered salvaged if no major amputation was performed within 30 days after the procedure. Limb salvage was evaluated on participants with at least one follow-up visit. This primary end point was met if the lower limit of the 95% CI of the primary end point rate was >85.7% and was derived from an aggregate historical control of 95.7% observed under current standards of care.

RESULTS

Between December 17, 2019, and December 5, 2022, 119 participants were enrolled across 13 investigational sites in the United States (108 participants) and 3 sites in Europe (11 participants). Of 285 screened participants, screen failures occurred in 58.2% (166/285; details are presented in Appendix 4) and 41.8% (119/285) were enrolled. Of 108 participants enrolled in the United States, 45.4% (49/108) consented after the procedure. Before the 30-day follow-up visit, eight participants exited the study early and two missed the 30-day follow-up, but were subsequently evaluated. This resulted in 109 participants in the 30-day follow-up analyses (Figure).

Baseline characteristics. Demographics and patient characteristics and comorbidities are presented in Table I. The mean age of this cohort was 66.3 ± 13.27 years, with 54.6% at ≥65 years old, 46.2% female, and 67.2% White. Of the patients included, 86.6% presented with a history of hypertension, 21.0% with atrial fibrillation, and 37.8% with diabetes mellitus. Prior intervention on the affected limb occurred in 53.8% of patients, and included surgical (47.9%) and endovascular (42.9%) revascularization.

Ischemic severity at baseline was classified as Rutherford I (viable) in 10.9% (13/119), IIa (marginally threatened) in 54.6%, and IIb (immediately threatened) in 34.5% (Table II). The mean preprocedural ankle-brachial index (ABI) for the treated index limb was 0.40 ± 0.32.

Thrombus characteristics. Thrombi were most commonly located in the popliteal artery, affecting 58.0% of patients (69/119), followed by the superficial femoral artery in 45.4% (54/119) (Table II). For patients with thrombus in native vessels only, the femoral-popliteal region was involved in 93.9% of patients (93/99), the tibial region in 42.4% (42/99), and the pedal region in 2.0% (2/99). Thrombus load affected multiple vessels in 69.7% of patients (69/99), with more than four vessels involved in 12.1 of patients % (12/99). Mean thrombus length was 125.7 ± 124.7 mm, with a mean lesion diameter of 5.4 ± 1.8 mm (Table II).

Table I. Demographics and comorbidities

Demographics	Mean ± SD or % (n/N)
Age, years	66.3 ± 13.27
Sex, female	46.2 (55/119)
Race[a]	
Asian	0.8 (1/119)
Black or African American	20.2 (24/119)
White	67.2 (80/119)
Other	2.5 (3/119)
Not reportable (European sites)	9.2 (11/119)
Comorbidities	
Cardiovascular history and risk factors	
Angina	8.4 (10/119)
Atrial fibrillation	21.0 (25/119)
Coronary artery disease	32.8 (39/119)
Heart failure	12.6 (15/119)
Hypertension	86.6 (103/119)
Hyperlipidemia	84.0 (100/119)
Vascular history	
Chronic limb ischemia	47.1 (56/119)
Prior revascularization of affected limb	53.8 (64/119)
Endovascular[b] (includes balloon and stent)	42.9 (51/119)
Surgical[b] (includes endarterectomy, bypass graft, and graft revisions)	47.9 (57/119)
Bypass graft	22.7 (27/119)
Autogenous graft	3.4 (4/119)
Prosthetic graft	19.3 (23/119)
Amputation of the contralateral limb	4.2 (5/119)
Amputation of the ipsilateral limb, below tarsometatarsal joint	5.9 (7/119)
Other history	
Cancer	21.0 (25/119)
Renal failure/ insufficiency	10.1 (12/119)
Diabetes mellitus	37.8 (45/119)
Tobacco use within last 10 years	53.8 (64/119)
Concomitant medications, at baseline	
Statin use — single	77.3 (92/119)
Statin use — combination	1.7 (2/119)
Hormone replacement therapy	2.5 (3/119)
Anticoagulant	71.4 (85/119)
Antiplatelet	55.5 (66/119)

[a]More than one race may be selected.
[b]More than one revascularization category may be selected.

Procedural characteristics. Procedural characteristics are presented in Table III. The median aspiration time was 22 minutes (interquartile range , 12.0-47.0 minutes). Estimated blood loss volume was <400 mL in 82.8% of patients (96/116). There were 12 cases of distal embolization, 10 of which were resolved during the index procedure. Of the remaining two cases, one was reported as an AE that was resolved with thrombolysis after the index procedure. The other was not reported as an AE, because the investigator determined that it was not significant clinically and did not require any treatment. Overnight stays in the intensive care unit during the index procedure were reported in 30.3% of patients (36/119). Of these 36 patients, the median intensive care unit stay was 2.5 days (interquartile range, 1.5-4.4 days). Overnight thrombolytics were used in 19.3% of cases (23/119).

Primary and secondary outcomes. Primary and secondary outcomes are provided in Table IV. The limb salvage rate at 30 days was 98.2% (109/111; 95% CI, 93.6%-99.8%). Of the two patients who underwent a major amputation within 30 days, one was a 54-year-old man with Rutherford IIa ALI with a prior diagnosis of chronic limb ischemia with prior endarterectomy and femoral-anterior tibial polytetrafluoroethylene with vein patch bypass graft in the index limb. Preprocedural assessments included a modified SVS runoff score of 16, ABI of 0, and TIMI flow 0. The target thrombus measuring 627 mm was in the bypass graft and was completely removed using Indigo at the index procedure. After the procedure, TIMI flow 3 was established and the modified SVS runoff score improved by 2.5 points. However, the bypass graft repeatedly occluded despite additional surgical revascularization at 2 and 4 days after the index procedure and a below-the-knee amputation was performed 7 days after the index procedure. The other patient was a 75-year-old woman with Rutherford IIa ALI with type 1 diabetes who previously had two digits amputated from the target limb owing to a nonhealing wound. Preprocedural assessments included an modified SVS runoff score of 18.5, ABI of 0, and TIMI flow 0. Target thrombus measuring 60 mm was in the right superficial femoral and popliteal arteries and was

Table II. Baseline characteristics

Baseline characteristic (n = 119)	% (n/N) or mean ± SD or median [IQR]
Thrombus location	
Iliac	5.9 (7/119)
Common femoral	11.8 (14/119)
Superficial femoral	45.4 (54/119)
Profunda	5.0 (6/119)
Popliteal	58.0 (69/119)
Tibioperoneal trunk	23.5 (28/119)
Peroneal	21.0 (25/119)
Anterior tibial	20.2 (24/119)
Posterior tibial	15.1 (18/119)
Dorsalis pedis	1.7 (2/119)
Other: distal SFA and popliteal overlap	0.8 (1/119)
In graft	16.8 (20/119)
Baseline thrombus and lesion evaluation	
Target thrombus length, mm (n = 113)	
Mean ± SD	125.7 ± 124.7
Median [IQR]	80.0 [40.0-197.0]
Range (min, max)	3.0, 627.0
Target lesion diameter, mm (n = 97)	
Mean ± SD	5.4 ± 1.8
Median [IQR]	6.0 [4.0-6.0]
Range (min, max)	1.0, 10.0
Tandem lesion	18.5 (22/119)
Baseline ischemic severity[a] (n = 119)	
Rutherford I. Viable	10.9 (13/119)
Rutherford IIa. Threatened marginally	54.6 (65/119)
Rutherford IIb. Threatened immediately	34.5 (41/119)
Baseline modified SVS runoff score[a] (n = 113)	10.0 [6.5-16.0]

IQR, interquartile range; *SD*, standard deviation; *SFA*, superior femoral artery; *SVS*, society for vascular surgery.
[a]Rutherford classification and modified SVS runoff scores were site reported.

Table III. Procedural characteristics

Procedural characteristic (n = 119)	% (n/N)
Estimated blood loss volume, mL[a]	
<100	32.8 (38/116)
100-199	19.8 (23/116)
200-399	30.2 (35/116)
400-699	13.8 (16/116)
≥700	3.4 (4/116)
Anticoagulant administered during procedure	90.8 (108/119)
Distal embolization	10.1 (12/119)
Distal embolization resolved	83.3 (10/12)
Distal embolization not resolved	16.7 (2/12)
Procedure times	
Indigo aspiration time,[b] minutes (n = 83)	
Mean ± SD	32.8 ± 36.83
Median [IQR]	22.0 [12.0-47.0]
Range (min, max)	1.0, 275.0
Adjunctive treatment of thrombus	
IA rtPA, overnight use	19.3 (23/119)
Mechanical thrombectomy, not Indigo	2.5 (3/119)
Cutdown and open thrombectomy	0.8 (1/119)
Post-thrombectomy treatment of underlying lesion	
Balloon	67.2 (80/119)
Stent	32.8 (39/119)
Lithotripsy	1.7 (2/119)
Laser atherectomy	0.8 (1/119)
Hospital and ICU stay during index visit	
Patient had an ICU stay	30.3 (36/119)
Length of ICU stay, days (n = 36)	
Mean ± SD	3.8 ± 3.68
Median [IQR]	2.5 [1.5-4.4]
Range (min, max)	0.3, 15.0

IA, Intra-arterial; *ICU*, Intensive care unit; *IQR*, interquartile range; *rtPA*, recombinant tissue plasminogen activator; *SD*, standard deviation.
[a]Estimated blood loss was calculated by subtracting the amount of saline flush used from the total amount of aspirated material in the canister.
[b]Time from first Indigo Aspiration Catheter insertion to last Indigo Aspiration Catheter removal.

partially removed using Indigo and post-thrombectomy balloon angioplasty for underlying lesion was performed. After the procedure, the modified SVS runoff score improved by 9 points. TIMI flow could not be assessed because the site did not capture images after all additional treatments at index were performed. The patient continued to report increased leg pain owing to anterior tibial stenosis and underwent multiple balloon angioplasty procedures at 7 and 13 days after the index procedure and eventually had a below the knee amputation at 25 days after the index procedure.

The modified SVS runoff score was improved in 70.8% of patients (75/106; 95% CI, 61.1%-79.2%). Rutherford classifications also improved after discharge in 86.5% of patients (83/96), as compared with preprocedural scores. Patency at 30 days was achieved in 89.4% of patients (101/113). Mortality rate at 30 days was 3.4% (4/119).

Table IV. Primary and secondary outcomes

Outcomes	% (n/N)	95% CI
Limb salvage and mortality at day 30		
Limb salvage[a] at day 30	98.2% (109/111)	(93.6%-99.8%)
Mortality at day 30	3.4% (4/119)	(0.9%-8.4%)
Secondary efficacy analysis		
TIMI 2/3 flow rate immediate postprocedure[2] (core laboratory)	96.3% (105/109)	(90.9%-99.0%)
Change in Modified SVS runoff score (postprocedure[b] minus preprocedure) (n = 106)		
Mean ± SD	6.3 ± 5.49	NA
Median [IQR]	6.0 [0.0-11.0]	(4.0-9.0)
Range (min, max)	−1.0, 18.0	NA
Categorical change in modified SVS runoff (postprocedure[c] minus preprocedure)		
Improved	70.8% (75/106)	(61.1%-79.2%)
Stable	28.3% (30/106)	(20.0%-37.9%)
Worsening	0.9% (1/106)	(0.0%-5.1%)
Patent at 30 days[d]	89.4% (101/113)	(82.2%-94.4%)

CI, confidence interval; *IQR*, interquartile range; *SD*, standard deviation; *SVS*, society for vascular surgery; *TIMI*, thrombolysis in myocardial infarction.
[a]Limb salvage defined as no amputations proximal to the transmetatarsal joint.
[b]Patients with no follow-up visits or a visit <10 days after procedure were excluded from this analysis.
[c]Postprocedure is defined as the result after all additional treatment, when available; otherwise it is the post-Indigo result.
[d]Patency was defined as no retreatment owing to distal embolization, reocclusion, or revascularization failure on target limb within 30 days. Patients with no follow-up visits and who spent <10 days enrolled were excluded from this analysis.

Table V. Adverse events (*AEs*) within 30 days of the procedure

AE[a,b,c,d]	All events (patients, rate)	All serious events (patients, rate)	Device-related events (patients, rate)
Minor bleeding	1 (1%-0.8%)	0 (0%-0.0%)	0 (0%-0.0%)
Major bleeding, periprocedural (within 48 hours)	5 (5%-4.2%)	5 (5%-4.2%)	0 (0%-0.0%)
Major bleeding, not periprocedural	2 (2%-1.7%)	2 (2%-1.7%)	0 (0%-0.0%)
Peripheral/distal embolism	4 (3%-2.5%)	4 (3%-2.5%)	1 (1%-0.8%)
Vessel dissection	2 (2%-1.7%)	2 (2%-1.7%)	0 (0%-0.0%)
Pseudoaneurysm	4 (4%-3.4%)	4 (4%-3.4%)	0 (0%-0.0%)
Arterial thrombosis	3 (3%-2.5%)	3 (3%-2.5%)	0 (0%-0.0%)
Compartment syndrome [e]	4 (4%-3.4%)	4 (4%-3.4%)	0 (0%-0.0%)

[a]Patients can be captured in multiple groups.
[b]All events with start date within 30 days postprocedure.
[c]Event was considered related if it is probably or definitely related.
[d]Rate out of all enrolled patients (n = 119).
[e]Treated with postoperative fasciotomy.

Safety and AEs. The periprocedural major bleed rate was 4.2% (5/119), none of which were device related. All patients with major bleeds were female. Four patients met the criteria for major bleeding owing to a transfusion of ≥2 U PRBC and one met criteria owing to a decrease in hemoglobin of >5 g/dL. Of the five patients, four had a preprocedural hemoglobin value of <10 g/dL and hematocrit of ≤31%, and two had a reported history of chronic anemia. One patient (0.8%) experienced a device-related AE, a distal embolism. The patient had an occlusion from the right common internal iliac, external iliac, and common femoral arteries to the superficial femoral and profunda origin. After thrombectomy, a residual clot from the external iliac was noted to have traveled 2 cm distally into the common femoral artery and profunda origin and was treated with overnight lysis after the index procedure. All AEs that occurred within 30 days of index procedure are described in Table V. Overall, 6.7% of patients (8/119) underwent a fasciotomy during the study: 3.4% of patients (4/119) underwent a prophylactic

fasciotomy at the index procedure and 3.4% of patients (4/119) underwent a fasciotomy for symptomatic compartment syndrome. The latter group were reported as AEs.

Subgroup analyses. A majority of patients (53.8%) enrolled had prior intervention for peripheral artery disease on the affected limb. We compared patients with previous intervention vs those with no previous intervention and found no significant differences with respect to limb salvage at 30 days, patency at 30 days, change in modified SVS runoff score, improvement of Rutherford classification, mortality at 30 days, periprocedural major bleeding, or device-related SAEs. However, patients with previous intervention were more likely to have TIMI 2/3 immediately after the procedure (100% vs 91.8%; $P = .0381$). Full results are presented in Appendix 5.

We also compared outcomes for patients who were Rutherford class I or IIa at baseline with patients who were Rutherford class IIb at baseline. We did not find any significant differences in limb salvage at 30 days, patency at 30 days, procedural success, median change in modified SVS runoff score, mortality at 30 days, periprocedural major bleeding, or device-related SAEs.

DISCUSSION

Acute ischemia of the lower extremity remains an emergent vascular condition, affecting an estimated 1.5 patients per 10,000 persons per year,[1,2,17] with a similar incidence in males and females.[4] The condition carries a considerable burden of morbidity and mortality, with a high incidence of limb loss despite urgent revascularization.[1,2,17]

Results from this prospective, real-world, international study at 30 days substantiate the efficacy and safety of mechanical aspiration thrombectomy as a firstline treatment for patients with LE-ALI. In this study, the primary end point was achieved with a target limb salvage rate of 98.2% at 30 days, and the secondary efficacy end point met with a primary patency rate of 89.4% at 30 days.

These outcomes align well with, or are better than, contemporary trials of firstline mechanical thrombectomy, which report rates of target limb salvage at 30 days ranging from 89.9% to 97.9%,[18-20] and ≤100%[21] in a retrospective study of 37 patients using manual aspiration as firstline therapy. In these studies, patency rates up to 30 days were reported at 88.0%,[21] 90.5%,[18] and 100%.[20] The target limb salvage rates achieved in the STRIDE study also compare favorably with both surgical revascularization and CDT, where among patients with ALI treated with either thrombolytic agents or surgery, rates of in-hospital amputation can reach 10% to 15%.[1,17]

The secondary safety end points in the STRIDE study were met with a periprocedural major bleeding rate of 4.2% and a device-related SAE rate of 0.8% (Table V). The rate of all-cause mortality at 30 days was 3.4%. These outcomes were again comparable with data from studies using mechanical thrombectomy as a firstline therapy, where reported bleeding complications could range from 0.60%,[22] 5.00%,[21] to 11.76%.[20] Mortality at 30 days from these same studies were 9.0%, 10.8% (at 12 months), and 5.8%, respectively. By contrast, European Society for Vascular Surgery guidelines report higher rates of major bleeding at 30 days for surgical revascularization (between 0.7% and 30.0%) as well as for thrombolysis (≤5.6%-38.7%).[2] The high risk of associated major bleeding is a notable limitation of CDT. Endovascular aspiration thrombectomy using the Indigo System is a safe, effective minimally invasive treatment option that can provide rapid revascularization and may offer the option to eliminate thrombolytic use for some patients. Nevertheless, there is undoubtably a subset of patients for whom some form of adjunctive thrombolysis may be performed for a variety of reasons. Individual case characteristics or physician preference certainly factor into this decision. The STRIDE study permitted adjunctive thrombolytics to be used at the discretion of the treating physician so as to adhere to real-world practice. As such, we found that overnight thrombolytics were used in 19.3% of patients (23/119). Often, such adjunctive treatment was chosen in more complex patient scenarios as reflected in the STRIDE study baseline characteristics: 22.7% of patients (27/119) had bypass grafts, 36.1% (43/119) had stents, 69.7% (69/99) had thrombus in multiple vessels, and 34.5% (41/119) were classified as Rutherford IIb. Despite the use of adjunctive thrombolytics, we believe that the use of Indigo as a firstline strategy for treating ALI, may have decreased or eliminated the need for thrombolytics in some patients. Other studies have reported rates of post-treatment thrombolytic use ranging from 7.0%[20] to 21.8%[18] when using alternative mechanical thrombectomy devices in similarly complex populations.

STRENGTHS AND LIMITATIONS

To our knowledge, this is the largest, prospective, international, real-world study evaluating the use of aspiration thrombectomy in the treatment of LE-ALI. Strengths of this registry include adjudication by an imaging core laboratory for revascularization rates and the inclusion of a cohort of patients that were evaluated across multiple settings and operators. The STRIDE study also enrolled a patient population with near-parity of both males and females, a distribution that is rarely studied or reported in considering therapeutic options for ALI. Limitations of this prospective study include the lack of a comparator arm and central adjudication by independent medical reviewers, and that investigator assessment of thrombus origin (embolic or thrombotic) was not collected. In addition, a subset of patients provided consent after the procedure owing to the urgent nature of this condition.

CONCLUSIONS

Aspiration thrombectomy using the Indigo Aspiration System as firstline treatment provided a safe and effective endovascular treatment for patients with LE-ALI. Results from the STRIDE study showed a high rate (98.2%) of successful limb salvage at 30 days, with few periprocedural complications. Mechanical aspiration thrombectomy provides a viable treatment option for patients with LE-ALI.

We would like to thank the STRIDE study investigators and study coordinators for their immense contributions to this study. This study was funded by Penumbra Inc. (Alameda). The authors acknowledge Penumbra employees R. Kaimal, MS, for statistical support and W. Ho, PhD, and T. McBride, PhD, for writing assistance.

AUTHOR CONTRIBUTIONS

Conception and design: TM, AP, HW, JR, KN, DD, AD, PM, FA, JC
Analysis and interpretation: TM, JC
Data collection: TM, AP, HW, JR, KN, DD, AD, PM, FA, JC
Writing the article: TM, JC
Critical revision of the article: TM, AP, HW, JR, KN, DD, AD, PM, FA, JC
Final approval of the article: TM, AP, HW, JR, KN, DD, AD, PM, FA, JC
Statistical analysis: TM
Obtained funding: Not applicable
Overall responsibility: TM

DISCLOSURES

T.M. reports a consulting agreement with Penumbra. P.M. reports a speaker/consultant disclosure with Penumbra. F.A. reports a speaker/consultant disclosure Penumbra. The remaining authors report no conflicts.

REFERENCES

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg*. 2007;33:S1–S75.
2. Björck M, Earnshaw JJ, Acosta S, et al. Editor's choice - European society for vascular surgery (ESVS) 2020 clinical practice guidelines on the management of acute limb ischaemia. *Eur J Vasc Endovasc Surg*. 2020;59:173–218.
3. Baril DT, Ghosh K, Rosen AB. Trends in the incidence, treatment, and outcomes of acute lower extremity ischemia in the United States Medicare population. *J Vasc Surg*. 2014;60:669–677.e662.
4. Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM. Population-based study of incidence, risk factors, outcome, and prognosis of ischemic peripheral arterial events: implications for prevention. *Circulation*. 2015;132:1805–1815.
5. Aboyans V, Ricco JB, Bartelink MEL, et al. Editor's choice - 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2018;55:305–368.
6. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2017;69:e71–e126.
7. Leung DA, Blitz LR, Nelson T, et al. Rheolytic pharmacomechanical thrombectomy for the management of acute limb ischemia: results from the PEARL registry. *J Endovasc Ther*. 2015;22:546–557.
8. Investigators TS. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. *Ann Surg*. 1994;220:251–266. discussion: 266-8.
9. Ouriel K, Shortell CK, DeWeese JA, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg*. 1994;19:1021–1030.
10. Ouriel K, Veith FJ, Sasahara AA. Thrombolysis or peripheral arterial surgery: phase I results. TOPAS Investigators. *J Vasc Surg*. 1996;23:64–73. discussion: 74-5.
11. Morrison HL. Catheter-directed thrombolysis for acute limb ischemia. *Semin Intervent Radiol*. 2006;23:258–269.
12. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. *N Engl J Med*. 1998;338:1105–1111.
13. Kolte D, Kennedy KF, Shishehbor MH, et al. Endovascular versus surgical revascularization for acute limb ischemia: a propensity-score matched analysis. *Circ Cardiovasc Interv*. 2020;13:e008150.
14. Shishehbor MH. Acute and critical limb ischemia: when time is limb. *Cleve Clin J Med*. 2014;81:209–216.
15. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.
16. Duval S, Keo HH, Oldenburg NC, et al. The impact of prolonged lower limb ischemia on amputation, mortality, and functional status: the FRIENDS registry. *Am Heart J*. 2014;168:577–587.
17. Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. *N Engl J Med*. 2012;366:2198–2206.
18. Heller S, Lubanda JC, Varejka P, et al. Percutaneous mechanical thrombectomy using rotarex(R) S device in acute limb ischemia in infrainguinal occlusions. *BioMed Res Int*. 2017;2017:2362769.
19. Liang S, Zhou L, Ye K, Lu X. Limb salvage after percutaneous mechanical thrombectomy in patients with acute lower limb ischemia: a retrospective analysis from Two institutions. *Ann Vasc Surg*. 2019;58:151–159.
20. Liu L, Zhao J, Bi J, et al. Percutaneous mechanical atherothrombectomy using the rotarex device in acute ischemic disease of lower limbs: a China retrospective multicenter study on 186 patients. *Ann Vasc Surg*. 2022;85:146–155.
21. Oguzkurt L, Ozkan U, Gumus B, Coskun I, Koca N, Gulcan O. Percutaneous aspiration thrombectomy in the treatment of lower extremity thromboembolic occlusions. *Diagn Interventional Radiol*. 2010;16:79–83.
22. Fluck F, Stephan M, Augustin A, Rickert N, Bley TA, Kickuth R. Percutaneous mechanical thrombectomy in acute and subacute lower-extremity ischemia: impact of adjunctive, solely nonthrombolytic endovascular procedures. *Diagn Interv Radiol*. 2021;27:206–213.

Submitted Aug 7, 2023; accepted Oct 22, 2023.

Additional material for this article may be found online at www.jvascsurg.org.

DATA SUPPLEMENT (online only).

Appendix 1. Study Exclusion Criteria.

1. Life expectancy <1 year.
2. Target vessel size <2 mm.
3. Lower extremity acute limb ischemia secondary to dissections, vasculitis, and/or target vessel trauma.
4. Amputation in the ipsilateral limb.
5. Pregnancy or positive pregnancy test according to site specific standards of care (only required for women of childbearing potential, serum or urine acceptable).
6. Absolute contraindication to contrast administration.
7. Patient is unwilling or unable to comply with protocol follow-up schedule and/or based on the investigator's judgment the patient is not a good study candidate.
8. Currently participating in an investigational drug or device clinical trial that may confound the study end points. Patients in observational, natural history, and/or epidemiological studies not involving intervention are eligible.
9. Target thrombus in a saphenous vein bypass graft.

Appendix 2. Procedure information—catheters used

Penumbra catheters used[a]	% (n = 119)
CAT3	4.2% (5/119)
CAT5	2.5% (3/119)
CAT6	31.9% (38/119)
CAT8	35.3% (42/119)
Lightning 7	31.1% (37/119)
Lightning 8	8.4% (10/119)
Lightning 12	4.2% (5/119)
CAT RX	5% (6/119)
CATD	1.7% (2/119)

[a]Multiple devices may be used in a single participant.

Appendix 3. Rutherford Recommended standards for reports dealing with lower extremity ischemia: Revised version. Disease severity was categorized according to recommended standards for lower extremity ischemia (Rutherford et al. 1997).

Category Ia. The limb is viable not immediately threatened. No sensory loss or muscle weakness is apparent. Doppler flow signal is clearly audible in pedal arteries.

Category IIa. The limb is marginally threatened; salvageable if treated promptly. Sensory loss is none to minimal (toes). No muscle weakness is apparent. Doppler signals are not clearly audible in pedal arteries.

Category IIb. The limb is immediately threatened; salvageable with immediate revascularization. Sensory loss is mild to moderate, coupled with persistent ischemic rest pain. Muscle weakness is mild to moderate. Doppler signals are not clearly audible in pedal arteries.

Category III. The limb suffers irreversible ischemic change with major tissue loss or permanent nerve damage. Sensory loss and muscle weakness/paralysis are profound. Doppler signals are not audible for pedal arterial or venous flow.

Reference: Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version [published correction appears in J Vasc Surg 2001 Apr; 33(4):805]. J Vasc Surg. 1997; 26(3):517-538. https://doi.org/10.1016/s0741-5214(970045-4)

Appendix 4. Reasons for screen failure

Reason patient was not enrolled	All screen failures (n = 166)
Inclusion criteria not met	53.6% (89/166)
Patient age ≥18 years	1.2% (2/166)
Patient presents with acute (≤14 days) occlusion of lower limb artery(ies) (below inguinal ligament)	17.5% (29/166)
Patient with a Rutherford category IIa or IIb score	4.2% (7/166)
Patient with a Rutherford category I, IIa, or IIb score (Protocol version D or higher)	4.2% (7/166)
Frontline treatment with Indigo Aspiration System	15.7% (26/166)
Informed consent is obtained from either patient or legally authorized representative	12.0% (20/166)
Exclusion criteria met	39.8% (66/166)
Life expectancy <1 year	3.0% (5/166)
Target vessel size <2 mm	0.0% (0/166)
LE ALI secondary to dissections vasculitis and/or target vessel trauma	7.2% (12/166)
Amputation in the ipsilateral limb	5.4% (9/166)
Pregnancy or positive pregnancy test according to site-specific standards of care	0.0% (0/166)
Absolute contraindication to contrast administration	0.0% (0/166)
Patient is unwilling or unable to comply with protocol follow-up schedule and/or based on the investigator's judgment the patient is not a good study candidate	19.3% (32/166)
Currently participating in an investigational drug or device clinical trial that may confound the study end points	1.8% (3/166)
Target thrombus in a saphenous vein bypass graft	3.0% (5/166)
Patient met the entry criteria but declined to participate	6.6% (11/166)
Other reason for screen failure[a]	0.6% (1/166)

ALI, acute limb ischemia; *LE*, lower extremity.
Patients may have more than one reason for screen failure.
[a]Patient screen failed owing to surgery performed by a nonapproved/activated surgeon.

Appendix 5. Primary outcomes in patients with previous intervention on target limb vs no previous intervention on target limb

Selected end points	Previous intervention on target limb (n = 64)	No previous intervention on target limb (n = 55)	*P* value[a]	Difference (95% CI)[a]
Limb salvage at 30 days	98.4 (61/62)	98 (48/49)	1.0000	0.4% (−7.3% to 9.4%)
Mortality at 30 days	1.6 (1/64)	5.5 (3/55)	.3344	−3.9% (−13.9% to 3.8%)
Major periprocedural bleeding	3.1 (2/64)	5.5 (3/55)	.6612	−2.3% (−12.7% to 6.1%)
Device-related SAEs	1.6 (1/64)	0.0 (0/55)	1.0000	1.6% (−5.2% to 8.6%)
Patent at 30 day	84.4 (54/64)	95.9 (47/49)	.0652	−11.5% (−23.4% to 0.5%)
TIMI 2/3 flow rate immediate postprocedure (core laboratory)	100 (60/60)	91.8 (45/49)	.0381	8.0% (1.0% to 19.2%)
Change in modified SVS runoff score	6.0 [0.0-9.0]	7.5 [0.0-12.0]	.3209	

SAE, serious adverse event; *SVS*, society for vascular surgery.
Values are % (n/N) or median [interquartile range].
[a] *P* value is Wilcoxon for continuous variables and Fisher exact for categorical. The 95% CI is calculated using Fisher's exact method.