Eur J Vasc Endovasc Surg (2021) 61, 820–828

Safety and Efficacy of Vacuum Assisted Thrombo-Aspiration in Patients with Acute Lower Limb Ischaemia: The INDIAN Trial

Gianmarco de Donato [a,*], Edoardo Pasqui [a], Massimo Sponza [b], Francesco Intrieri [c], Angelo Spinazzola [d], Roberto Silingardi [e], Giuseppe Guzzardi [f], Maria Antonella Ruffino [g], Giancarlo Palasciano [a], Carlo Setacci [a], the INDIAN trial collaborators

[a] University of Siena, Siena, Italy
[b] Ospedale S. Maria della Misericordia, Udine, Italy
[c] Ospedale Santa Annunziata, Cosenza, Italy
[d] ASST Crema, Crema, Italy
[e] University of Modena, Modena, Italy
[f] Ospedale Maggiore della Carità, Novara, Italy
[g] AOU Città della Salute e della Scienza, Torino, Italy

WHAT THIS PAPER ADDS

This is the first prospective trial investigating the safety and efficacy of vacuum assisted thrombo-aspiration systems in patients with acute lower limb ischaemia in a controlled setting. Results of this investigation give more evidence for a shift of treatment recommendation towards endovascular options in patients with acute lower limb ischaemia, as already suggested by the recent European Society for Vascular Surgery/European Society for Cardiology guidelines.

Objective: The aim was to evaluate the short term safety and effectiveness of the Penumbra/Indigo aspiration thrombectomy Systems (Penumbra Inc.) in patients with acute lower limb ischaemia. (ALLI). Recently, endovascular vacuum assisted thrombectomy devices, similar to those used in the management of acute ischaemic stroke, have become available for peripheral arteries, but data are still scarce.

Methods: To assess vessel patency, a modified Thrombolysis in Myocardial Infarction (TIMI) classification, called TIPI (Thrombo-aspiration In Peripheral Ischaemia), is proposed. The TIPI flow is assessed at presentation, immediately after treatment with the study device, and after all adjuvant procedures. The primary outcome is the technical success of the thrombo-aspiration with the investigative system, defined as near complete or complete revascularisation TIPI 2 – 3. Safety and clinical success rate were collected at one month.

Results: One hundred and fifty patients were enrolled. The mean age was 72.4 years and 73.3% were male. Rutherford grade on enrolment was I in 16%, IIa in 40.7%, and IIb in 43.3% with a mean ankle brachial index of 0.19. Primary technical success (TIPI 2 – 3 flow) was achieved in 88.7% of patients. Adjunctive procedures included angioplasty/stenting of chronic atherosclerotic lesions (n = 39), thrombolysis (n = 31), covered stenting (n = 15), and supplementary Fogarty embolectomy (n = 6). After all interventions, assisted primary technical success was 95.3% (TIPI 2 – 3 in 143/150). No systemic bleeding complications or device related serious adverse events were reported. At one month follow up, one death, and one below the knee amputation were recorded. Primary patency was 92% (138/150), and the re-intervention rate was 7.33%, resulting in an assisted primary and secondary patency of 94% and 99.33%, respectively.

Conclusion: Results from the INDIAN registry reveal that mechanical thrombectomy using the Indigo system is safe and effective for revascularisation of ALLI as a primary therapy.

Keywords: Acute limb ischaemia, Endovascular treatment, Limb ischaemia, Limb salvage Malperfusion, Thrombo-aspiration
Article history: Received 17 August 2020, Accepted 7 January 2021, Available online 27 February 2021

INTRODUCTION

Acute lower limb ischaemia (ALLI) is still considered to be a significant event, carrying a considerable risk of amputation (up to 30%) and high peri-operative morbidity and mortality, especially in the elderly population (20% – 30%).[1–4]

Since the development of the balloon embolectomy catheter by Thomas Fogarty in 1963, surgical thrombo-embolectomy has been considered the gold standard

* Corresponding author. Department of Medicine, Surgery and Neuroscience, University of Siena, Viale Bracci, 53100, Siena, Italy.
E-mail address: dedonato@unisi.it (Gianmarco de Donato).

https://doi.org/10.1016/j.ejvs.2021.01.004

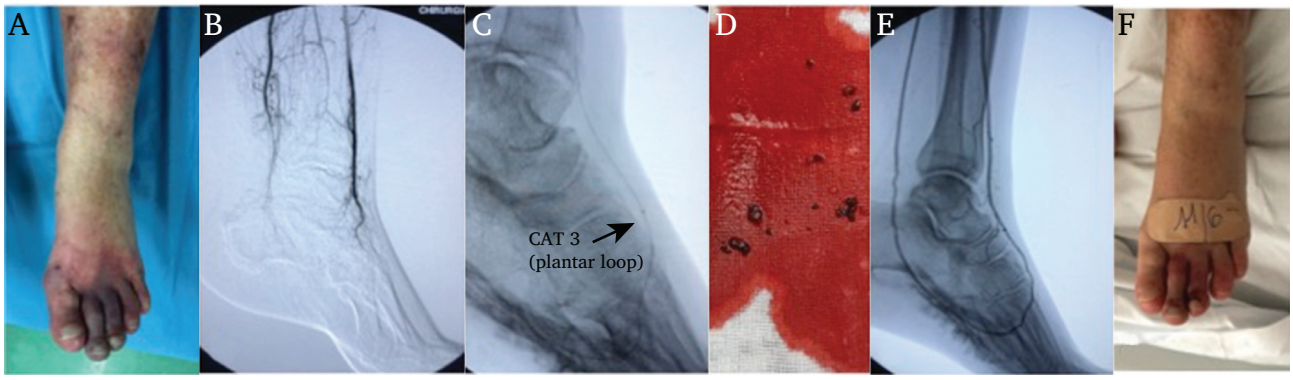


Figure 1. (A) Clinical presentation of the acute forefoot ischaemia with good pulsation of anterior and posterior tibial artery at the ankle. (B) Angiography shows acute below ankle (BTA) vessel occlusion. (C) Advancing the Indigo CAT3 through the BTA vessels with the plantar loop technique. (D) Macroscopic aspect of the thrombi aspirated. (E) Angiography after mechanical thrombo-aspiration revealed patency of the plantar arch. (F) Clinical appearance on post-operative day 1.

treatment.[5] A decade later, Dotter *et al.* introduced the concept of endovascular lysis of the acute clot, then modified to intra-arterial catheter directed selective thrombolysis (CDT).[6] Results from randomised trials comparing surgical embolectomy to CDT reveal that thrombolysis had the most significant advantage in acute prosthetic bypass graft occlusions. In contrast, patients with ALLI due to native arterial occlusions tend to show inferior results after thrombolysis, consisting of higher rates of haemorrhage and stroke at 30 days and increased risks of distal embolisation.[7,8]

Surgical management of ALLI has been considered the preferred treatment for years, but it has also been associated with a non-satisfactory revascularisation rate due to the presence of residual thrombus in distal vessels.[9]

Consequently, many new endovascular devices have been proposed to increase treatment success, decrease complications, and rapidly improve perfusion. Percutaneous manual thrombo-aspiration was the first technique proposed,[10] followed by a series of percutaneous mechanical thrombectomy (PMT) devices based on a different mechanism of action (mechanical fragmentation, aspiration, rheolytic thrombectomy and their combinations).

Many of the first generation mechanical endovascular devices for thrombus removal have failed to be adequately successful or have been associated with unacceptably high complication rates. The reasons have been mainly related to the limited trackability, the risk of vessel injury, and/or the incidence of incomplete revascularisation.[11]

Since 2005, the Penumbra mechanical thrombectomy System (Penumbra Inc, Alameda, CA, USA) became available in Europe and the United States for the revascularisation of occluded intracranial vessels in patients with acute ischaemic stroke. The Penumbra system uses vacuum aspiration as its primary mechanism of action. A flexible, atraumatic large bore catheter is delivered to the site of occlusion, and aspiration is applied directly to the lesion itself. To maintain lumen patency of the large bore catheter, a Penumbra Separator™ can be used at the tip of the catheter to facilitate aspiration of the clot continuously.

Using their proprietary catheter tracking technology and patented Separator technology for mechanical clot engagement, Penumbra launched the Indigo System in 2014, available from 3 F to 8 F, and specially designed for peripheral application and to potentially decrease the occurrences of artery damage, haemolysis, and distal embolisation described with other techniques.

The objective of this clinical investigation (INDIAN Registry: The Indigo System in Acute Lower-Limb Malperfusion; ClinicalTrials.gov ID code NCT03386370) was to evaluate the early safety and effectiveness of the endovascular Indigo aspiration thrombectomy systems (Penumbra Inc) in patients with ALLI in a controlled setting.[12]

MATERIALS AND METHODS

The INDIAN REGISTRY is an interventional, physician initiated, multicentre, prospective trial of patients with a diagnosis of ALLI treated with Penumbra/Indigo devices (Penumbra Inc, Alameda, CA, USA). This project was intended to be a national platform where every physician invited to participate could register his or her procedural data.

Before enrolling patients into the registry, all participating centres completed a minimum caseload of 20 procedures with the device under investigation. The ethics committee of each hospital was informed of the protocol design and endorsed the project.

Data were collected prospectively from 16 Italian centres and analysed by the Coordinator Centre.

Every physician was responsible for evaluating clinical events. The study was designed and sponsored by the Principal Investigators (G.d.D. and C.S.) from University of Siena, Italy.

Patient selection

The registry enrolled consecutive patients presenting with ALLI lasting $<$ 14 days considered suitable for thrombo-

Table 1. The innovative classification for Thrombo-aspiration In Peripheral Ischaemia (TIPI) modified from Thrombolysis in Myocardial Infarction (TIMI) classification

Description	TIPI score
No recanalisation of the thrombotic occlusion	0
Incomplete or partial recanalisation of the thrombotic occlusion with no distal flow	1
Incomplete or partial recanalisation of the thrombotic occlusion with any distal flow	2
Complete recanalisation of the thrombotic occlusion with normal distal flow	3

aspiration by the investigative device according to operator's experience and preference, and to the standard of care of each investigational centre.

Patients' baseline clinical features were registered: hypertension, diabetes, atrial fibrillation, obesity (defined as body mass index $>$ 30 kg/m^2), renal insufficiency (defined by serum creatinine $>$ 1.2 mg/dL), dyslipidaemia, smoking, coronary artery disease, and history of peripheral and cerebrovascular interventions. Inclusion criteria also included ALLI Rutherford classification 1, 2a and 2b; age $>$ 18 years; signed informed consent for treatment and follow up visit; eligibility for the investigative mechanical thrombo-aspiration System (Penumbra Inc). Exclusion criteria included: estimated time of intraluminal thrombus of $>$ 14 days; contraindication to antiplatelet therapy, anticoagulants, or thrombolytic drugs; a history of prior life threatening contrast medium reaction; life expectancy less than six months; treatment refusal and unstable haemodynamic condition at onset of procedure.[12]

At the start of the study, catheters Indigo 8 (STR/TORQ/XTORQ), 6, 5, 3, and Separators had obtained CE approval. The system works on an over the wire platform.

Description of intervention

At the beginning of the procedure, an angiogram typically localises the clot and the aspiration catheter is advanced just proximal to the occlusion. The choice of the Indigo System catheter is based on the vessel's diameter, with a 1:1 sizing whenever possible; for multiple thrombus sites, more than one catheter can be used. The thrombo-aspiration manoeuvres start with the engagement of the thrombus by the catheter tip, followed by the activation of the vacuum.[13]

The use of the Separator to facilitate the thrombus aspiration process by fragmentation of the clot and ensuring catheter tip patency was left to the operator's preference (Fig. 1).

Adjunctive endovascular and/or surgical procedures were allowed after thrombo-aspiration in order to treat underlying chronic atherosclerotic lesions or to remove residual thrombus.

Outcome definitions

To assess vessel patency, an innovative modified Thrombolysis in Myocardial Infarction (TIMI) classification[14] called TIPI (Thrombo-aspiration In Peripheral Ischaemia) was used (Table 1).

The TIPI flow was assessed at presentation, immediately after treatment with the study device, and after all additional interventions.

The primary endpoint of the study was primary technical success of the mechanical thrombo-aspiration with the investigative System, defined as a TIPI 2 — 3 flow (near complete or complete revascularisation of the occluded artery). Assisted primary technical success was defined as TIPI 2 — 3 flow after any adjuvant procedures.

The following secondary endpoints were also assessed: clinical success at one month follow up defined as an improvement of Rutherford classification of one class or more compared with the pre-procedural Rutherford classification; safety rate at discharge defined as the absence of any serious adverse events, such as any clinical event that is fatal, life threatening, or judged to be severe by the investigator, that resulted in persistent or significant disability; primary patency at one month, defined as a target lesion without haemodynamically significant stenosis or re-occlusion on duplex ultrasound ($>$ 50%).

Statistical analysis

Continuous data are reported as mean $\pm$ standard deviation and categorical variables as fractions. The Student test was used for independent tests to match groups on continuous variables, after demonstrating data distribution normality. All statistical analyses were performed using Statistical Package for the Social Sciences (version 13; SPSS Inc. Chicago, IL, USA) and GraphPad Prism (GraphPad Software Inc. San Diego, CA, USA).

Medical therapy

Pre-procedure. After admission, all patients with a confirmed diagnosis of ALLI were treated with heparin (unfractionated or low molecular weight).

During the procedure. Weight adjusted (70 IU/kg) heparin was administered and repeated as necessary to maintain an activated clotting time of 225 to 250 seconds throughout the procedure.

Post-procedure. The administration of heparin (unfractionated or low molecular weight) in the peri-operative period was left to the operator's preference. On discharge aspirin (75 — 100 mg/day) plus clopidogrel (75 mg/day) or ticlopidine (500 mg/day) was continued for at least 30 days after the intervention. Single antiplatelet therapy (either aspirin, clopidogrel, or ticlopidine) was continued indefinitely. Patients with atrial fibrillation were discharged on anticoagulant plus single antiplatelet therapy, which was typically discontinued at one month.

Table 2. Baseline demographics of 150 patients with acute lower limb ischaemia

Characteristic	Patients (n = 150)
Age − y	72.4 ± 13.8
Male sex	110 (73.3)
Hypertension	123 (82)
Diabetes	35 (23.3)
Atrial fibrillation	43 (28.6)
Obesity	21 (14)
Renal insufficiency	19 (12.6)
Dyslipidaemia	70 (46.6)
Smoking	52 (34.6)
Current smoking	45 (30)
Coronary artery disease	33 (22)
Previous peripheral arterial intervention	68 (45.3)
Previous cerebrovascular intervention	6 (4)

Data are presented as n (%) or mean ± standard deviation.

Table 3. Details of the Indigo device used in 150 patients with acute lower limb ischaemia

Indigo device	First device (n = 150)	Second device (n = 23)
CAT 8 TORQ	52 (34.7)	1 (4.4)
CAT 8 XTORQ	35 (23.3)	0 (0)
CAT 6	49 (32.7)	12 (52.2)
CAT 5	8 (5.3)	5 (21.7)
CAT 3	6 (4)	5 (21.7)
Separator	67 (44.7)	9 (39.1)

Data are presented as n (%).

RESULTS

Patient and acute limb ischaemia characteristics on admission

From October 2017 to June 2019, the registry prospectively collected the data of the first 150 patients presenting with ALLI and treated by mechanical thrombectomy with the Indigo/Penumbra system. During the same period 61 patients were not enrolled in the registry for a number of reasons: preference/limited experience with the device of the on call operator (n = 18), unavailability of correct Indigo catheter size (n = 8), lack of informed consent (n = 3), estimated time of intraluminal thrombus of > 14 days (n = 13), contraindication to antiplatelet therapy, anticoagulants, or thrombolytic drugs (n = 5), refusal of treatment (n = 4) and 10 were admitted with a Rutherford classification score of III.

The pre-procedural assessment was assessed according to the Rutherford classification: I, viable 16% (24/150); IIa, threatened marginally 40.7% (61/150); and IIb, threatened immediately 43.3% (65/150). On admission, the mean ankle brachial index (ABI) was 0.19 ± 0.2.

The mean age of the patients was 72.4 years (SD 13.8; range 36 − 101). Baseline demographic features are described in Table 2.

The aetiology of the ALLI was considered to be embolic in 16.7% (25/150), thrombotic 46.7% (70/150), while in the remaining 36.6% (53/150), it was judged to be unknown.

The acute ischaemia occurred in native arteries in 68% (102/150), and as secondary to previous peripheral endovascular or open intervention in 32% (48/150) (n = 26 PTA and/or stenting; n = 16 bypasses, of which 14 prosthetic and two vein grafts; n = 6 immediately following Fogarty balloon catheter embolectomy failure).

Extent and localisation of thrombus varied in the studied population and was classified as (1) diffuse limb thrombosis (from the common femoral artery to below the knee [BTK] vessels) in 44/150 (29.3%); (2) aorto-iliac occlusion in 18/150 (12%); (3) isolated occlusion in the femoral region in 27/150 (18%); (4) popliteal BTK thrombosis 59/150 (39.4%); (5) isolated below the ankle thrombosis 2/150 (1.3%). Fig. 2 shows the localisation of thrombus per single artery.

The mean length of the occlusion was 110 mm (minimum 5 mm, maximum 600 mm).

Before any intervention, acute ischaemia was classified as TIPI 0/1 in 97.3% of cases (146/150), and TIPI 2 in 2.7% (4/150).

Details of Indigo devices used are shown in Table 3.

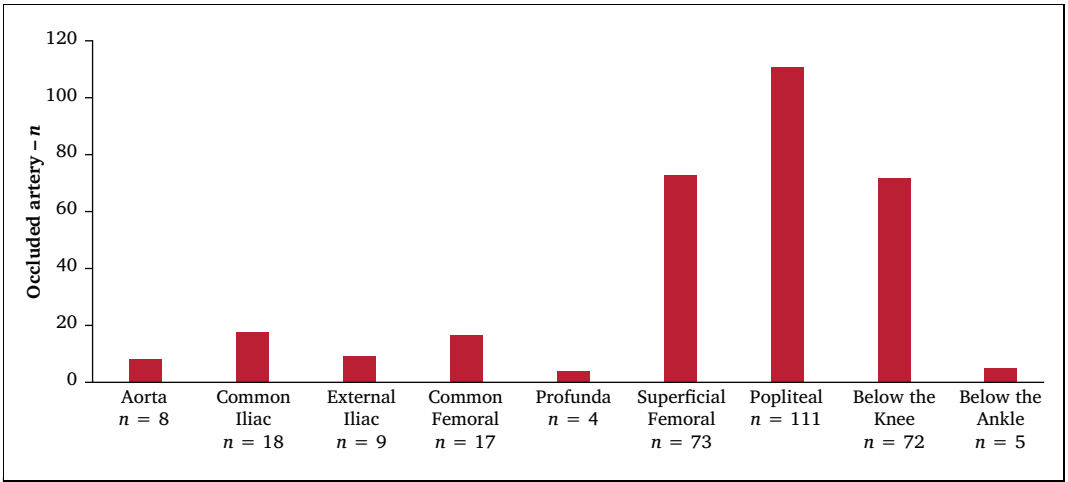


Figure 2. Location of thrombus per occluded artery in 150 patients with acute lower limb ischaemia.

Table 4. Overview of all adjunctive procedures after Indigo device assisted thrombo-aspiration in 91 patients with acute lower limb ischaemia

Adjuvant procedure	Reason for adjuvant procedure	
	Underlying chronic lesion (n = 39)	Residual thrombosis (n = 52)
Endovascular procedures, PTA ± stenting or covered stenting	39 (100)	15 (28.8)
Intra-arterial thrombolysis	0 (0)	21 (40.4)
Intra-arterial thrombolysis followed by PTA ± stenting	0 (0)	10 (19.3)
Fogarty embolectomy	0 (0)	6 (11.5)

Data are presented as n (%). PTA = percutaneous transluminal angioplasty.

Efficacy data

Procedural access was percutaneous in 94% of cases (femoral $n = 141$, brachial $n = 2$). Groin surgical cutdown was used in seven patients (post-Fogarty embolectomy $n = 6$, and for occluded bypass $n = 1$).

After use of the thrombo-aspiration system and before any other interventions, flow grade was classified as TIPI 3 in 54% (81/150), TIPI 2 in 34.7% (52/150), TIPI 1 in 6.6% (10/150), and TIPI 0 in 4.7% (7/150). Primary technical success (near complete or complete revascularisation TIPI 2 − 3) was achieved in 88.7% of patients.

Adjunctive procedures were performed in 91 cases (60.6%): 39 of them for the presence of underlying chronic atherosclerotic lesions, 52 for residual thrombus. For chronic lesions, complete revascularisation was achieved by an adjuvant endovascular procedure (angioplasty/stenting).

For residual thrombosis, local thrombolysis was administrated in 31 cases (followed by angioplasty/stenting in 10 patients), an additional stent/covered stent was implanted in 15 cases, and supplementary Fogarty embolectomy was performed in six cases (Table 4).

When CDT was used as the adjuvant procedure the mean amount of thrombolytic agent was 10.5 mg (range 5 − 25 mg) for recombinant tissue plasminogen activator (rtPA), and 1.1 million units (range 0.6 − 2.5 million) for urokinase, with a mean duration of treatment of 15.5 hours (range 3 − 36 hours).

After all interventions flow was assessed as TIPI 3 in 76% (114/150), TIPI 2 in 19.3% (29/150), TIPI 1 in 3.3% (5/150), and TIPI 0 in 1.3% (2/150).

As a result, assisted primary technical success after all interventions was achieved in 95.3% of patients (Fig. 3).

Table 5 summarises TIPI flow pre- and post-procedure in patient subgroups according to the type of vessel occlusion.

Safety results

Mean procedure time was 86 ± 48 minutes, with an average of fluoroscopy time of 14 ± 11.4 minutes. Mean blood loss during thrombo-aspiration manoeuvres was 242 ± 132 mL (range 20 − 600 mL).

There were no vessel wall injuries related to the investigated system.

No device related serious adverse events were reported, although one device related event occurred (0.66%) consisting of detachment of a small part of the Separator's tip (2 mm), that remained trapped in a severely diseased tibioperoneal trunk during thrombo-aspiration of a femoral to below knee popliteal bypass. After several unsuccessful attempts at endovascular capture, it was decided to stabilise the foreign body against the arterial wall of the anterior tibial artery with a short balloon expandable stent.

Additional fasciotomy was needed in eight cases (5.3%).

Heparin (unfractionated or low molecular weight) was administered post-operatively in 66% of patients for a mean 3.5 days (range 2 − 10 days). At discharge, all patients were on dual antiplatelet therapy till the one month follow up, except 43 patients (28.6%) with concomitant atrial fibrillation who received single antiplatelet treatment in addition to anticoagulant therapy.

One patient (0.66%) had acute renal failure the day after intervention and experienced complete resolution after temporary haemodialysis.

Acute re-thrombosis (within 24 hours of the procedure) occurred in 2.66% of cases (three femoropopliteal bypasses; one post-stenting).

Re-intervention was performed in the three bypass cases (2%): intra-arterial slow infusion fibrinolytic therapy was administrated promptly in all cases, plus repeat mechanical thrombo-aspiration with Indigo in one of them, with clinical resolution of the thrombosis. This latter patient had already experienced the above mentioned intraprocedural device related adverse event; of note, at the time of the re-intervention, the stent in the anterior tibial artery was patent.

The patient with acute stent re-occlusion had only mild symptoms and was managed medically.

Three arterial access bleeding complications occurred (2%), solved with additional manual compression ($n = 2$) or surgical repair ($n = 1$), and not resulting in prolonged hospitalisation (> 3 days). No systemic bleeding complications were registered.

Mean hospital stay was 3 ± 2.7 days (range 1-10 days). There was no death, but there was one below ankle amputation in a patient with concomitant critical limb threatening ischaemia and very poor distal outflow vessels, although near complete revascularisation (TIPI 2) had been achieved with endovascular thrombo-aspiration at the level of acute on chronic occlusion.

On discharge, the mean ABI was significantly increased (0.9 ± 0.15, $p < .001$). The safety rate at discharge was 98.7% (148/150).

Follow up data

At one month follow up, only one death was registered due to the severity of general clinical conditions, and no other amputation was recorded.

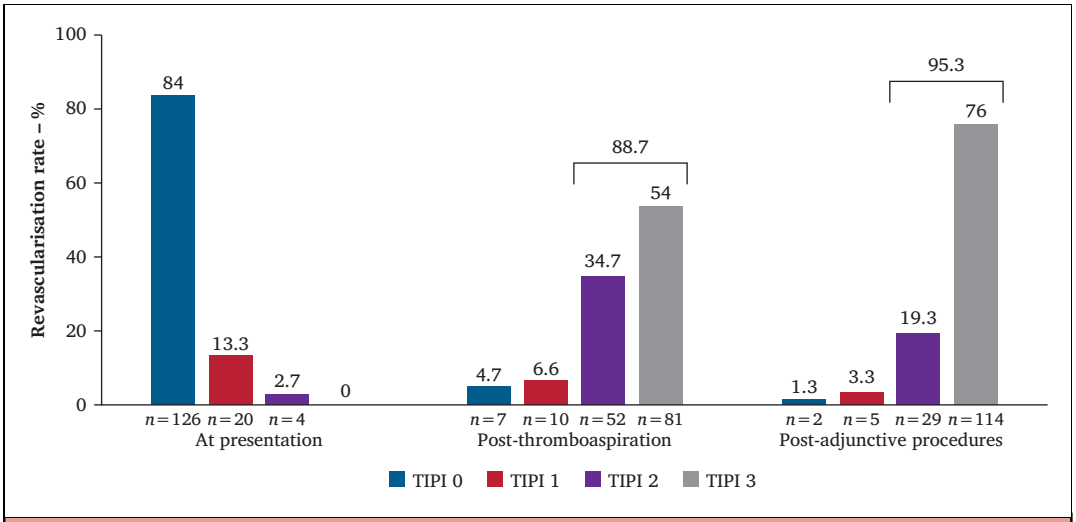


Figure 3. Revascularisation outcome based on Thrombo-aspiration In Peripheral Ischaemia (TIPI) flow grade classification registered at the time of admission, after thrombo-aspiration and after adjunctive procedures in 150 patients presented with acute lower limb ischaemia. TIPI score of 2 or 3 was achieved in 88.7% and 95.3% of patients after thrombo-aspiration and after adjunctive procedures, respectively.

Clinical success was 98.7% (148/150). The clinical limb status of patients was classified as viable in 136 cases (91%) and threatened marginally in 14 cases (9%). Mean ABI was 0.9 ± 0.3.

The primary patency at one month was 92% (138/150). Endovascular re-interventions were performed in 11 patients (7.33%), for complete occlusion ($n = 8$) or restenosis $> 50\%$ ($n = 3$). Assisted primary and secondary patency at one month were 94% and 99.33%, respectively.

At six months, among patients that were occluded one month after the intervention, two underwent above knee amputation. No other amputations were recorded, while two non-procedure related deaths occurred.

DISCUSSION

The most recent European Society for Vascular Surgery guidelines for the management of ALLI suggest that endovascular thrombectomy should be considered (recommendation 25, class IIa, level C), in particular for patients with Rutherford grade IIb acute limb ischaemia.[15]

Several endovascular techniques for thrombus removal have been explored over the last two decades,[11] but some of them have failed to be adequately efficacious or have been associated with unacceptable complication rates. One of the main difficulties has been to design a device that can remove adequate volumes of thrombus of variable age while also maintaining an acceptably small size, flexibility, and ease of use.

PMT using the Angiojet device showed higher reperfusion success rates than CDT, but at the cost of more distal embolisation. A cohort analysis matching PMT alone and PMT with thrombolysis revealed improved technical success, shorter procedures, and a similar amputation rate to the PMT alone group. The drawback of PMT was the inability to use the device in small calibre vessels in the leg, and the risk that haemolysis may lead to hyperkalaemia, haemoglobinuria, and renal damage.[16]

The Indigo system represents a latest generation system for thrombo-embolic disease, and is explicitly designed to address the limitations of conventional technology. The device was created based on the success of the Penumbra System in the neurovasculature for reperfusion of large vessel occlusion in stroke patients. By including neither a rotational component, nor hydrodynamic forces, the risk of vessel injury and haemolysis is truly minimised.

The results of the present registry showed that the investigative device is safe and effective as the primary treatment of ALLI lasting less than 14 days. Localisation of the thrombus was quite variable in the cohort of patients, although in the majority of cases, patients presented with thrombus in the popliteal or BTK vessels (Fig. 1). Near complete or complete revascularisation (TIPI grade 2 — 3 flow) was achieved in 88.7% of the total population after treatment with the study device and before any other

Table 5. TIPI (Thrombo-aspiration In Peripheral Ischaemia) evaluation after Indigo procedure alone and after all interventions according to the type of occlusion in 150 patients with acute lower limb ischaemia

Type of occlusion	TIPI 2–3 after Indigo procedure	TIPI 2–3 after all interventions
Native arteries	89/102 (87.3)	95/102 (93.1)
Post-endovascular procedures	22/26 (84.6)	26/26 (100)
Post-bypass	12/12 (100)	12/12 (100)
Post-bypass and Fogarty embolectomy	4/4 (100)	4/4 (100)
Post-Fogarty embolectomy	6/6 (100)	6/6 (100)
Total	133/150 (88.7)	143/150 (95.3)

Data are presented as *n* (%). TIPI = thrombo-aspiration in peripheral ischaemia

interventions, and the were no distal embolisations. Notably, the range of available sizes of the Indigo catheters, the trackability of the system, and the possibility to switch to a smaller one in a co-axial fashion made it possible to reach clots in very distal arteries. No cases of inability to advance the catheter in small calibre vessels in the leg were recorded, which is typically considered a limitation for other techniques.

The technical success rate obtained is slightly better than that reported in the treatment of acute intracranial large vessel occlusion (TIMI 2 — 3 81.6%), a condition where mechanical thrombectomy has been recognised as the mainstay therapy.[17]

Adjunctive use of endovascular or surgical treatment (i.e., PTA, stenting, or CDT) increased this successful rate up to 95.3%. The device was particularly useful when the thrombosis was secondary to previous endovascular intervention, bypasses, or after incomplete reperfusion by Fogarty embolectomy (TIPI 2 — 3 100%).

The use of the Indigo mechanical thrombectomy system as primary treatment of ALLI was safe, (without any serious adverse device related events) and no major bleeding complications. One adverse device related event (0.66%) without clinically relevant outcome occurred and was low compared with the 4.2% rate reported in the PEARL Registry,[18] which investigated the use of another thrombectomy system for ALLI.

Unlike thrombolysis, which often requires prolonged infusion times,[19] the investigative device was able to provide rapid restoration of flow to thrombosed vessels in settings when time is typically an issue (43.3% of the patient population had a Rutherford grade IIb immediately threatened ALLI). This technique, even if use of continuous thrombolysis in a lower percentage was necessary, may also be favourable in patients that have contraindications to thrombolysis, mainly increased risk of bleeding, such as recently operated patients, cancer, previous intracerebral haemorrhage, and also those patients that cannot cooperate (not possible to lie still for two days receiving thrombolysis, language barrier, aphasia or mental disorder).

This may also explain the low rate of fasciotomy (5.3%) compared with the reported rate of nearly 30%.[20]

Although a relatively high adjuvant lysis therapy rate after the investigative device (31/150, 20.7%) was noted, the average amount of drug used (10.5 mg rtPA, 1.1 million unit urokinase) was typically lower than that reported in a recent meta-analysis when lysis was the only treatment, and this may further explain the low bleeding complication rate reported.[21] Moreover, the economic impact of the device may have sometimes led the operators to prefer the use of a reduced amount of lysis rather than extra Indigo catheters to remove limited residual thrombosis.

Up to now, a few reports have described the safety and the efficacy of thrombo-aspiration with Indigo in ALI. In an early experience of 30 patients, the improvement in blood flow across a lesion by improvement in TIMI score was obtained in 85% of BTK vessel lesions, and in 53.9% of above the knee vessel lesions.[22]

A previous multicentre registry enrolling 79 patients reported data on the utility of thrombo-aspiration with Indigo, the PRISM trial (A retrospective Analysis of Technical Success Using the Penumbra and Indigo Systems for Mechanical Thrombectomy in Periphery, Clinical Trial.gov ID code NCT02085551). Compared with the results from the INDIAN registry, similar efficacy (primary technical success 87.2%, assisted primary technical success of 96.2%) and safety rates (no device related adverse events) were reported.[13]

A recent single centre four year experience of 43 Indigo procedures for ALLI reported similar favourable safety results, but only moderate effectiveness (success rate of 51%) that led the authors to conclude how the description of the optimal technique should be further refined.[23] Notably, use of the Separator was not described in their experience. It is believed that the better results are related to a more precise technique, including the 1:1 sizing of the Indigo System catheter to the target vessel diameter in all cases, the use of the Separator in almost half of the case and the use of more than one catheter per case when necessary.

Although prospective and including all consecutive patients, the present investigation has some limitations. First, the study design was single arm and did not include a control group, moreover patients were somehow selected by the operator who decided on the eligibility for thrombo-aspiration by the investigative device according to their own experience and preference. Second, participation in the registry was permitted only for experienced endovascular operators with proven familiarity with the investigational device, third, the use of adjunctive endovascular procedures, including PTA, stenting, and CDT in a considerable number of patients after treatment with the study device, may have influenced the clinical outcomes significantly, so offering a less clear view of the value of the mechanical thrombo-aspiration system itself and finally there was no core laboratory evaluation of angiographic results.

The present results from this ongoing prospective multicentre registry reveal the safety and technical effectiveness of the Indigo mechanical thrombectomy system as initial treatment in selected patients with different arterial occlusion settings lasting < 14 days (TIPI 2 — 3 flow in 88.7%, increasing up to 95.3% after adjuvant procedures).

Continuing the enrolment of patients in a further phase of the registry (Indian UP) will allow a further better definition of the optimal technique and of the ideal candidates for this technology.

CONFLICT OF INTEREST

G.d.D. received travel grants from Penumbra.

ACKNOWLEDGEMENTS

Principal institutions (investigators) participating in the Indian Registry: Ospedale Sant'Eugenio, Rome (Stefano Bartoli, MD; Andrea Siani, MD; Federico Accrocca, MD); ASST Crema (Angelo Spinazzola, MD; Giovanni Leati, MD; Riccardo Foà,

MD; Aldo Arzini, MD; Luca Boccalon, MD); Policlinico di Bari (Raffele Pulli, MD; Davide Marinazzo, MD); Ospedale San Filippo Neri (Sonia Ronchey, MD; Stefano Fazzini, MD); Ospedale Santa Annunziata, Cosenza (Francesco Intrieri, MD; Vincenzo Molinaro, MD); ASST degli Spedali Civili di Brescia (Raffaele Cuomo, MD; Marco Ravanelli, MD; Giulia Bonera, MD; Giorgio Novicelli, MD); Ospedale Maggiore della Carità, Novara (Giuseppe Guzzardi, MD; Carmelo Stanca, MD; Andrea Galbiati, MD); Ospedale S. Maria della Misericordia, Perugia (Massimo Lenti, MD; Giacomo Isernia, MD; Gioele Simonte, MD); IRCCS Ospedale Sacro Cuore Don Calabria, Verona (Antonio M. Jannello, MD; Luca Garriboli, MD); AOU Città della Salute e della Scienza, Torino (Dorico Righi, MD; Maria Antonella Ruffino, MD; Andrea Discalzi, MD; Denis Rossato, MD; Andrea Mancini, MD; Pierluigi Muratore, MD); Ospedale S. Maria della Misericordia, Udine (Massimo Sponza, MD); Policlinico S. Matteo, Pavia (Pietro Quaretti, MD; Lorenzo Paolo Moramarco, MD; Nicola Cionfoli, MD); Policlinico di Modena (Roberto Silingardi, MD; Antonio Lauricella, MD; Stefano Gennai, MD); Policlinico Umberto I, La Sapienza, Roma (Francesco Speziale, MD; Pasqualino Sirignano, MD; Wassim Mansour, MD); ASST San Carlo Borromeo, Milano (Raffaello Dallatana, MD; Davide Santuari, MD; Sara Segreti, MD); Ospedale A. Perrino, Brindisi (Giorgio Sbenaglia, MD; Gabriele Maritati, MD); Ospedale Civile Ss. Antonio e Biagio e Cesare Arrigo, Alessandria (Stefano Barbero, MD; Ivan Gallesio, MD); Ospedale S. Giovanni Bosco, Torino (Daniele Savio, MD; Luca di Maggio, MD; Andrea Boghi, MD; Chiara Comelli, MD; Alessandro Rapellino, MD); Ospedale di Circolo e Fondazione Macchi, Varese (Matteo Tozzi, MD; Marco Franchin, MD; Marco Tadiello MD); AO Ordine Mauriziano, Torino (Andrea Gaggiano MD, Michelangelo Ferri MD, Andrea Viazzo, MD; Paola Manzo, MD); Azienda Ospedaliera Regionale San Carlo, Potenza (Pierluigi Cappiello, MD; Andrea Esposito, MD); Azienda Ospedaliera Sant'Andrea, Roma (Michele Rossi, MD); University of Siena (Gianmarco de Donato, MD; Edoardo Pasqui, MD; Giovanni Giannace, MD; Claudia Panzano, MD; Giuseppe Alba, MD; Gaia Grottola, MD; Brenda Brancaccio, MD, Giulia Casilli, MD; Giulia Ferrante, MD; Tommaso Lazzarotto, MD; Michele Giubbolini, MD; Giuseppe Galzerano, MD; Claudio Baldi, MD; Walter Guerrieri, MD, Domenico Benevento, MD; Alessandro Cappelli, MD; Giancarlo Palasciano, MD; Carlo Setacci, MD).

REFERENCES

1 de Donato G, Gussoni G, de Donato G, Andreozzi GM, Bonizzoni E, Mazzone A, et al. The ILAILL study: iloprost as adjuvant to surgery for acute ischemia of lower limbs: a randomized, placebo-controlled, double-blind study by the Italian Society for Vascular and Endovascular Surgery. *Ann Vasc Surg* 2006;**244**:185–93.

2 The STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischaemia of the lower extremity. *Ann Surg* 1994;**220**:251–8.

3 Ouriel K, Veith FJ, Sasahara AA, for the Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. *N Engl J Med* 1998;**338**:1105–11.

4 Piffaretti G, Angrisano A, Franchin M, Ferrario M, Rivolta N, Bacuzzi A, et al. Risk factors analysis of thromboembolectomy for acute thromboembolic lower extremity ischemia in native arteries. *J Cardiovasc Surg (Torino)* 2018;**59**:810–6.

5 Fogarty TJ, Cranley JJ, Krause RJ, Strasser ES, Hafner CD. A method for extraction of arterial emboli and thrombi. *Surg Gynecol Obstet* 1963;**116**:241–4.

6 Dotter CT, Rosch J, Seaman AJ. Selective clot lysis with low dose streptokinase. *Radiology* 1974;**111**:31–7.

7 Comerota AJ, Weaver FA, Hosking JD, Froehlich J, Folander H, Sussman B, et al. Results of a prospective, randomized trial of surgery versus thrombolysis for occluded lower extremity bypass grafts. *Am J Surg* 1996;**172**:105–12.

8 Palfreyman SJ, Booth A, Michaels JA. A systematic review of intra-arterial thrombolytic therapy for lower-limb ischaemia. *Eur J Vasc Endovasc Surg* 2000;**19**:143–57.

9 Henke PK. Contemporary management of acute limb ischemia: factors associated with amputation and in-hospital mortality. *Semin Vasc Surg* 2009;**22**:34–40.

10 Sniderman KW, Bodner L, Saddekni S, Srur M, Sos TA. Percutaneous embolectomy by transcatheter aspiration. Work in progress. *Radiology* 1984;**150**:357–61.

11 de Donato G, Pasqui E, Setacci F, Palasciano G, Nigi L, Fondelli C, et al. Acute on chronic limb ischemia: From surgical embolectomy and thrombolysis to endovascular options. *Semin Vasc Surg* 2018;**31**:66–75.

12 de Donato G, Pasqui E, Giannace G, Setacci F, Benevento D, Palasciano G, et al. The Indigo System in Acute Lower-Limb Malperfusion (INDIAN) Registry: Protocol. *JMIR Res Protoc* 2019;**8**:e9972.

13 Saxon RR, Benenati JF, Teigen C, Adams G, Sewall LE, Trialists PRISM. Utility of a power-aspiration-based extraction technique as an initial and secondary approach in the treatment of peripheral arterial thromboembolism: results of the multicenter PRISM trial. *J Vasc Interv Radiol* 2018;**29**:92–100.

14 Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I: comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;**76**:142–54.

15 Björck M, Earnshaw JJ, Acosta S, Gonçales FB, Cochennec F, Debus ES, et al. 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.

16 Byrne RM, Taha AG, Avgerinos E, Marone LK, Makaroun MS, Chaer RA. Contemporary outcomes of endovascular interventions for acute limb ischemia. *J Vasc Surg* 2014;**59**:988–95.

17 Penumbra Pivotal Stroke Trial Investigators. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke* 2009;**40**:2761–8.

18 Leung DA, Blitz LR, Nelson T, Amin A, Soukas PA, Nanjundappa A, et al. Rheolytic pharmacomechanical thrombectomy for the management of acute limb ischemia: results from the PEARL registry. *J Endovasc Ther* 2015;**22**:546–57.

19 Van Den Berg JC. Thrombolysis for acute arterial occlusion. *J Vasc Surg* 2010;**52**:512–5.

20 Hemingway J, Emanuels D, Aarabi S, Quiroga E, Tran N, Starnes B, et al. Safety of transfer, type of procedure, and factors predictive of limb salvage in a modern series of acute limb ischemia. *J Vasc Surg* 2019;**69**:1174–9.

21 Ebben HP, Jongkind V, Wisselink W, Hoksbergen AWJ, Yeung KK. Catheter directed thrombolysis protocols for peripheral arterial occlusions: a systematic review. *Eur J Vasc Endovasc Surg* 2019;**57**:667–75.

22 Baumann F, Sharpe 3rd E, Peña C, Samuels S, Benenati JF. Technical results of vacuum-assisted thrombectomy for arterial

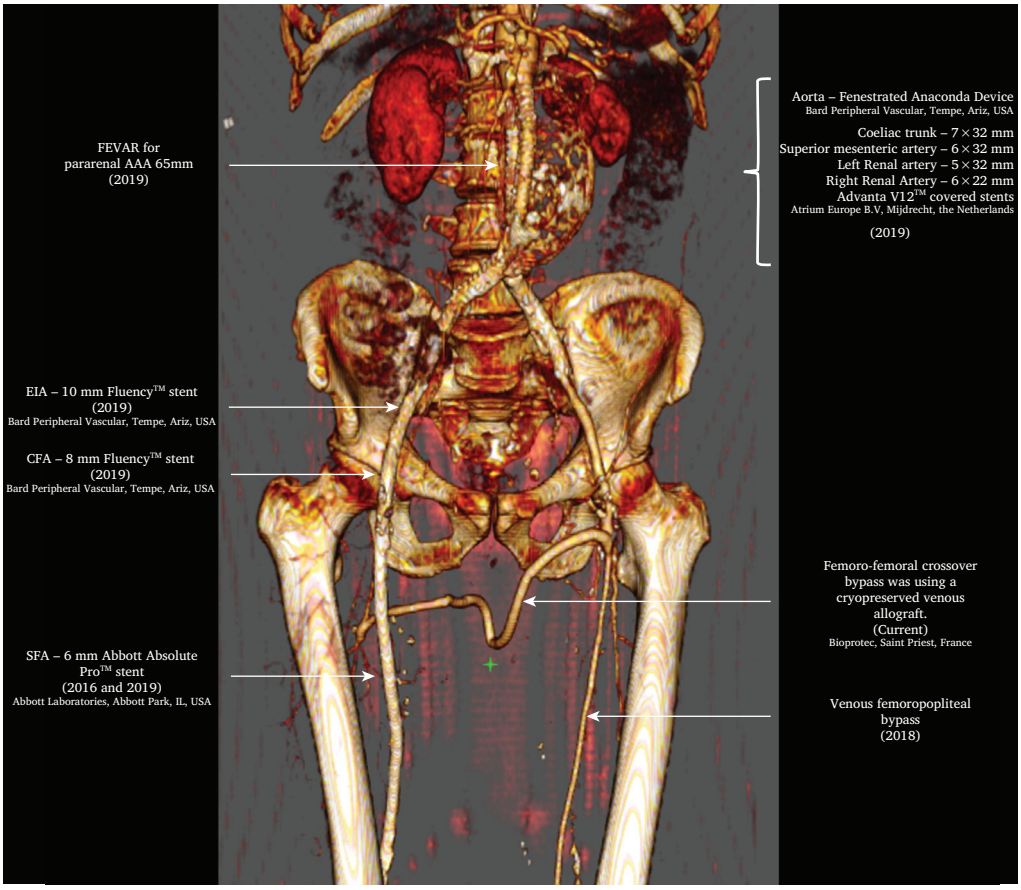
clot removal in patients with acute limb ischemia. *J Vasc Interv Radiol* 2016;**27**:330–5.
23 Lopez R, Yamashita TS, Neisen M, Fleming M, Colglazier J, Oderich G, et al. Single-center experience with indigo aspiration thrombectomy for acute lower limb ischemia. *J Vasc Surg* 2020;**72**:226–32.

Eur J Vasc Endovasc Surg (2021) 61, 828

COUP D'OEIL

Remembering an Old Technique: Retroscrotal Perineal Femorofemoral Bypass for Ischaemic Ulcer of the Anterior Thigh

Calin Gheorghe Precup *, **Nellie Della-Schiava**
Service de chirurgie vasculaire et endovasculaire, Etablissement Edouard Herriot, Hospices Civils de Lyon, Lyon, France



A 61 year old male (after multiple previous bilateral peripheral arterial procedures and fenestrated endovascular aortic aneurysm repair) consulted for buttock claudication and ischaemic ulceration of the anterior right thigh. Computed tomography angiography showed patent common and external iliac arteries, common and superficial femoral arteries (previously stented), and occlusions of right internal iliac, deep circumflex iliac, and proximal deep femoral arteries. After failed endovascular attempts, a femorofemoral crossover bypass was performed using a cryopreserved venous allograft. Owing to ischaemic necrosis of the thigh, perineal retroscrotal tunnelling was preferred. Dual antiplatelet therapy was initiated post-operatively. Tunnelling in this lesser known region allowed successful wound healing after several months.

* Corresponding author. Service de chirurgie vasculaire et endovasculaire, Etablissement Edouard Herriot, Hospices Civils de Lyon, 5 Place d'Arsonval, 69003, Lyon, France.
E-mail address: calin-gheorghe.precup@chu-lyon.fr (Calin Gheorghe Precup).

https://doi.org/10.1016/j.ejvs.2021.02.005