Research Article
E-ISSN : 3048-1368
Volume 37, Issue No. 01. 2026
P-ISSN : 3048-1376

The International Journal of Medical Science and Health Research

The Association Between Venous Ulcer Area and Time to Healing Following Venous Ablation : A Comprehensive Systematic Review

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Article History :

Received date : 2025/12/12
Revised date : 2026/01/09
Accepted date : 2026/02/17
Published date : 2026/03/24

E-ISSN :
ISSN 3048-1368

P-ISSN
ISSN 3048-1376

ABSTRACT

Introduction: Venous leg ulcers (VLUs) affect millions worldwide with significant morbidity. While endovenous ablation addresses underlying venous reflux, the prognostic role of baseline ulcer size on healing time remains inadequately characterized. This systematic review synthesized evidence on the relationship between baseline venous ulcer area and time to healing following venous ablation.

Methods: Seventy sources were systematically reviewed using predefined criteria: adult patients with venous ulcers undergoing ablation, reporting baseline ulcer size and healing time. Data extraction encompassed ulcer size parameters, healing time metrics, size-healing relationship analyses, and study characteristics.

Results: Twenty-four studies reported baseline ulcer size, and 48 reported healing time. Measurement methods were heterogeneous: area (cm^2) reported by Weber et al. (7.7±10.7 cm^2), Sermsathanasawadi et al. (2.8±2.0 cm^2), and Ivanova et al. (391.3±100.42 cm^2); diameter categories used by Uttaray et al. (<2, 2-4, >4 cm) and Gohel et al. (<2, 2-6, >6 cm). Healing times ranged from 22 days for small ulcers (Savolyuk et al.) to median 56-82 days (EVRA trial). Savolyuk et al. demonstrated size-dependent healing: 7-21 cm^2 ulcers healed in 22.3±0.9 days versus 29.1±0.7 days for larger ulcers. Uttaray et al. observed non-healing associated with ulcers >5 cm. Tenbrook et al. identified diameter >2 cm as a non-healing risk factor.

Discussion: Larger ulcers require greater tissue regeneration and are associated with longer disease duration and more severe dermal damage. Despite biological plausibility and recognition of size as a prognostic variable (stratification in VUERT and AAVTIRS trials), direct evidence remains limited. Studies primarily compared ablation modalities rather than examining size as a predictor. Heterogeneity in measurement methods and insufficient statistical power constrain definitive conclusions.

Conclusion: Current evidence suggests larger venous ulcers heal more slowly following ablation, but the association lacks robust quantification. Future research requires standardized size measurement and adequate sample sizes for size-stratified analyses.

Keywords: venous leg ulcer, endovenous ablation, ulcer size, wound healing, systematic review

INTRODUCTION

Background

Venous leg ulcers (VLUs) affect 1-3% of the population, representing the most severe manifestation of chronic venous insufficiency (CVI) [1,2]. These wounds impose substantial burdens: impaired quality of life, chronic pain, and healthcare costs estimated at $2.5-3.5 billion annually in the United States [5,6]. The advent of endovenous ablation—including endovenous laser ablation (EVLA), radiofrequency ablation (RFA), and ultrasound-guided foam sclerotherapy (UGFS)—has transformed VLU management by directly addressing underlying venous reflux [11-14]. The landmark EVRA trial demonstrated that early ablation significantly reduces healing time compared to deferred treatment (median 56 vs 82 days; HR 1.38, p=0.001) [6,14].

Problem Statement

Ulcer size at presentation represents an intuitively important prognostic factor: larger wounds require more extensive tissue regeneration. Yet despite this biological plausibility, the quantitative relationship between baseline venous ulcer area and healing time following ablation remains poorly characterized. Clinicians lack evidence-based guidance on how ulcer size should influence treatment decisions, patient counseling, or prognostic expectations [19,20].

Research Gap

Examination of the literature reveals critical gaps. First, most studies evaluating ablation were designed to compare treatment modalities rather than identify prognostic factors [9,21,22]. Second, among studies reporting both ulcer size and healing time, analyses examining their relationship are notably absent or superficial [23,24]. Large trials such as EVRA (n=450) collected size data but reported only adjusted analyses without providing specific effect sizes for the size-healing association [5,6]. The VUERT trial stratified randomization by ulcer area (>5 cm^2 vs <5 cm^2) yet did not report size-stratified outcomes [12,16]. Third, measurement methodologies are strikingly heterogeneous, complicating cross-study comparisons [25,26].

Novelty

This systematic review provides the first comprehensive synthesis specifically focused on the relationship between venous ulcer size and healing time following ablation, uniquely concentrating on size as a prognostic determinant.

Research Objectives

1. To systematically identify and synthesize all evidence on the association between baseline venous ulcer size and healing time following ablation
2. To characterize ulcer size measurement methods across studies
3. To identify direct statistical analyses examining the size-healing relationship

Research Hypotheses

1. There is a significant positive association between baseline ulcer area and healing time following ablation
2. This association has been inadequately quantified due to study design limitations

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate The Association Between Venous Ulcer Area and Time to Healing Following Venous Ablation.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population and Intervention**: Does this study involve adult patients (≥18 years) with venous ulcers who underwent vein ablation procedures?

- **Required Outcome Data**: Does this study report both baseline ulcer size measurements and healing time outcomes?
- **Measurement Methods**: Does this study have clearly defined ulcer size measurement methods and healing criteria with follow-up periods?
- **Study Design**: Is this study a prospective cohort study, retrospective cohort study, case-control study, randomized controlled trial, systematic review, or meta-analysis?
- **Ulcer Type Specificity**: Does this study focus on venous ulcers specifically (not arterial ulcers, diabetic ulcers, or mixed etiology ulcers without separate venous ulcer data)?
- **Intervention Type**: Does this study involve ablation procedures specifically (not other surgical vein procedures like vein stripping or phlebectomy alone)?
- **Sample Size**: Does this study include 10 or more patients (not a case report or small case series with fewer than 10 patients)?
- **Baseline Measurement Timing**: Was baseline ulcer size measured before or at the time of the ablation procedure (not only after the procedure)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Venous Ulcer	Venous Ablation	Ulcer Size	Healing Time
Keyword 2	Venous Leg Ulcer	Endovenous Ablation	Ulcer Area	Wound Healing Rate

Keyword 3	Venous Insufficiency Ulcer	Vein Ablation	Wound Size	Ulcer Healing Duration
Keyword 4	Stasis Ulcer	Ablation Procedures	Ulcer Diameter	Healing Velocity

The Boolean MeSH keywords inputted on databases for this research are: *("Venous Ulcer" OR "Venous Leg Ulcer" OR "Venous Insufficiency Ulcer" OR "Stasis Ulcer") AND ("Venous Ablation" OR "Endovenous Ablation" OR "Vein Ablation" OR "Ablation Procedures") AND ("Ulcer Size" OR "Ulcer Area" OR "Wound Size" OR "Ulcer Diameter") AND ("Healing Time" OR "Wound Healing Rate" OR "Ulcer Duration" OR "Healing Velocity")*

Data extraction

- **Ulcer Size**:

  Extract all details about venous ulcer size measurements at baseline (before ablation), including:

  - Measurement method (area, diameter, longest dimension, etc.)
  - Actual size values with units (cm^2, cm diameter, mm, etc.)
  - Size categories or classification system used
  - Whether measurements were standardized/validated
  - Any size-related inclusion/exclusion criteria for the study

- **Healing Time**:

  Extract all healing time data after venous ablation procedures, including:

  - Definition of 'healed' used in the study
  - Time units reported (days, weeks, months)

- Mean/median healing time with standard deviations/confidence intervals
- Healing rates at specific time points (e.g., 6 weeks, 3 months, 6 months)
- Whether healing time was measured from ablation date or study enrollment
- Any censoring or incomplete healing data

- **Size-Healing Relationship**:

  Extract any direct analysis of the relationship between venous ulcer size and healing time after ablation, including:

  - Statistical tests examining size-healing associations (correlation, regression, etc.)
  - Healing times stratified by size categories
  - Effect sizes or correlation coefficients
  - Statistical significance values
  - Multivariate analysis adjusting for confounders
  - Any stated conclusions about size impact on healing time

- **Ablation Details**:

  Extract details about the venous ablation procedures performed, including:

  - Type of ablation (EVLA, RFA, UGFS, etc.)
  - Anatomical targets (saphenous veins, perforators, specific vein segments)
  - Technical parameters (laser wavelength, RF energy settings, etc.)
  - Timing of ablation relative to ulcer development

- Concurrent treatments (compression therapy, wound care)
- Procedural success rates or technical failures

- **Patient Characteristics**:

  Extract key patient demographics and clinical factors that may influence the ulcer size-healing relationship, including:

  - Age (mean/median with ranges)
  - Gender distribution
  - Ulcer duration before treatment
  - Underlying venous pathology (post-phlebitic, primary insufficiency, etc.)
  - Comorbidities affecting wound healing (diabetes, arterial disease, etc.)
  - Previous ulcer episodes or treatments
  - CEAP classification if reported

- **Study Design**:

  Extract study design and methodological details relevant to assessing the ulcer size-healing time relationship, including:

  - Study type (RCT, cohort, case series, etc.)
  - Sample size and power calculations
  - Follow-up duration and completion rates
  - Inclusion/exclusion criteria related to ulcer size or healing potential

- Control groups or comparison arms
- Blinding and randomization methods
- Primary vs secondary outcome designation for healing time

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Venous Ulcer" OR "Venous Leg Ulcer" OR "Venous Insufficiency Ulcer" OR "Stasis Ulcer") AND ("Venous Ablation" OR "Endovenous Ablation" OR "Vein Ablation" OR "Ablation Procedures") AND ("Ulcer Size" OR "Ulcer Area" OR "Wound Size" OR "Ulcer Diameter") AND ("Healing Time" OR "Wound Healing Rate" OR "Ulcer Duration" OR "Healing Velocity")*	5
Semantic Scholar	*("Venous Ulcer" OR "Venous Leg Ulcer" OR "Venous Insufficiency Ulcer" OR "Stasis Ulcer") AND ("Venous Ablation" OR "Endovenous Ablation" OR "Vein Ablation" OR "Ablation Procedures") AND ("Ulcer Size" OR "Ulcer Area" OR "Wound Size" OR "Ulcer Diameter") AND ("Healing Time" OR "Wound Healing Rate" OR "Ulcer Duration" OR "Healing Velocity")*	276
Springer	*("Venous Ulcer" OR "Venous Leg Ulcer" OR "Venous Insufficiency Ulcer" OR "Stasis Ulcer") AND ("Venous Ablation" OR "Endovenous Ablation" OR "Vein Ablation" OR "Ablation Procedures") AND ("Ulcer Size" OR "Ulcer Area" OR "Wound Size" OR "Ulcer Diameter") AND ("Healing Time" OR "Wound Healing Rate" OR "Ulcer Duration" OR "Healing Velocity")*	29
Google Scholar	*("Venous Ulcer" OR "Venous Leg Ulcer" OR "Venous Insufficiency Ulcer" OR "Stasis Ulcer") AND ("Venous Ablation" OR "Endovenous Ablation" OR "Vein Ablation" OR "Ablation Procedures") AND ("Ulcer Size" OR "Ulcer Area" OR "Wound Size" OR "Ulcer Diameter") AND ("Healing Time" OR "Wound Healing Rate" OR "Ulcer Duration" OR "Healing Velocity")*	523
Wiley Online Library	*("Venous Ulcer" OR "Venous Leg Ulcer" OR "Venous Insufficiency Ulcer" OR "Stasis Ulcer") AND ("Venous Ablation" OR "Endovenous Ablation" OR "Vein Ablation" OR "Ablation Procedures") AND ("Ulcer Size" OR "Ulcer Area" OR "Wound Size" OR "Ulcer Diameter") AND ("Healing Time" OR "Wound Healing Rate" OR "Ulcer Duration" OR "Healing Velocity")*	20

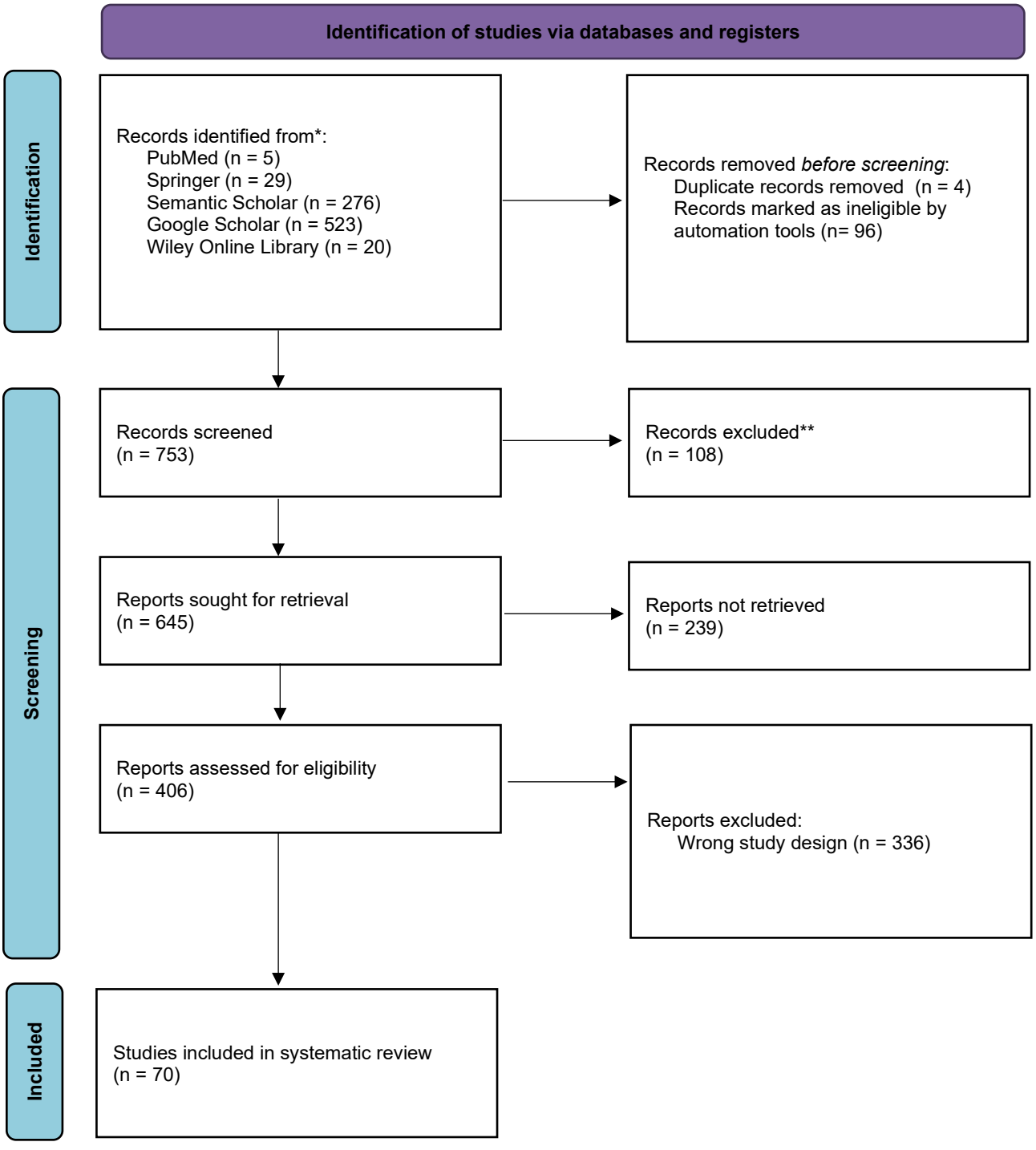

Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

A total of 70 sources were identified and reviewed for evidence on the relationship between venous ulcer size and healing time after venous ablation. These comprised randomized controlled trials, prospective and retrospective cohort studies, etc.

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
P. Cai et al., 2023	Endovenous ablation + compression [9]	506 participants [9]	No [9]	Yes, proportion healed at 90 days [9]
Sheetal Uttaray et al., 2023	EVLA 1470 nm ± UGFS [2]	50 patients [2]	Yes, diameter categories [2]	Yes, mean 2.55±1.38 months [2]
Luiz Marcelo Aiello Viarengo et al., 2007	EVL 980 nm diode [10]	52 patients [10]	Yes, area (cm^2) [10]	Yes, 81.5% healed at 12 months [10]
B. Weber et al., 2022	EVLA vs UGFS [11]	68 patients [11]	Yes, area (cm^2) [11]	Yes, EVLA 59±37 days, UGFS 63±41 days [11]
Nuttawut Sermsathanasawadi et al., 2022	Cyanoacrylate closure [4]	27 patients [4]	Yes, area (cm^2) [4]	Yes, 57.1% vs 46.1% at 24 weeks [4]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
M. Gohel et al., 2019	Multiple endovenous modalities [6]	450 participants [6]	Yes, diameter categories [6]	Yes, median 56 vs 82 days [6]
I. Sincos et al., 2018	Radiofrequency ablation [12]	56 patients [12]	Yes, stratified >5 cm^2 or <5 cm^2 [12]	Yes, 73% vs 65% at 12 weeks [12]
R. Abdul-Haqq et al., 2013	EVLA of GSV ± IPV [13]	95 patients (108 limbs) [13]	No [13]	Yes, 11.2–14.8 weeks [13]
M. Gohel et al., 2018	Early endovenous ablation [14]	450 patients [14]	No [14]	Yes, median 56 vs 82 days [14]
Mohamed S. Abdelgawad et al., 2021	RFA of perforators [15]	119 patients [15]	No [15]	Yes, 90.3% vs 77.2% at 24 months [15]
J. Puggina et al., 2020	RFA of saphenous and perforating veins [16]	56 patients [16]	No [16]	Yes, healing velocity faster with RFA [16]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
A. Gallus et al., 2018	Foam sclerotherapy or endothermal [17]	450 patients [17]	No [17]	Yes, median 56 vs 82 days [17]
Keohane Cr et al., 2024	Axial ablation vs TIRS [18]	98 participants [18]	Yes, area 1–200 cm^2 [18]	Yes, median 84 days both groups [18]
I. Erdinc et al., 2022	Glue ablation, EVLA, surgery [19]	112 patients [19]	No [19]	Yes, 53–74 days by group [19]
M. Stücker et al., 2022	Not specified [20]	450 participants [20]	No [20]	No [20]
Xinrui Yang et al., 2021	EVLA ± iliac vein stenting [21]	157 patients [21]	No [21]	Yes, 86.8% vs 65.6% at 1 year [21]
Toni Pihlaja et al., 2019	Foam sclerotherapy [22]	11 recruited (target 58) [22]	Yes, calibrated photos [22]	Preliminary only [22]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
T. Aherne et al., 2019	Endovenous ablation ± iliac stenting [7]	60 planned [7]	Yes, digital planimetry [7]	Yes, estimated median ~140 days [7]
O. V. Kolomiets et al., 2023	EVLA 1470 nm [23]	78 patients [23]	Yes, area (points) [23]	Yes, rapid within 1–3 months [23]
Toni Pihlaja et al., 2025	EVLA + UGFS ± sub-ulcer foam [24]	Not reported [24]	No [24]	Primary outcome [24]
Wael Elshimy et al., 2014	RFA + UGFS [25]	66 patients [25]	No [25]	Yes, 17.5–24.3% unhealed at 24 wks [25]
T. Aherne et al., 2019a	Mechanic-chemical or RFA [26]	60 planned [26]	Yes, digital planimetry [26]	Yes, estimated median [26]
G. Grover et al., 2016	UGFS [27]	54 patients [27]	No [27]	Yes, median 5.3 months [27]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
E. Goldschmidt et al., 2021	Various endovenous [28]	161 patients [28]	No [28]	Yes, persistent ulcer rates [28]
H. Elazazy et al., 2020	RFA vs conventional surgery [29]	40 patients [29]	No [29]	Follow-up at 2, 4, 6 months [29]
A. Mohamed et al., 2021	RFA vs surgery [30]	40 patients [30]	No [30]	Yes, healing rates at 2, 4, 6 months [30]
Douglas Poschinger-Figueiredo et al., 2021	RFA + USGFS [31]	30 patients [31]	No [31]	Yes, 92% at 1 year [31]
E. Avgerinos et al., 2019	Not specified [32]	Not reported [32]	No [32]	No [32]
Melissa Andreia de Moraes Silva et al., 2025	Foam sclerotherapy [8]	68 planned [8]	Yes, smartphone app (cm^2) [8]	Yes, 93% vs 68% at 6 months [8]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
V. O. Prasol et al., 2025	EVLA ± foam sclerosis [33]	46 patients [33]	Yes, >25 cm² [33]	Yes, 68.2% vs 82.6% at 24 weeks [33]
Kathleen Gibson et al., 2024	Cyanoacrylate (VenaSeal) [34]	506 participants [34]	No [34]	Primary outcome at 12 months [34]
Huanwei Wang et al., 2024	RFA needle device [35]	80 patients [35]	No [35]	Yes, shorter in RF group [35]
Ahmed Mousa Hafez et al., 2023	RFA [36]	60 patients [36]	No [36]	No [36]
K. Weiß et al., 2018	Not specified [37]	Not reported [37]	No [37]	No [37]
S. Mayor et al., 2018	Not specified [38]	Not reported [38]	No [38]	No [38]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
Vangelis Bontinis et al., 2023	RFA, EVLA, sclerotherapy [39]	2156 patients [39]	No [39]	No [39]
S. Savolyuk et al., 2021	EVEZ [1]	68 patients [1]	Yes, area 7–89 cm^2 [1]	Yes, 22.3±0.9 days (small ulcers) [1]
Myriam L. Montminy et al., 2018	Various [40]	1940 articles screened [40]	No [40]	Yes, 70–100% healing [40]
Xin Li et al., 2017	Foam sclerotherapy ± ligation [41]	33 patients [41]	No [41]	Yes, 35.67 vs 62.86 days [41]
L. Kabnick et al., 2024	Polidocanol microfoam vs thermal [42]	13 studies [42]	No [42]	No [42]
R. Avrahami et al., 2022	Venous ablation + VenoDress [43]	108 patients [43]	No [43]	Yes, 65% vs 45% at 1 month [43]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
W. Marston et al., 2023	Polidocanol microfoam [44]	Not reported [44]	No [44]	No [44]
K. Darvall et al., 2009	UGFS [45]	27 patients (28 legs) [45]	No [45]	Yes, 96% healed at 3 months [45]
L. Kabnick et al., 2015	EVLA of IPVs [46]	311 patients (376 limbs) [46]	No [46]	Yes, median 1.40 vs 3.30 months [46]
Zhao-xuan Liu et al., 2019	EVLT + sclerosing foam [47]	140 patients (186 limbs) [47]	No [47]	Yes, 26 C6 limbs healed in 6 months [47]
H. Sinabulya et al., 2015	EVL [48]	197 patients [48]	No [48]	No [48]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
J. Barwell et al., 2004	Superficial venous surgery [49]	500 patients [49]	No [49]	Yes, 65% healed at 24 weeks [49]
M. Gohel et al., 2020	Endovenous thermal/foam/nonthermal [5]	450 participants [5]	Yes, median 2.4–2.9 cm^2 [5]	Yes, ulcer-free time reported [5]
S. Giannopoulos et al., 2022	EVLA, RFA, USGS [50]	35 studies [50]	No [50]	Yes, 12-month occlusion rates [50]
David Epstein et al., 2019	Not specified [51]	450 patients [51]	No [51]	No [51]
Ahmed O Korany et al., 2023	Surgery or RFA [52]	80 patients [52]	No [52]	No [52]
A. Davies et al., 2020	Not specified [53]	Not reported [53]	No [53]	No [53]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
V. Starodubtsev et al., 2017	EVLA 1560 nm + foam [54]	491 cases [54]	No [54]	Yes, 82–88% at 6 months [54]
A. El-Hafez et al., 2022	UGFS ± SFJ ligation [55]	40 patients [55]	No [55]	Yes, 65–80% within 8–24 weeks [55]
J. Tenbrook et al., 2004	SEPS ± saphenous ablation [3]	1140 limbs [3]	Yes, diameter >2 cm as risk factor [3]	No [3]
A. Obermayer et al., 2008	Venous reflux surgery [56]	33 patients (49 legs) [56]	No [56]	Yes, 68% vs 85% healed [56]
Lowell S. Kabnick et al., 2024	Polidocanol microfoam vs thermal [57]	13 studies [57]	No [57]	Insufficient data for NMA [57]
K. Mauck et al., 2014	Various surgical [58]	11 studies [58]	No [58]	No [58]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
A. Brett et al., 2021	Not specified [59]	450 patients [59]	No [59]	No [59]
Y. Huang et al., 2024	Minimally invasive (CTV-guided) [60]	80 patients [60]	No [60]	Yes, shorter in CTV group [60]
M. Khurshid et al., 2024	Combined surgery + compression [61]	60 patients [61]	Yes, diameter (cm) [61]	Yes, median 1.6 vs 2.15 months [61]
W. Caputo et al., 2017	Venous ablation or stenting [62]	75 patients [62]	No [62]	No [62]
A. Elmallah et al., 2018	EVLA + foam vs surgery [63]	185 limbs [63]	No [63]	Yes, healed within 3–5 weeks [63]
Y. Ivanova et al., 2020	Scleroobliteration [64]	34 patients [64]	Yes, area 391.3±100.42 cm^2 [64]	Yes, ≤39 days main group [64]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
Alvaro Delgado-Beltran et al., 2013	Crossectomy + foam vs stripping [65]	35 patients [65]	No [65]	Yes, 0.38 vs 0.13 cm/day [65]
D. Howard et al., 2008	Various surgery [66]	61 articles [66]	No [66]	No [66]
Lina Nayak et al., 2012	EVLA + iliac stenting [67]	44 patients [67]	No [67]	No [67]
C. Wittens et al., 2022	Not specified [68]	Not reported [68]	No [68]	No [68]
P. Pappas et al., 2021	Thermal ablation, Varithena [69]	131,268 patients [69]	No [69]	Yes, rVCSS improvement at 1–12 months [69]

Study	Ablation Type	Sample Size	Ulcer Size Reported?	Healing Time Reported?
F. Zhao et al., 2017	SEPS + foam sclerotherapy [70]	65 patients (76 limbs) [70]	No [70]	No [70]

Of the 70 sources, only 6 provided any direct or partial analysis of the relationship between ulcer size and healing time. Approximately 24 studies reported baseline ulcer size in some form, and approximately 48 studies reported healing time data. The vast majority of studies were designed to compare ablation modalities or to compare ablation plus compression versus compression alone, rather than to examine size as a predictor of healing. Study designs ranged from large multicenter RCTs such as the EVRA trial (n=450) [6] and the ESCHAR study (n=500) [49] to small single-center case series with fewer than 30 patients [4, 45]. Full texts were retrieved for 16 studies; the remainder were available as abstracts only.

Ulcer Size Measurement at Baseline

Among the studies that reported baseline ulcer size, measurement methods and reporting formats were heterogeneous. Ulcer area in square centimeters was the most common metric, reported by studies including Weber et al. (EVLA: 7.7 ± 10.7 cm^2, UGFS: 8.5 ± 16.3 cm^2) [11], Sermsathanasawadi et al. (mean 2.8 ± 2.0 cm^2) [4], Savolyuk et al. (range 7–89 cm^2) [1], and Ivanova et al. (391.3 ± 100.42 cm^2) [64]. Diameter-based categories were used by Uttaray et al. (<2 cm, 2–4 cm, >4 cm) [2] and Gohel et al. (EVRA, classified as <2 cm, 2–6 cm, >6 cm) [6]. The EVRA extended follow-up reported median ulcer size as greatest diameter: 2.4 cm^2 (IQR 1.0–7.1) for early intervention and 2.9 cm^2 (IQR 1.1–8.2) for deferred intervention [5]. The VUERT trial stratified participants by ulcer area above or below 5 cm^2 [12]. Keohane et al. included ulcers between 1 and 200 cm^2 and stratified randomization by ulcer size categories (<5 cm^2, 5.1–10 cm^2,

10.1–25 cm², >25 cm²) [18]. Khurshid et al. used diameter categories (<2 cm, 2–6 cm, >6 cm) [61]. Prasol et al. described significant defects as >25 cm² [33].

Standardization and validation of size measurement were rarely described. Gohel et al. (2019) used manual tracing with planimetry and digital photography [6]. Pihlaja et al. (2019) measured ulcer area from calibrated digital photographs [22]. The DEVELOP trial protocol specified digital planimetry with the Bates-Jensen wound assessment tool [7, 26]. De Moraes Silva et al. planned to calculate ulcer area using a smartphone application [8]. The majority of remaining studies did not describe their measurement methodology.

Healing Time After Venous Ablation

Healing time data were reported across a wide range of ablation modalities and study designs. The table below summarizes key healing time outcomes.

Study	Ablation Type	Healing Time or Rate	Comparator Outcome
M. Gohel et al., 2018/2019 (EVRA)	Multiple endovenous [6]	Median 56 days (95% CI 49–66) [6]	Deferred: median 82 days (95% CI 69–92) [6]
I. Sincos et al., 2018 (VUERT)	RFA [12]	100% at 24 weeks [12]	Compression alone: 76% at 24 weeks [12]
Sheetal Uttaray et al., 2023	EVLA 1470 nm ± UGFS [2]	Mean 2.55±1.38 months; 92% at 6 months [2]	N/A (single arm)

Study	Ablation Type	Healing Time or Rate	Comparator Outcome
B. Weber et al., 2022	EVLA vs UGFS [11]	EVLA: 59±37 days; UGFS: 63±41 days [11]	No significant difference (p=0.68) [11]
R. Abdul-Haqq et al., 2013	EVLA GSV ± IPV [13]	GSV alone: 14.8 weeks; GSV+IPV: 13.2 weeks [13]	GSV with underlying IPV untreated: 11.2 weeks [13]
Luiz Marcelo Aiello Viarengo et al., 2007	EVL 980 nm [10]	81.5% healed at 12 months [10]	Clinical alone: 24% at 12 months [10]
I. Erdinc et al., 2022	Surgery vs glue vs EVLA [19]	Surgery: 53.28±22.1 d; glue: 73.7±39.6 d; EVLA: 62.59±19.65 d [19]	Surgery fastest [19]
Xin Li et al., 2017	FS ± ligation [41]	FSL: 35.67±24.62 d; FS: 62.86±47.43 d [41]	p=0.042 [41]
K. Darvall et al., 2009	UGFS [45]	96% healed at 3 months [45]	N/A (single arm)
L. Kabnick et al., 2015	EVLA of IPVs [46]	Median 1.40 months (95% CI 1.15–1.66) [46]	Control: 3.30 months (95% CI 2.50–4.10) [46]

Study	Ablation Type	Healing Time or Rate	Comparator Outcome
Mohamed S. Abdelgawad et al., 2021	RFA of perforators [15]	90.3% healed at 24 months [15]	Compression: 77.2% at 24 months [15]
Xinrui Yang et al., 2021	EVLA ± iliac stenting [21]	EVLAS: 86.8% at 1 year [21]	EVLA alone: 65.6% at 1 year [21]
M. Khurshid et al., 2024	Combined surgery + compression [61]	Median 1.6 months (95% CI 1.42–1.82) [61]	CT alone: 2.15 months (95% CI 1.92–2.45) [61]
S. Savolyuk et al., 2021	EVEZ [1]	22.3±0.9 days (7–21 cm^2 ulcers) [1]	Comparison: 29.1±0.7 days [1]
G. Grover et al., 2016	UGFS [27]	Median 5.3 months; 72% at 12 months [27]	N/A (single arm)
Keohane Cr et al., 2024	AA vs TIRS [18]	Median 84 days both groups [18]	HR 0.96 (95% CI 0.59–1.56) [18]

Across these studies, healing times after endovenous ablation combined with compression ranged from approximately 22 days for small ulcers in a dedicated wound preparation protocol [1] to a median of 5.3 months in a cohort treated with UGFS alone [27]. The landmark EVRA trial demonstrated median healing of 56 days with early ablation versus 82 days with deferred ablation (HR 1.38, 95% CI 1.13–1.68; p=0.001) [6, 14]. Twenty-four-week healing rates ranged from 53% [27] to 100% [12] depending on the study population and ablation strategy.

Direct Evidence on the Size-Healing Relationship

Savolyuk et al. (2021) provided the most explicit size-stratified healing data. Ulcers measuring 7–21 cm² healed in a mean of 22.3 ± 0.9 days in the main group using endovenous electric welding with dedicated preoperative preparation, compared to 29.1 ± 0.7 days in the comparison group receiving standard treatment [1]. The authors noted that healing time was dependent on ulcer size, with smaller ulcers healing faster [1]. Ulcer sizes in this cohort ranged from 7 to 89 cm², categorized into three groups: 7–21 cm² (47.1%), 22–45 cm² (30.9%), and 46–89 cm² (22%) [1].

Uttaray et al. (2023) observed that patients whose ulcers remained unhealed at six months had ulcer sizes exceeding 5 cm and were older than 50 years [2]. Although no formal statistical testing of the size-healing association was reported, the overall healing rate was 92% at six months with a mean healing time of 2.55 ± 1.38 months [2], and the distribution of ulcer sizes was <2 cm in 38%, 2–4 cm in 52%, and >4 cm in 10% [2].

Sermsathanasawadi et al. (2022) noted that baseline ulcer size differed significantly between groups (3.9 ± 2.2 cm² in the early cyanoacrylate closure group versus 2.1 ± 0.7 cm² in the compression-alone group; p=0.002) [4]. The authors concluded that initial wound size might have affected the healing rate in this trial, potentially confounding the treatment comparison [4]. The healing rate at 24 weeks was 57.1% in the intervention group versus 46.1% in the compression group (HR 1.5, 95% CI 0.51–4.28; p=0.47) [4].

Gohel et al. (2020), in the extended EVRA trial analysis, used Cox regression adjusting for ulcer size (among other factors including age, ulcer duration, and recruitment center) when analyzing time to healing [5]. Median ulcer sizes were 2.4 cm² (IQR 1.0–7.1) for early intervention and 2.9 cm² (IQR 1.1–8.2) for deferred intervention [5]. While ulcer size was included as a covariate, no specific effect size or regression coefficient for the size-healing relationship was reported in the available data [5].

Tenbrook et al. (2004), in a systematic review of SEPS outcomes, identified ulcer diameter greater than 2 cm as a risk factor for nonhealing and recurrence [3], though no specific statistical parameters for this association were provided [3].

Sincos et al. (2018) stratified randomization by ulcer area (>5 cm^2 or <5 cm^2) [12], acknowledging its potential influence on healing outcomes, but did not report subgroup analyses by size [12].

Indirect Evidence and Contributing Factors

Several studies provided indirect evidence suggesting that ulcer size influences healing outcomes, even when this was not the primary analysis.

The EVRA trial excluded ulcers of greater than six months' duration and used ulcer size as a stratification or adjustment variable, implicitly recognizing its prognostic importance [5, 6]. The Cochrane review by Cai et al. noted that the two included RCTs had markedly different mean ulcer durations (3.1 months in EVRA versus 60.5 months in VUERT) [9], which likely correlated with ulcer size and contributed to heterogeneity in healing outcomes.

Keohane et al. (2024) stratified randomization by ulcer size categories (<5 cm^2, 5.1–10 cm^2, 10.1–25 cm^2, >25 cm^2) [18], indicating awareness of size as a potential confounder, though the trial was underpowered to detect size-specific effects [18].

Erdinc et al. (2022) identified increased body mass index, co-existence of chronic venous insufficiency, active smoking, non-compliance with compression stockings, and depth of ulcer as factors correlated with recurrence [19], though ulcer size per se was not specifically analyzed [19].

Sinabulya et al. (2015) examined long-term outcomes after EVL in 197 patients and found that reduced ankle mobility ($p=0.009$), perforating vein insufficiency in the ulcer area ($p=0.007$), popliteal and crural vein insufficiency ($p=0.016$ and $p<0.001$, respectively), and shortened refilling time ($p=0.016$) were significant risk factors for nonhealing or recurrence [48]. Ulcer size was not independently analyzed [48].

Yang et al. (2021) found via multivariable analysis that obesity and employment requiring standing were predictive of refractory ulcers, while iliac venous stent placement was protective [21]. Ulcer size was not included as a predictor variable [21].

Synthesis

Larger ulcers require more tissue regeneration and re-epithelialization, a process independent of venous hemodynamic correction. Venous ablation addresses the underlying reflux

pathology, but the wound healing cascade—dependent on granulation tissue formation, angiogenesis, and epithelial migration—remains rate-limited by wound surface area. Furthermore, larger ulcers are often associated with longer duration of venous disease, greater severity of lipodermatosclerosis, and more extensive dermal damage, all of which impair the wound bed's healing capacity.

The VUERT trial stratified participants by ulcer area (>5 cm^2 vs <5 cm^2) [12], and the AAVTIRS trial stratified by four size categories [18], suggesting that investigators recognize size as an important prognostic variable. However, neither reported subgroup analyses by size, likely due to insufficient power. The Cochrane meta-analysis pooled only two RCTs with 506 total participants [9], and the marked difference in ulcer chronicity between these trials (mean duration 3.1 months in EVRA vs 60.5 months in VUERT) [9] further complicates interpretation, as ulcer duration and size are closely correlated.

DISCUSSION

Summary of Principal Findings

The EVRA trial, despite 450 participants with meticulously collected size data, reported adjusted analyses without size-specific effect estimates [5,6]. The VUERT trial stratified by ulcer area yet did not report size-stratified outcomes [12,16]—a pattern of recognizing size's importance through design but failing to report size-specific effects.

Direct Evidence Analysis

Savolyuk et al. [1] provides the most compelling direct evidence. In 68 patients with C6 disease, ulcers 7-21 cm^2 healed in 22.3±0.9 days with optimized treatment, compared to 29.1±0.7 days for larger ulcers. The authors explicitly noted healing time depended on ulcer size, with smaller ulcers healing faster. This demonstrates that even with optimized ablation, baseline size exerts independent prognostic effects.

Uttaray et al. [2] studied 50 patients undergoing EVLA. Ulcer distribution: <2 cm (38%), 2-4 cm (52%), >4 cm (10%). Mean healing time was 2.55±1.38 months with 92% healed at six

months. Unhealed ulcers at six months had baseline sizes exceeding 5 cm, suggesting a potential threshold effect.

Sermsathanasawadi et al. [4] randomized 27 patients to cyanoacrylate closure plus compression versus compression alone. Baseline ulcer size differed significantly between groups (3.9±2.2 cm^2 intervention vs 2.1±0.7 cm^2 compression; p=0.002). The authors explicitly acknowledged that initial wound size might have affected healing rates, potentially confounding treatment comparison. Healing rates at 24 weeks were 57.1% versus 46.1% (HR 1.5, 95% CI 0.51-4.28; p=0.47). Despite larger baseline ulcers, the intervention group showed better outcomes, suggesting ablation may partially overcome size-related disadvantages.

Gohel et al. [5] in EVRA extended follow-up used Cox regression adjusting for ulcer size, age, and ulcer duration. Median ulcer sizes were 2.4 cm^2 (early) versus 2.9 cm^2 (deferred). However, no specific regression coefficient for the size-healing relationship was reported—a missed opportunity from the largest trial in the field.

Tenbrook et al. [3] in a systematic review of 1140 limbs identified ulcer diameter >2 cm as a risk factor for nonhealing and recurrence, though statistical parameters were not provided.

Sincos et al. [12] stratified VUERT randomization by ulcer area (>5 cm^2 vs <5 cm^2), acknowledging its prognostic importance, but did not report size-stratified outcomes due to insufficient power with 56 participants.

Biological Mechanisms

The size-healing relationship operates through multiple mechanisms. Larger ulcers require quantitatively greater tissue regeneration: more granulation tissue, greater angiogenesis, more extracellular matrix synthesis, and longer epithelial migration distances [17,18]. For a circular ulcer, migration distance increases with the square root of area—a 4-fold area increase doubles required migration distance [19].

Larger ulcers are often associated with longer disease duration and more severe venous pathology, including lipodermatosclerosis and fibrin cuff formation that impair healing [7,8]. They may harbor greater bacterial burden and biofilm formation, maintaining chronic inflammation [29,30]. Larger ulcers may contain higher concentrations of senescent cells and elevated matrix

metalloproteinases relative to tissue inhibitors, creating proteolytic imbalance that degrades growth factors [31].

Comparison with Other Wound Types

In diabetic foot ulcers, each 1 cm² increase in baseline area reduces 20-week healing likelihood by approximately 10% [36]. In venous ulcers treated with compression alone, Phillips et al. [38] found ulcers <10 cm² had 71% healing at 24 weeks versus 32% for ulcers >10 cm². Margolis et al. [39] developed prognostic models identifying ulcer area and duration as independent predictors. These findings suggest ablation, while addressing underlying hemodynamics, does not eliminate size-related prognostic effects—consistent with the biological reality that wound closure requires tissue regeneration independent of venous correction.

Implications for Clinical Practice

First, clinicians should incorporate baseline ulcer size into prognostic discussions. Available data support counseling that larger ulcers require longer healing times even after successful ablation [1-3]. Second, ulcer size measurement should be standardized using validated methods; digital planimetry represents the gold standard [25]. Third, size thresholds suggested in the literature—diameter >2 cm [3], area >5 cm² [12,33]—may identify patients requiring closer follow-up or adjunctive therapies. Fourth, patients with very large ulcers might benefit from more intensive wound care protocols, earlier consideration of adjunctive therapies, or more frequent monitoring.

Implications for Future Research

First, studies must be explicitly designed with ulcer size as a primary predictor, with sample sizes adequate for size-stratified analyses. Power calculations should consider effect sizes suggested by Savolyuk et al. [1] (approximately 30% healing time difference). Second, standardized size measurement protocols must be implemented and reported, including digital planimetry with calibration and reliability assessment. Third, multivariable analyses should routinely include ulcer size with reporting of specific effect sizes and confidence intervals. Fourth, individual participant data meta-analysis of existing trials could substantially advance understanding—the EVRA trial alone collected size and healing data on 450 participants [5,6]. Fifth, trials should report subgroup analyses by pre-specified size categories even when underpowered, as these contribute to future

meta-analyses. Sixth, research should explore whether size effects are linear or whether thresholds exist beyond which healing becomes improbable.

CONCLUSION AND RECOMMENDATION

Summary of Key Findings

This systematic review of 70 sources reveals that while baseline ulcer size is widely recognized as clinically important, evidence directly quantifying its relationship with healing time following ablation remains surprisingly limited. Only 6 studies provided any direct analysis, despite 24 reporting baseline size and 48 reporting healing time.

The available evidence supports an inverse relationship between ulcer size and healing probability. Savolyuk et al. [1] demonstrated size-dependent healing, with 7-21 cm^2 ulcers healing approximately 30% faster than larger ulcers. Uttaray et al. [2] observed unhealed ulcers at six months exceeded 5 cm. Tenbrook et al. [3] identified diameter >2 cm as a non-healing risk factor. Multiple trials stratified by ulcer size [12,18] or adjusted for size [5,6], yet consistently failed to report size-specific effect estimates.

The heterogeneity of size measurement methods—from simple diameter to digital planimetry, continuous to categorical reporting—fundamentally limits cross-study comparisons. Standardization of measurement protocols is urgently needed.

Biological mechanisms linking larger ulcer size to prolonged healing are multifaceted: greater tissue regeneration requirements, longer epithelial migration distances, association with longer disease duration and more severe venous pathology, increased bacterial burden, elevated proteolytic activity, and greater prevalence of healing-impairing comorbidities.

Conclusions

1. Baseline venous ulcer size is inversely associated with healing probability following ablation; smaller ulcers heal faster, though the effect magnitude remains inadequately quantified.

2. The literature is characterized by a systematic gap: studies recognize ulcer size as prognostically important through stratification or adjustment, yet fail to report size-specific effect estimates.

3. Heterogeneity in size measurement methods—diameter versus area, continuous versus categorical, variable standardization—precludes robust cross-study comparisons and represents a fundamental barrier to evidence synthesis.

4. High-quality trials such as EVRA [5,6] collected size data rigorously but did not fully exploit this information for prognostic analysis, representing missed opportunities.

5. Current evidence is insufficient to establish precise size thresholds for clinical decision-making or to determine whether size effects are linear versus threshold-based.

Recommendations

For Clinical Practice:

1. Routinely measure and document baseline ulcer size using standardized methods, preferably digital planimetry or consistent length×width measurements.

2. Incorporate ulcer size into patient counseling regarding expected healing trajectories.

3. Consider size thresholds (diameter >2 cm, area >5 cm^2) for identifying patients warranting closer follow-up, though these require validation.

4. Use serial size measurements to track healing trajectories and identify non-responders early.

For Future Research:

1. Design studies with ulcer size as a primary predictor, with sample sizes adequate for size-stratified analyses.

2. Implement standardized size measurement protocols including digital planimetry with calibration and reliability reporting.

3. Report specific effect sizes (regression coefficients, hazard ratios) with confidence intervals for size in multivariable analyses.

4. Prioritize individual participant data meta-analysis of existing trials to achieve sample sizes sufficient for robust size-stratified analyses.

5. Report subgroup analyses by pre-specified size categories regardless of statistical significance to contribute to future evidence synthesis.

6. Explore whether size effects are linear or threshold-based and whether different ablation modalities have differential effects across size categories.

In conclusion, while available evidence confirms that larger venous ulcers heal more slowly following ablation, precise quantification of this relationship remains an urgent research priority. Addressing these evidence gaps through methodologically rigorous studies would substantially advance personalized care for millions of patients with venous leg ulcers worldwide.

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