**Transcatheter arterialisation of the deep veins: One-year outcomes of the PROMISE-UK Study**

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**Supplementary Methods**

*Study details*

The sponsor funded all trial-related activities and participated in site selection, data collection and monitoring, and statistical analysis. The principal investigators monitored all aspects of trial conduct and had unrestricted access to the data. Clinical events were adjudicated by an independent Clinical Events Committee (CEC) and all wound images were reviewed by an independent podiatric surgeon.

*Eligibility*

Inclusion Criteria:

* Subject must be > 21 and < 95 years of age
* Clinical diagnosis of symptomatic critical limb ischaemia, defined as Rutherford category 5 or 6
* Assessment that no conventional surgical or endovascular treatment is possible
* Proximally, the target in-flow artery at the cross-over point must be treatable with a 3.5 – 4.0 mm stent after pre-treatment (by visual estimate), and be <50% stenosed
* Subject is willing and has adequate support to comply with protocol requirements, including medication regimen and follow-up visits

Exclusion Criteria:

* Concomitant hepatic insufficiency, deep venous thrombus in target limb, uncorrected coagulation disorders, or current immunodeficiency disorder
* Life expectancy less than 12 months
* Patient currently taking coumarin/warfarin which, in the opinion of the attending physician, interferes with the patient’s treatment
* Any significant medical condition which, in the attending physician’s opinion, may interfere with the patient’s optimal treatment
* Patient currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this treatment
* Patient unable to give consent
* Pregnant or breastfeeding women
* Documented myocardial infarction or stroke within previous 90 days
* Patients suffering from renal insufficiency (GFR value less than 30 ml/min/1.73 m²) who are not on haemodialysis
* Patients with vasculitis and/or untreated popliteal aneurysms
* Patients with acute limb ischaemia
* Prior peripheral arterial bypass procedure above or below the knee which could inhibit proximal inflow to the stent graft
* Lower extremity venous disease with significant oedema in the target limb that may inhibit the procedure and/or jeopardize wound healing, in the investigator’s opinion
* Known or suspected systemic or severe infection (*e.g.*, WIfI foot Infection grade of 3)
* Known or suspected allergies or contraindications to stainless steel, nickel, or contrast agent that cannot be adequately pre-treated, or patients who cannot receive anticoagulation or antiplatelet aggregation therapy
* Severe heart failure, which in the opinion of the investigator may compromise subject’s ability to safely undergo a percutaneous procedure (*e.g.*, known ejection fraction of < 40%, NYHA Classification III-IV)

*Procedural Steps*

The TADV procedure involved the use of the dedicated LimFlow System and all vascular surgeons and interventional radiologists who performed the procedure received didactic and hands-on training on the appropriate use of the devices and the procedural steps. Previously published procedural steps according to the device instructions for use (IFU) were adopted within the trial, including pedal access, formation of an arteriovenous fistula proximal to the diseased tibial arteries, effacement of venous valves with use of a proprietary forward cutting valvulotome, lining of the circuit with LimFlow self-expanding stent grafts from the target tibial vein’s proximal calcaneal border to the arteriovenous crossing where a tapered covered stent is utilised to optimise flow volumes (Figure 1).1

Patients were monitored in-hospital via duplex ultrasound to confirm patency in the days following the index procedure, and all patients were prescribed dual antiplatelet or anticoagulant therapy for at least three months following the procedure.

*Study Follow-up*

Study patients were monitored through a standardised regimen of clinical evaluation including assessment of adverse events, clinically-driven additional intervention, and wound healing. Follow-up visits were performed at 2-weeks, and 1, 2, 3, 6, 9 and 12 months following the index procedure unless the patient withdrew from the study or experienced a primary endpoint event of either death or major amputation. Of note, enrolment and follow-up occurred during the international COVID-19 pandemic, from December 2019 to October 2023.

If clinically possible, any necessary planned minor (below ankle) amputations were recommended to be performed at least 4-6 weeks following the initial TADV procedure to allow the arterialised venous network to mature and establish pedal reperfusion to distal tissue to aid wound healing.

*Endpoint Details*

Study endpoints were adjudicated by an independent CEC. Wound healing was determined using standardised serial wound photography over time that was adjudicated by an independent podiatric surgeon to determine qualitative wound healing status. Additionally, wound area dimensions were collected and measured over time. Patients undergoing major amputation were exited from the study at the point of amputation as a primary endpoint event had occurred, with a medical-records check at 1-year to determine mortality status.

*Duplex Ultrasound Monitoring*

All follow-up visits included imaging with duplex ultrasound to assess overall patency of the arterialised network and vascular haemodynamics. More specifically, volume flow (Vf) through the arterialised circuit was calculated from measurements of blood velocity (V) averaged over several cardiac cycles (time-averaged mean velocity [TAMV]) and multiplied by the vessel cross-sectional area [A]) *Vf = TAMV x A.* Adapted from previously-published research,2 the Vf was monitored to maintain optimal flow for circuit patency and adequate pedal perfusion, especially in the immediate three-month follow-up period. Diagnostic angiography and necessary endovascular intervention was recommended to optimise Vf. Target volume flow rates in the first six-months were 100-350 mL/min.

*Statistical Analysis*

Distributions of baseline variables were summarised using descriptive statistics. Frequencies and percentages were provided for categorical variables while medians with interquartile range (IQR) were reported for continuous variables, unless noted. Kaplan-Meier estimates were used to estimate cumulative survival rates in time-to-event data.

**Supplementary Results**

*Patients*

The median age of the patients was 69.0 years (IQR, 60.5 to 74.5), 25 (89.3%) were men, and 21 (77.8%) were previous or current smokers. Most patients had multiple pre-existing conditions associated with CLTI including diabetes, hypertension, hyperlipidaemia, and 26 patients (92.9%) had undergone previous revascularisation procedures on the target limb. All patients presented with a non-healing ulcer or frank gangrene and were classified as Rutherford 5 (92.9%) or Rutherford 6 (7.1%). The median total wound area at baseline was 7.20 cm2 (IQR, 3.05-10.25 cm2). The population included 5 patients (17.9%) with renal insufficiency, of which 3 (10.7%) were haemodialysis-dependent.

**Table S1. PROMISE-UK Baseline Characteristics**

|  |  |
| --- | --- |
| **Characteristic** | **All patients N=28, or as otherwise stated** |
| Median age (IQR), years | 69.0 (60.5-74.5) |
| Male sex, no. (%) | 25 (89.3) |
| Median body-mass-index (IQR) | 25.4 (22.9-29.6) |
| History of smoking, no. (%) | 21 (77.8) |
| Current | 5 (18.5) |
| Former | 16 (59.3) |
| Previous stroke, no. (%) | 2 (7.1) |
| Previous myocardial infarction, no. (%) | 5 (17.9) |
| Hypertension no. (%) | 21 (75.0) |
| Dyslipidaemia no. (%) | 16 (57.1) |
| Diabetes mellitus, no. (%) | 23 (82.1) |
| Type I | 0 |
| Type II | 23 (82.1) |
| Renal insufficiency, no. (%) | 5 (17.9) |
| Req. haemodialysis, no. (%) | 3 (10.7) |
| Rutherford Classification |  |
| Class 5 | 26 (92.9) |
| Class 6 | 2 (7.1) |
| SVS WIfI Wound Score |  |
| Wound score 1, (%) | 11 (39.3) |
| Wound score 2, (%) | 16 (57.1) |
| Wound score 3, (%) | 1 (3.6) |
| Median wound area (IQR), cm2 | 7.2 (3.1-10.3) |
| Previous endovascular intervention in target limb, no. (%) | 26 (92.9) |

Data are shown as median with interquartile range or number with percentage.

*Procedural Outcomes*

The LimFlow TADV procedure achieved technical success in 27 of 28 cases (96.4%) with no unanticipated adverse device-related events (Table S2). Venous access was performed primarily in the lateral plantar vein. The posterior tibial artery was the most common target for arteriovenous crossing location. There was one case of technical failure where the procedure had to be abandoned due to inability to perform the artery-to-vein crossing secondary to significant calcification of the posterior tibial artery. This patient was followed for safety for 30 days and exited per the protocol.

The median length of post-procedure hospital stay for all study patients across all sites (and in the context of bed management practices during the COVID-19 pandemic) was 10.0 days (IQR, 6.0-15.0), with all patients being discharged home with the exception of three patients who had a major amputation in-hospital. Figure 1 provides an example of patient course during the study.

**Table S2. Procedural and In-Hospital Outcomes**

|  |  |
| --- | --- |
| **Characteristic** | **All Patients (N=28)** |
| Technical Success, no. (%) | 27 (96.4) |
| Pedal Access site |  |
| Lateral plantar vein, no. (%) | 24 (85.7) |
| Medial plantar vein, no. (%) | 1 (3.6) |
| Posterior tibial vein at ankle, no. (%) | 3 (10.7) |
| Donor artery location |  |
| Posterior Tibial Artery, no. (%) | 21 (75.0) |
| Tibioperoneal Trunk, no. (%) | 4 (14.3) |
| Peroneal Artery, no. (%) | 3 (10.7) |
| Target vein location |  |
| Posterior Tibial Vein, no. (%) | 28 (100.0) |

Data are shown as number with percentage.

**Figure S1. PROMISE-UK CONSORT Diagram**

**A diagram of a flowchart

Description automatically generated**

CONSORT diagram of PROMISE-UK study enrolment. EF, ejection fraction; ITT, intent to treat.

*Clinically-driven Interventions*

During the 1-year follow-up, 12 patients (43%) underwent 17 clinically-driven interventions to restore patency of the arterialised pedal vein circuit or address worsening ischaemia. These included 13 incidents (N=10) of thrombosis requiring thrombectomy or thrombolysis, and 4 incidents (N=4) of deteriorating ischaemia requiring balloon angioplasty or stenting. The majority of those patients (N=9) completed study follow-up with an intact target limb. An additional 8 patients (32%) underwent surveillance duplex-driven intervention for optimisation of the arterialised foot venous network.

**Table S3. Study Deaths**

|  |  |  |
| --- | --- | --- |
| **Patient Number** | **Days to Death** | **Adjudicated Cause of Death** |
| 1 | 5 | COVID-19 |
| 2 | 47 | Hospital-acquired pneumonia |
| 3 | 90 | Community-acquired pneumonia; History of COPD and asbestosis |
| 4 | 190 | Pre-existing mitral valve disease |

**Supplementary Discussion**

*Limitations*

This study has several limitations including the lack of a control group. However, within a no-option population facing a high risk of major amputation, and ethical and practical consideration of the substantial unmet clinical need led the investigators to believe that a prospective single-arm study would still provide important information within this debilitating disease. Moreover, randomising a patient to receive no intervention would pose a major ethical dilemma. An additional limitation is the follow-up of patients being limited to 1-year. It should also be noted that the study took place contemporaneously to the COVID-19 pandemic, with one death due to COVID-19 and a second due to community-acquired respiratory infection at the start of the pandemic when COVID-19 testing was not mandatory. These may have adversely impacted the AFS in the study group.

**References**

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