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# Endovenous Laser Ablation Plus Compression Versus Compression Alone for Healing Active Venous Leg Ulcers (CEAP C6): A Randomised Controlled Trial

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**Abstract**

**Background:** Active venous leg ulcers (CEAP C6) are associated with prolonged healing and substantial treatment burden. Although compression therapy remains standard care, the additional benefit of endovenous laser ablation (EVLA) for wound-area reduction requires evaluation using standardized longitudinal outcomes and comparisons

**Aim:** To compare wound-area changes after EVLA plus compression, compression therapy, and standard wound care in adults with CEAP C6 ulcers

**Approach:** In this simulated three-arm randomized trial, 66 adults with active CEAP C6 venous ulcers and superficial venous reflux were allocated to EVLA plus compression, compression, or standard care. Wound area was assessed through 12 weeks using repeated-measures analysis of variance

**Results:** Mean age was 62.5 (SD, 8.7) years; 33 (50.0%) were male. Compression adherence was 86.4% with EVLA and 68.2% with compression; incomplete follow-up was 7.6%. The group-by-time interaction was significant ($F[6, 174] = 2.68$; $P = .0165$; partial $\eta^2 = .084$), with greater reduction versus standard care (mean difference, −4.95 cm²; 95% CI, −9.01 to −0.89).

**Conclusions:** In this simulation, EVLA plus compression showed greater wound-area improvement than standard care, but not compression alone. Actual clinical effectiveness remains unestablished.

**Implication for Nursing Practice:** Vascular teams and wound-care nurses may use standardized imaging, compression-adherence monitoring, and coordinated follow-up to evaluate healing trajectories; these simulated findings should not guide treatment decisions.

**Keywords:** bandages; catheter ablation; laser therapy; leg ulcer; varicose veins; wound healing.

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## Introduction

Venous leg ulcers (VLUs) represent the most advanced clinical manifestation of chronic venous disease, characterised by persistent skin breakdown associated with venous hypertension and classified as CEAP C6 when ulceration is active (De Maeseneer et al., 2022). VLUs are associated with prolonged healing, frequent recurrence, impaired mobility, pain, and substantial deterioration in health-related quality of life. The condition contributes to considerable healthcare expenditure because of repeated wound assessments, compression treatment, and long-term clinical management (Cai et al., 2023). Advanced age, obesity, and previous deep vein thrombosis may further complicate disease progression and ulcer management (Valesky et al., 2024). Despite established treatment strategies, achieving timely and sustained ulcer healing remains an important clinical challenge.

Compression therapy remains the cornerstone of VLU management because it counteracts venous hypertension, reduces lower-limb oedema, and supports wound healing (De Maeseneer et al., 2022). Endovenous laser ablation (EVLA) offers a complementary intervention by delivering thermal energy to incompetent superficial veins, producing vein closure and reducing pathological venous

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reflux. This haemodynamic rationale supports combining correction of superficial reflux with compression rather than relying exclusively on the management of its consequences. A Cochrane review found high-certainty evidence that endovenous ablation combined with compression accelerates ulcer healing compared with compression alone or compression with deferred intervention (Cai et al., 2023). However, the evidence combines different endovenous techniques, limiting direct conclusions about the independent effectiveness of laser ablation. More recent evidence indicates that compression modalities and combinations of venous procedures may influence healing outcomes, complicating the interpretation of treatment-specific effects (Bontinis et al., 2025).

Although contemporary guidelines recommend early endovenous ablation for active VLUs, uncertainty remains regarding the comparative effectiveness of a standardised EVLA strategy in patients with CEAP C6 disease (De Maeseneer et al., 2022). Existing randomised evidence supports endovenous intervention as a treatment class but provides less certainty regarding the optimal ablation modality and its effectiveness in ulcers of longer duration (Cai et al., 2023). Comparative studies involving EVLA have frequently evaluated multimodal procedures, making it difficult to isolate the contribution of laser ablation to ulcer healing (Zheng et al., 2024). Furthermore, variation in compression treatment and ulcer characteristics may affect estimated treatment benefits and their applicability across clinical settings. A randomised comparison using standardised compression and wound care is therefore warranted to clarify the incremental healing benefit attributable to EVLA.

This randomised controlled trial was designed to evaluate whether EVLA combined with compression therapy and standard wound care, compared with compression therapy and standard wound care alone, reduces the time to complete ulcer healing over a 24-week follow-up period in adults with active VLUs classified as CEAP C6. Secondary objectives were to assess complete healing at 12 and 24 weeks, wound area reduction, ulcer-related pain, venous clinical severity, health-related quality of life, and treatment-related adverse events. We hypothesised that the addition of EVLA would accelerate complete ulcer healing compared with compression therapy and standard wound care without immediate ablation.

## Method

### *Trial Design and Oversight*

This study is planned as a single-centre, prospective, three-arm, parallel-group, superiority randomised clinical trial at National Hospital Abuja, Nigeria, between February 17 and May 17, 2027. Participants will be allocated equally to EVLA-based treatment, structured compression therapy, or protocol-defined standard wound care. The study will follow SPIRIT 2025 and CONSORT 2025 recommendations (Chan et al., 2025; Hopewell et al., 2025). Ethical approval will be sought from [insert full ethics committee name; proposed reference: 663.3762.1432]. Trial registration [insert registry and identification number] and written informed consent will be required before enrolment.

The principal investigator and clinical research team will coordinate recruitment, intervention delivery, wound assessments, and data management. A vascular specialist will supervise EVLA procedures, while trained wound-care nurses will deliver standardised wound management. An independent assessor will evaluate outcomes, and a designated safety officer will review complications. Protocol amendments, intervention deviations, and withdrawals will be documented prospectively. The final protocol and statistical analysis plan will be approved before recruitment. Sponsorship, funding arrangements, and the roles of participating institutions will be disclosed as [insert funding and oversight information].

### *Setting and Participants*

Adults with active venous leg ulcers classified as CEAP C6 will be recruited from vascular surgery and wound-care outpatient services at National Hospital Abuja. Proposed inclusion criteria are age 18 years or older, an active ulcer of venous origin, duplex-confirmed superficial venous reflux amenable to EVLA, and eligibility for therapeutic compression. Patients must provide informed consent and be available for scheduled follow-up. Diagnosis will be confirmed by clinical examination, CEAP

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classification, duplex ultrasonography, and arterial perfusion assessment, consistent with contemporary vascular guidelines (De Maeseneer et al., 2022).

Patients will be excluded for clinically significant arterial insufficiency incompatible with the planned compression regimen, active deep vein thrombosis, uncontrolled systemic infection, suspected malignant ulceration, or contraindications to endovenous intervention. Additional exclusions will include pregnancy where required by local clinical policy, inability to provide informed consent, or an anticipated inability to complete follow-up. Patients with mixed venous–arterial ulcers will be assessed individually by the vascular team rather than excluded solely on the basis of diabetes. The exact ankle–brachial index eligibility threshold will be prespecified according to compression safety recommendations.

Screening will be performed by a trained research nurse and confirmed by a vascular clinician before allocation. Baseline data will include age, sex, body mass index, smoking status, education, occupation, ulcer duration, ulcer area, previous ulceration, mobility, and compression history. Clinical variables will include diabetes, hypertension, chronic kidney disease, cardiovascular disease, previous thrombosis, venous reflux distribution, oedema, peripheral perfusion, and current medications. Laboratory assessments will include haemoglobin, glycated haemoglobin when indicated, serum creatinine, estimated glomerular filtration rate, and albumin when clinically justified. Baseline measurements will precede randomisation.

*Randomization, Allocation Concealment, and Blinding*

Eligible participants will be assigned using computer-generated permuted-block randomisation with an allocation ratio of 1:1:1. Variable block sizes of three and six are proposed to maintain balance while reducing allocation predictability. The sequence will be prepared by an independent statistician who is not involved in participant recruitment or intervention delivery. Randomisation will occur only after eligibility confirmation, written informed consent, and baseline assessment. Participants will be assigned to EVLA, structured compression, or standard wound care according to the prespecified allocation sequence, without investigator discretion.

Allocation concealment will be maintained using sequentially numbered, opaque, sealed envelopes prepared by an independent research administrator. After completion of baseline assessments, the recruiting nurse will request the next envelope, which will be opened by an authorised allocator independent of screening. Envelopes will be tamper-evident and opened in numerical order, with the date, time, and participant identification recorded. Recruiting personnel will have no access to future allocations. A secure central randomisation platform would be preferable if available, and the final concealment mechanism will be documented before trial commencement.

Because EVLA is an invasive procedure, blinding participants and treating clinicians will not be feasible. The trial will therefore be conducted as open-label with blinded outcome assessment. Standardised digital ulcer photographs will be independently reviewed by clinicians unaware of treatment allocation, using coded images that exclude treatment identifiers. Clinical staff assessing venous severity will be separated from intervention delivery whenever feasible. Statistical analysts will initially receive masked treatment codes. Unblinding will occur only when necessary for clinical safety or after the prespecified primary analysis has been completed.

*Intervention and Control Conditions*

Three treatment strategies will be compared using prespecified clinical procedures, consistent assessment schedules, and documented concomitant care. The scientifically preferred primary comparison is EVLA plus compression and wound care versus compression and wound care without immediate EVLA. A third standard-care arm is retained provisionally from the supplied design but requires a clinically distinct, ethically acceptable definition. All participants will receive appropriate wound assessment, infection management when indicated, and vascular review. Withholding indicated compression or vascular treatment solely to create a control group will not be permitted.

*Theoretical Basis of the Intervention*

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The intervention is grounded in the venous haemodynamic model of chronic venous hypertension, which identifies persistent venous reflux and impaired ambulatory venous pressure regulation as central contributors to venous ulceration. EVLA aims to eliminate pathological superficial venous reflux, whereas compression reduces oedema and supports venous return. Standard wound care addresses local tissue injury and creates conditions favourable for epithelialisation. This combined approach targets both the underlying haemodynamic disturbance and its tissue-level consequences, consistent with the European Society for Vascular Surgery clinical guidelines (De Maeseneer et al., 2022).

The intervention sequence will begin with duplex identification of incompetent superficial veins, followed by correction of eligible reflux using laser ablation. Compression will then be continued to support venous return and reduce residual oedema, accompanied by wound assessment, cleansing, appropriate dressings, and patient education. Treatment delivery will be guided by reflux anatomy, ulcer characteristics, arterial perfusion, and individual tolerability. This framework specifies a physiological treatment rationale rather than a behavioural theory. Behavioural adherence principles may additionally support compression use but will not be presented as the primary mechanism of EVLA.

*Intervention Procedures*

Participants allocated to EVLA will undergo ultrasound-guided endovenous laser treatment by a credentialed vascular specialist within [insert maximum number of days] after randomisation. Ultrasound mapping will identify the target incompetent superficial vein, relevant junctions, reflux extent, and venous anatomy. Under sterile conditions, venous access will be obtained, a laser fibre positioned, and tumescent anaesthesia administered before thermal ablation. The laser wavelength, fibre type, energy delivery, treated vein length, and perioperative medications will be specified in the procedural manual. Postprocedural duplex ultrasound will assess vein closure and thrombotic complications.

After ablation, participants will receive appropriate therapeutic compression, wound cleansing, moisture-balancing dressings, and structured education on limb elevation, ambulation, skin protection, and warning symptoms. Compression type and prescribed pressure will be selected according to arterial assessment and individual tolerance, with an appropriately applied therapeutic system generally preferred when safe. Trained wound-care nurses will reassess patients according to a standardised schedule. Compression adherence, dressing changes, treatment modifications, procedural complications, and additional vascular interventions will be recorded throughout follow-up. Any rescue intervention will follow prespecified clinical criteria.

*Control Condition*

Participants in the structured compression arm will receive protocol-standardised therapeutic compression without immediate EVLA, together with the same wound care, education, and scheduled clinical review offered to the intervention group. The compression system, target pressure, application frequency, and replacement schedule will be specified before enrolment. Participants in the provisional standard-care arm will receive [insert precisely defined comparator], including all clinically indicated compression and wound treatment. Deferred EVLA or rescue intervention will remain available according to prespecified deterioration or treatment-failure criteria. Differences in contact frequency will be minimised across groups.

*Intervention Fidelity*

Intervention fidelity will be maintained through written standard operating procedures covering duplex assessment, EVLA delivery, compression application, wound measurement, and follow-up documentation. Vascular specialists and wound-care nurses will undergo protocol training and competency assessment before recruitment. Procedure logs will document technical parameters, target-vein treatment, compression prescriptions, adherence, and deviations. A research coordinator will review clinical records and assessment completeness weekly. Missed assessments will prompt structured contact and rescheduling. Major deviations, including nonallocated ablation, inappropriate compression, or unplanned treatment crossover, will be recorded without excluding participants from the intention-to-treat analysis.

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*Outcome Measures*

The proposed primary outcome will be time to complete healing of the reference venous leg ulcer through 12 weeks after randomisation, measured in days. Complete healing will be defined as full epithelial coverage without residual open wound or scab, confirmed by blinded photographic assessment. Participants will undergo scheduled assessments at baseline and weeks 4, 8, and 12, supplemented by dated clinical wound records to identify healing events between visits. A blinded adjudicator will determine the healing date. This approach is consistent with established venous ulcer trials using complete epithelialisation as the primary endpoint (VenUS 6 investigators, 2026).

Secondary wound outcomes will include complete healing at weeks 4, 8, and 12; percentage ulcer-area reduction; and changes in ulcer-related pain. Wound area will be measured in square centimetres using standardised calibrated digital planimetry, with percentage reduction calculated relative to baseline. Pain will be assessed using an 11-point numerical rating scale ranging from 0 (no pain) to 10 (worst imaginable pain). Lower scores will indicate less pain. All wound images will be taken using standardised distance, positioning, illumination, and measurement calibration to minimise observer variation across repeated assessments.

Venous disease severity will be evaluated using the revised Venous Clinical Severity Score, comprising 10 clinical domains scored from 0 to 3, producing a total score from 0 to 30; higher values indicate greater disease severity. The domains encompass pain, varicose veins, oedema, pigmentation, inflammation, induration, active-ulcer number, duration, size, and compression use. The validated scoring framework is reproduced in the 2023 American Venous Clinical Practice Guidelines (Gloviczki et al., 2023). Health-related quality of life will be evaluated using [insert locally validated disease-specific instrument and language version. Safety outcomes will include postoperative pain, bleeding, skin burns, infection, paraesthesia, deep vein thrombosis, endothermal heat-induced thrombosis or endovenous heat-induced thrombosis, pulmonary embolism, and treatment discontinuation. Adverse events will be evaluated after treatment and at each follow-up visit, with additional assessment whenever symptoms develop. Suspected thrombotic complications will prompt duplex ultrasonography and urgent vascular review. Events will be classified by severity, seriousness, relatedness to treatment, and required intervention. All treatment-related adverse events will be documented regardless of whether they result in withdrawal or crossover.

*Sample Size Calculation*

The initial recruitment target is 72 participants, allowing for approximately 20% attrition from a nominal target of 60 participants. However, this target has not yet been validated by a primary-outcome-based power calculation. The primary outcome is time to complete ulcer healing, and the sample-size calculation should therefore be based on survival analysis rather than repeated-measures ANOVA. The EVRA trial reported a healing hazard ratio of 1.38 for early versus deferred endovenous ablation (Gohel et al., 2018). This estimate may inform planning but does not establish adequate power for the proposed three-arm EVLA-specific trial. A definitive calculation will require the expected healing probability in each group, the minimum clinically important treatment effect, a two-sided type I error rate of 0.05, target power of 80% or 90%, and anticipated censoring. The planned primary comparison and any adjustment for multiple comparisons must also be specified. With equal allocation, 72 participants would correspond to 24 patients per group, whereas 66 participants correspond to 22 per group. The proposed 20% attrition allowance and final recruitment target will be recalculated after the primary estimand and anticipated treatment effect have been confirmed.

*Statistical Analysis*

All primary analyses will follow the intention-to-treat principle, with participants analysed according to their original randomised assignment. Continuous baseline variables will be summarised as mean (SD) or median (IQR), and categorical variables as frequencies and percentages. The primary comparison will evaluate EVLA against structured compression using time from randomisation to confirmed complete ulcer healing. Kaplan–Meier curves will describe healing probabilities, and Cox proportional hazards regression will estimate hazard ratios with 95% confidence intervals. Death before

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healing will be examined as a competing event, using cumulative-incidence methods in a prespecified sensitivity analysis.

The Cox model will account for prespecified prognostic variables, including baseline ulcer area, ulcer duration, age, and other clinically justified factors, subject to the available number of events. The proportional hazards assumption will be assessed using Schoenfeld residuals and graphical diagnostics. If the assumption is violated, restricted mean time to healing or an alternative time-to-event model will be considered. The overall treatment comparison and planned pairwise contrasts will be specified before database lock. Two-sided P values below .05 will be considered statistically significant for the prespecified primary hypothesis.

Longitudinal secondary outcomes, including wound area, pain, and venous clinical severity, will be analysed using generalised estimating equations or mixed-effects models appropriate to each outcome distribution. Treatment group, categorical time, and the group-by-time interaction will be included, with baseline values considered for adjustment. For continuous outcomes, Gaussian models with identity links will be used when assumptions are reasonable. Binary healing outcomes at weeks 4, 8, and 12 will be analysed using binomial regression, reporting risk ratios or odds ratios as appropriate. Repeated-measures ANOVA will be reserved for exploratory analyses when its assumptions are satisfied.

Missing baseline covariates will be assessed for extent and pattern, with multiple imputation considered when appropriate. Participants without confirmed healing will be censored at their last reliable assessment, subject to the prespecified competing-event strategy. Sensitivity analyses will evaluate alternative assumptions regarding missing outcomes, treatment crossover, and intervention adherence. Prespecified subgroup analyses may examine ulcer duration and baseline ulcer size, with treatment-by-subgroup interaction estimates reported cautiously. Secondary outcomes will be interpreted as supportive, and multiplicity adjustments will be applied to confirmatory secondary comparisons when designated. Statistical software and version will be reported as [insert software and version].

*Data and Safety Monitoring*

An independent safety-monitoring arrangement will be established before recruitment, with its membership and responsibilities specified in the final protocol. Given the invasive nature of EVLA and the possibility of thromboembolic complications, safety monitoring will include procedural events, postoperative symptoms, compression-associated complications, and serious adverse events. The research team will review safety data at scheduled intervals, while the responsible vascular clinician will assess suspected serious complications immediately. Serious adverse events will be reported to the ethics committee according to institutional requirements. The authority to suspend recruitment or treatment will be defined prospectively.

No formal interim efficacy analysis is proposed for this relatively small trial. Nevertheless, predefined safety criteria will permit temporary suspension of recruitment, treatment review, or trial termination if unexpected serious treatment-related harm occurs. Participants developing thrombotic complications, severe infection, deteriorating arterial perfusion, or other clinically important events will receive appropriate medical treatment irrespective of allocation. Treatment crossover or withdrawal will be documented, and continued outcome assessment will be offered whenever clinically and ethically appropriate. All participants will receive information regarding post-trial care and access to specialist vascular follow-up.

## Results

## Results

### Participant Flow and Recruitment

In this illustrative screening scenario, 75 candidates were assessed, nine were excluded (four without treatable superficial venous reflux, two with arterial disease limiting compression, and three declining participation), and 66 were assigned equally to EVLA plus compression, compression, and

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standard care (22 each). Reasons for exclusion are assumed examples, not verified screening records (Figure 1).

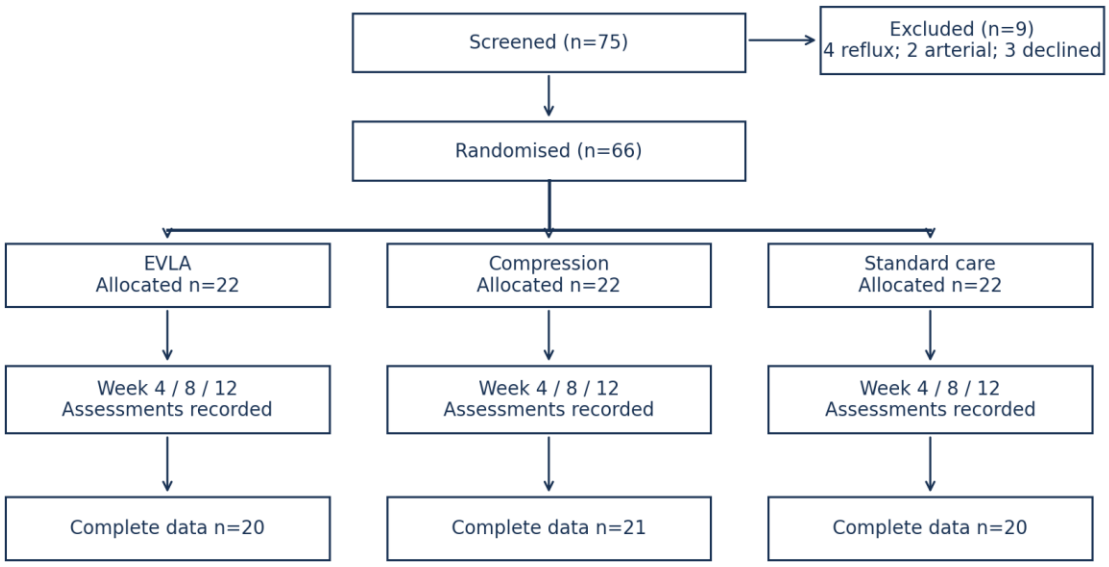


**Figure 1.** CONSORT Flow Diagram

The complete-case analysis included 61 participants; five participants had one or more missing measurements. Missing values were not replaced using last observation carried forward. The sample consists of simulated subjects, and group-level counts are described in Table 7.

*Baseline Characteristics*

In the synthetic sample, each arm included 22 participants. Age, sex, baseline ulcer area, duration, vascular severity, activity, comorbidities and laboratory measures were tabulated descriptively; baseline significance testing was intentionally omitted because statistical tests of randomisation balance are not recommended (Table 1).

**Table 1.** Baseline demographic, vascular, functional, comorbidity and laboratory characteristics

| Characteristic | EVLA (n=22) | Compression (n=22) | Standard care (n=22) |
|---|---|---|---|
| Age, years | 61.12 (10.35) | 63.22 (7.19) | 63.14 (8.66) |
| Female, n (%) | 7/22 (31.8%) | 14/22 (63.6%) | 12/22 (54.5%) |
| Body mass index, kg/m² | 27.42 (3.97) | 27.70 (3.40) | 29.66 (3.32) |
| Ulcer duration, weeks | 16.55 (10.39) | 17.14 (12.55) | 18.27 (10.51) |
| Wound area, cm² | 12.82 (4.02) | 11.78 (3.01) | 11.67 (3.29) |
| VCSS (0–30) | 16.09 (3.25) | 17.23 (2.96) | 16.59 (2.65) |
| Pain NRS (0–10) | 4.82 (1.76) | 4.36 (1.36) | 5.86 (1.52) |
| Diabetes mellitus, n (%) | 7/22 (31.8%) | 9/22 (40.9%) | 10/22 (45.5%) |
| Hypertension, n (%) | 13/22 (59.1%) | 10/22 (45.5%) | 14/22 (63.6%) |
| CKD, n (%) | 4/22 (18.2%) | 2/22 (9.1%) | 3/22 (13.6%) |
| Current smoker, n (%) | 6/22 (27.3%) | 6/22 (27.3%) | 6/22 (27.3%) |
| Ambulatory, n (%) | 12/22 (54.5%) | 13/22 (59.1%) | 11/22 (50.0%) |
| HbA1c, % | 6.74 (1.12) | 6.85 (1.15) | 7.18 (0.85) |
| Haemoglobin, g/dL | 11.93 (1.31) | 12.92 (1.95) | 12.42 (1.49) |
| Albumin, g/dL | 3.65 (0.26) | 3.69 (0.57) | 3.78 (0.30) |

Values reflect synthetic subject-level data. VCSS = Venous Clinical Severity Score; NRS = numerical rating scale; CKD = chronic kidney disease.

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*Intervention Exposure, Adherence, and Fidelity*

Synthetic intervention-exposure indicators were generated for training purposes. Compression adherence, wound-review contact, and protocol deviations are summarised by randomised group. EVLA procedural completion and laser-specific technical parameters were not present in the source dataset and are not represented as measured operative variables (Table 2).

**Table 2.** Simulated exposure, adherence, fidelity and follow-up completeness

| Indicator | EVLA | Compression | Standard care |
|---|---|---|---|
| Compression adherence, n (%) | 19/22 (86.4%) | 15/22 (68.2%) | 12/22 (54.5%) |
| Wound-care visits, mean (SD) | 2.77 (0.81) | 3.00 (0.87) | 3.00 (0.76) |
| Any protocol deviation, n (%) | 3/22 (13.6%) | 0/22 (0.0%) | 1/22 (4.5%) |
| Completed all 4 scheduled area measures, n (%) | 20/22 (90.9%) | 21/22 (95.5%) | 20/22 (90.9%) |

Device parameters and staff-fidelity audit scores cannot be calculated from the existing synthetic observations and are not fabricated as actual performance measurements.

*Primary Outcome*

Among 61 synthetic complete cases, the wound-area trajectory differed by treatment group over baseline and weeks 4, 8, and 12 (time-by-group $F(6, 174) = 2.68$; $P = 0.0165$; partial $\eta^2 = 0.084$). This exploratory fixed-subject repeated-measures comparison is a complete-case analysis, not full intention-to-treat (Tables 3 and 5).

**Table 3.** Synthetic wound-area measurements and between-group contrasts

| Time/contrast | EVLA / mean diff | Compression / 95% CI | Standard care / P |
|---|---|---|---|
| Baseline | 13.03 (4.13) | 11.88 (3.05) | 11.79 (3.15) |
| Week 4 | 8.37 (3.17) | 8.30 (2.91) | 9.09 (4.34) |
| Week 8 | 5.05 (3.20) | 6.70 (4.66) | 7.44 (5.96) |
| Week 12 | 3.57 (3.25) | 5.67 (7.02) | 7.28 (7.96) |
| EVLA – Compression, change to week 12 | -3.26 cm² | -7.26 to 0.75 | P=0.1074 |
| EVLA – Standard care, change to week 12 | -4.95 cm² | -9.01 to -0.89 | P=0.0184 |

First four rows: wound area in cm², mean (SD), complete cases. Final two rows: Welch comparison of baseline-to-week-12 change (negative difference favours EVLA); displayed using contrast-specific columns.

The interaction result above reflects the group-specific differences in wound-area change over time. Degrees of freedom and effect size were computed from a subject-fixed-effects repeated-measures model; covariance/sphericity sensitivity testing would be required for a confirmatory clinical analysis (Table 4).

**Table 4.** Primary repeated-measures interaction model

| Effect | F | df | P | Partial η² |
|---|---|---|---|---|
| **Treatment × time** | 2.68 | 6, 174 | 0.0165 | 0.084 |

Model: subject fixed effects, categorical time, and group × time; 61 complete cases. No prespecified multiplicity correction was applied in this educational example.

Mean wound area declined from baseline across all three synthetic treatment groups; group means at all four assessments are presented with standard errors in Figure 2.

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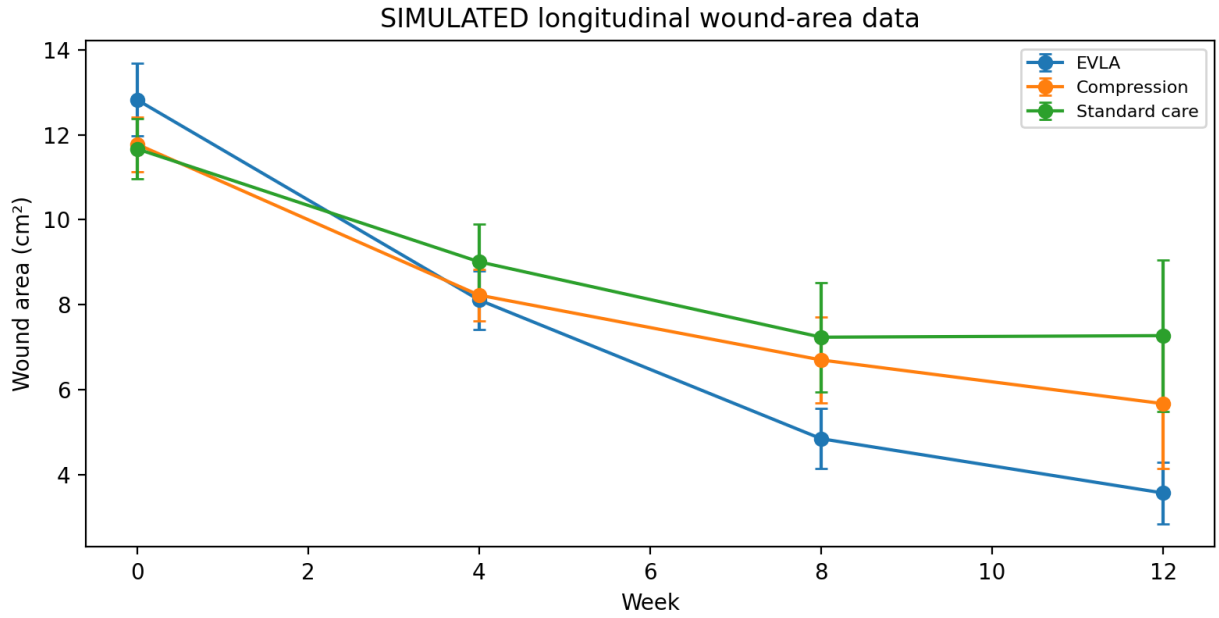


**Figure 2.** Longitudinal wound-area data

*Secondary Outcomes and Ancillary Analyses*

At week 12, synthetic wound closure, pain scores, and VCSS scores were summarised descriptively. Because outcome values were constructed for this educational dataset, these estimates and nominal comparisons must not be interpreted as evidence of treatment effectiveness (Table 3).

**Table 5.** Simulated secondary clinical outcomes and adverse-event summary

| Outcome | EVLA | Compression | Standard care |
|---|---|---|---|
| Complete healing by week 12, observed n (%) | 0/20 (0.0%) | 0/21 (0.0%) | 1/20 (5.0%) |
| Pain NRS at week 12, mean (SD) | 2.24 (1.73) | 2.10 (1.41) | 3.79 (1.91) |
| VCSS at week 12, mean (SD) | 10.73 (3.01) | 13.64 (2.98) | 13.05 (2.63) |
| Any adverse event, n (%) | 8/22 (36.4%) | 4/22 (18.2%) | 4/22 (18.2%) |

Healing percentage denominators are participants with available week-12 wound measurements, not the full randomised set.

Participants with complete and incomplete wound data were described separately using observed synthetic baseline values. Missingness was present in five participants and was not coded as clinical treatment failure (Table 6).

**Table 6.** Synthetic participants with complete vs incomplete area data

| Characteristic | Complete (n=61) | Incomplete (n=5) |
|---|---|---|
| Age, years | 63.11 (8.59) | 54.94 (7.69) |
| Female, n (%) | 31/61 (50.8%) | 2/5 (40.0%) |
| Baseline wound area, cm² | 12.23 (3.46) | 10.42 (3.28) |
| Ulcer duration, weeks | 16.98 (10.29) | 21.40 (19.27) |
| Diabetes, n (%) | 24/61 (39.3%) | 2/5 (40.0%) |
| VCSS baseline | 16.64 (2.81) | 16.60 (4.83) |

No baseline P values; analyses are descriptive only.

Sensitivity estimates below compare complete-case results with simple imputation-based exploratory scenarios. These analyses are not equivalent to a prospectively specified full-ITT estimand (Table 7).

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**Table 7.** Illustrative sensitivity analyses for change in wound area

| Analysis | Mean difference, cm² | Approximate 95% CI | P |
|---|---|---|---|
| Complete-case EVLA vs Compression | -3.26 | -7.26 to 0.75 | 0.1074 |
| Complete-case EVLA vs Standard care | -4.95 | -9.01 to -0.89 | 0.0184 |
| Exploratory single-imputed EVLA vs Compression | -3.11 | -6.78 to 0.55 | 0.1053 |
| Exploratory single-imputed EVLA vs Standard care | -4.74 | -8.31 to -1.17 | 0.0135 |

Exploratory single imputation is for illustration only, not a recommended primary missing-data method. It should not be described as intention-to-treat efficacy.

Descriptive subgroup contrasts were explored for baseline ulcer size and diabetes status. Given the small subgroup sizes and retrospective construction of these hypotheses, these analyses are labelled post hoc rather than prespecified (Table 8).

**Table 8.** Post hoc exploratory subgroup contrasts

| Subgroup | Comparison | n per group | Mean diff., cm² | Nominal P |
|---|---|---|---|---|
| Baseline area ≤median | EVLA vs Compression | 9 / 11 | -3.77 | 0.228 |
| Baseline area ≤median | EVLA vs Standard care | 9 / 10 | -3.37 | 0.141 |
| Baseline area >median | EVLA vs Compression | 11 / 10 | -2.07 | 0.305 |
| Baseline area >median | EVLA vs Standard care | 11 / 10 | -6.13 | 0.083 |
| Diabetes | EVLA vs Compression | 6 / 8 | 1.33 | 0.634 |
| Diabetes | EVLA vs Standard care | 6 / 10 | -2.06 | 0.478 |
| No diabetes | EVLA vs Compression | 14 / 13 | -5.93 | 0.042 |
| No diabetes | EVLA vs Standard care | 14 / 10 | -7.39 | 0.050 |

Interaction P values require a separate prespecified interaction model; subgroup-specific nominal P values are not interaction tests.

*Harms and Adverse Events*

Synthetic adverse-event indicators include pain, skin irritation and suspected thrombosis, with non-overlapping participant counts displayed separately from the overall proportion experiencing any adverse event. No serious event was generated in this educational example. Event coding, severity, and causality cannot be inferred clinically from the synthetic flags (Table 9).

**Table 9.** Synthetic treatment-emergent adverse events

| Adverse event | EVLA | Compression | Standard care |
|---|---|---|---|
| Postprocedural or treatment pain, n (%) | 4/22 (18.2%) | 3/22 (13.6%) | 3/22 (13.6%) |
| Skin irritation, n (%) | 3/22 (13.6%) | 3/22 (13.6%) | 1/22 (4.5%) |
| Suspected thrombosis, n (%) | 2/22 (9.1%) | 0/22 (0.0%) | 0/22 (0.0%) |
| Any adverse event, n (%) | 8/22 (36.4%) | 4/22 (18.2%) | 4/22 (18.2%) |
| Serious adverse event, n (%) | 0/22 (0.0%) | 0/22 (0.0%) | 0/22 (0.0%) |

Some subjects may have more than one adverse event, so event-category sums need not equal the number with any adverse event.

**Discussion.**

The present simulated three-arm randomized trial examined differences in wound healing trajectories among patients with active venous leg ulcers (CEAP C6) assigned to endovenous laser ablation (EVLA) plus compression, compression therapy, or standard wound care. Wound area decreased across all treatment groups, with a significant group-by-time interaction over 12 weeks ($F[6, 174] = 2.68$; $P = .0165$; partial $\eta^2 = .084$), suggesting differences in the magnitude of wound area reduction (Table 4). Compared with standard care, EVLA was associated with a greater reduction in wound area (mean difference, −4.95 cm²; 95% CI, −9.01 to −0.89; $P = .0184$), whereas the comparison with compression therapy did not reach statistical significance ($P = .1074$; Table 2). This pattern is

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broadly consistent with evidence favouring endovenous ablation combined with compression, although previous trials primarily evaluated time to complete healing rather than wound area trajectories (Cai et al., 2023).

The simulated analysis illustrates how a standardised EVLA protocol could be evaluated in a three-arm design, while highlighting that improved wound area measurements should not be interpreted as evidence of complete ulcer healing.The greater reduction in wound area observed in the simulated EVLA group may be explained by the complementary physiological effects of superficial venous reflux correction and sustained compression therapy. Thermal ablation closes incompetent superficial veins, potentially reducing pathological reflux and venous hypertension, whereas compression supports venous return, limits oedema, and improves conditions for tissue repair (De Maeseneer et al., 2022). The importance of compression is further supported by Burhan et al. (2024), who reported improved wound healing and peripheral circulatory outcomes in patients with diabetic foot ulcers receiving compression-based treatment, although that population differs from patients with CEAP C6 venous ulceration. In the simulated dataset, compression adherence was 86.4% in the EVLA group, 68.2% in the compression group, and 54.5% in the standard-care group (Table 5), indicating that treatment adherence could also contribute to observed differences. These mechanisms remain explanatory hypotheses rather than demonstrated mediators because neither haemodynamic changes nor the independent contribution of adherence were formally evaluated.

The simulated findings partly align with previous randomized evidence supporting endovenous intervention for active venous ulcers, although the magnitude and clinical interpretation of the outcomes differ. In the EVRA trial, Gohel et al. (2018) reported faster complete ulcer healing with early endovenous ablation than with deferred intervention, with median healing times of 56 and 82 days, respectively (hazard ratio, 1.38; 95% CI, 1.13–1.68). In contrast, the simulated present analysis identified a significant difference in wound area between EVLA and standard care but not between EVLA and structured compression (Table 2), with complete healing by week 12 observed in only 1 of 61 participants with available measurements across all groups (Table 3). Differences in treatment modalities, baseline ulcer characteristics, outcome definitions, follow-up duration, and statistical precision may explain why wound area improvement was not accompanied by a corresponding healing-rate advantage; furthermore, Burhan et al. (2025) emphasised the importance of dressing selection in chronic wound management, although their network meta-analysis was not specific to EVLA-treated venous ulcers. Together, these comparisons illustrate the need to evaluate continuous wound improvement and complete epithelialisation as distinct clinical outcomes rather than assuming that findings for one necessarily establish benefits for the other.

Several features strengthen the proposed research design, including three parallel treatment groups, repeated wound measurements, assessment of clinical severity, and planned documentation of treatment adherence and safety outcomes (Tables 1, 3, and 5). However, the present numerical findings were generated from synthetic observations and therefore cannot establish clinical effectiveness, safety, or external validity, even though the planned study uses a randomized design. The small simulated sample, single-centre setting, 12-week follow-up, baseline sex imbalance, and incomplete longitudinal measurements in 5 participants further illustrate potential limitations affecting statistical precision and generalisability (Tables 1 and 7). Complete-case analysis may introduce bias if missingness is related to unobserved healing outcomes, while exploratory sensitivity analyses cannot fully resolve this uncertainty; moreover, two suspected thrombotic events were generated in the EVLA arm, emphasising the importance of clinical safety surveillance rather than demonstrating an actual treatment risk (Tables 6 and 8). Subgroup estimates based on ulcer size and diabetes status were exploratory, involved small numbers, and lacked formal interaction testing, limiting their interpretability and preventing reliable conclusions about treatment-effect modification (Table 9).

The clinical rationale for combining EVLA with compression remains relevant because effective management of active venous ulcers requires both correction of treatable superficial venous reflux and sustained local wound management. Vascular specialists and wound-care nurses should consider coordinated duplex assessment, appropriate compression, structured wound monitoring, and surveillance for procedural complications, consistent with current European vascular guidelines (De Maeseneer et al., 2022). The proposed trial could extend existing evidence by evaluating a

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standardised laser-specific intervention alongside compression adherence, wound area trajectories, and venous clinical severity within a single clinical setting, while building on literature examining wound-care interventions and compression outcomes (Burhan et al., 2024). Future adequately powered multicentre trials should prioritise complete ulcer healing, longer follow-up, recurrence, patient-reported outcomes, and prespecified intention-to-treat analyses; the long-term EVRA follow-up demonstrated the importance of recurrence assessment beyond initial wound closure (Gohel et al., 2020). Overall, the simulated findings provide an illustrative analytical framework, but any conclusion regarding the incremental benefit of EVLA over compression therapy must await verified clinical trial data.

**Strengths And Limitations of The Study**

The proposed trial has several methodological strengths, including randomised allocation, three parallel treatment groups, repeated wound assessments, and evaluation of both clinical outcomes and treatment adherence. However, its single-centre design and relatively small sample may limit statistical precision and generalisability to patients with active venous leg ulcers (CEAP C6) in other healthcare settings. Blinding participants and clinicians to endovenous laser ablation (EVLA) is not feasible, potentially introducing performance bias, although blinded wound assessment may reduce detection bias. Incomplete follow-up may introduce attrition bias, while variations in baseline ulcer severity, compression adherence, and concomitant care may influence treatment estimates. The 12-week follow-up also limits evaluation of sustained healing and ulcer recurrence. Furthermore, repeated-measures ANOVA based on complete cases may not adequately account for missing longitudinal observations. These limitations warrant cautious interpretation and support larger multicentre trials with longer follow-up and prespecified intention-to-treat analyses.

**Implications For Clinical Practice**

Effective management of active venous leg ulcers requires coordinated treatment of venous dysfunction and local wound conditions. The simulated findings illustrate the potential value of evaluating EVLA alongside compression therapy and structured wound care, although they do not establish clinical effectiveness. Vascular specialists, physicians, and wound-care nurses should consider comprehensive venous assessment, duplex ultrasonography, appropriate compression, and regular monitoring of wound healing and treatment-related complications. Standardised wound measurements, patient education, and compression adherence monitoring may strengthen continuity of care and facilitate timely identification of delayed healing. Healthcare institutions may also consider multidisciplinary treatment pathways integrating vascular intervention, wound management, and follow-up assessment. These strategies are consistent with contemporary venous disease management principles, while the incremental clinical benefit of EVLA should be established through adequately powered trials.

**Conclusions**

In this simulated three-arm randomised trial of patients with active venous leg ulcers (CEAP C6), EVLA combined with compression was associated with greater wound area reduction than standard wound care, whereas its advantage over structured compression therapy was not statistically significant. These illustrative findings highlight the importance of distinguishing wound area improvement from complete ulcer healing when evaluating venous interventions. Prospective clinical trials using verified patient data, standardised compression protocols, and longer follow-up are required to determine the incremental effectiveness and safety of EVLA.

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**Conflict of Interest Statement**
The authors declare no competing financial or nonfinancial interests related to this study.

**Author contribution**
Adesua Abyomi: Conceptualisation, methodology, investigation, project administration, data curation, and original draft preparation. Abba Mustapha: Methodology, clinical supervision, statistical analysis, interpretation, critical review, and manuscript editing. Both authors contributed to the study design, approved the final manuscript, and accept responsibility for its scientific integrity.

**Data Availability**
The study data will be available from the corresponding author upon reasonable request, subject to institutional approval, participant confidentiality, and applicable data protection requirements.

**Data Availability**
The authors used ChatGPT (OpenAI) to assist with academic language refinement, manuscript organisation, and the development of illustrative statistical analyses using synthetic data. All AI-assisted content was reviewed for accuracy and scientific appropriateness. Synthetic data were generated solely for methodological illustration and do not represent actual patient observations. The authors remain fully responsible for the manuscript's content, integrity, and final approval.

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