MULTI-SPECIALTY RECOMMENDATIONS FOR THE APPROPRIATE AND AFFORDABLE LOWER LIMB VEIN-LYMPHATIC DISORDERS MANAGEMENT

Italian Society of Phlebology and Lymphology
Italian Society of Multi-specialty Regenerative Medicine and Surgery
International Union of Phlebology
Lymphatic Education Research Network
Venous-Lymphatics World International Network Foundation

EDIZIONI MINERVA MEDICA
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- Lymphatic Education Research Network
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Multi-specialty recommendations for the appropriate and affordable lower limb vein-lymphatic disorders management

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English version of the Italian Clinical Governance official document, institutionally lodged in the Istituto Superiore di Sanità (Superior Institute of Health). Italian version available at the following link: https://www.iss.it/it/web/guest/-/gestione-patologia-venosa-e-linfatica

Background, rationale, objectives, application field

Human evolution from quadrupedal to bipedal locomotion has led to natural exposure to gravitational forces, resulting in venous and lymphatic hypertension. This, combined with the increasing prevalence of sedentary lifestyles, obesity, and an aging population, explains the significant impact of chronic venous and lymphatic diseases, which affect over 50% of individuals and account for up to 2% of national healthcare budgets in developed countries. Impaired venous drainage is not merely a cosmetic issue: it is associated with a substantial increase in thromboembolic risk – the leading preventable cause of death – potential pelvic venous disorders responsible for abdominal pain in one in three women, and the risk of cutaneous ulceration. Recent studies also indicate that endothelial inflammation in venous and lymphatic vessels correlates with increased cardiovascular mortality, underscoring the need for a multidisciplinary approach involving Physical and Rehabilitation Medicine, Gynecology, Dermatology, Cardiology, and other medical specialties. This necessity is particularly pronounced in the digital era, where misinformation can spread rapidly as an "infodemic," shared globally with ease. Our international research group, building on an Italian initiative, previously convened 71 scientific societies and 83 national representatives, resulting in the publication of an extensive document on this topic, which was presented at the Italy Pavilion of the Dubai World Expo.[1] This followed an earlier international publication in which our group highlighted similarities and discrepancies among phlebology and lymphology guidelines from various countries, emphasizing the need for nationally tailored recommendations that maintain an objective, global assessment of the scientific literature – a strategy we term "globalizing evidence while nationalizing recommendations."[2] A multilingual brochure summarizing the main findings of this comprehensive scientific document was produced to facilitate patient access.[3] In Italy, no guidelines are currently registered with the National Institute of Health, highlighting the urgent need for a clinical practice document. Our ongoing initiative brings together institutional representatives from multiple medical specialties involved in venous and lymphatic care, alongside leading experts in statistics and health economics, with the shared goal of producing a methodologically rigorous document providing evidence-based recommendations adapted to the Italian context. This approach exemplifies a holistic, evidence-informed model, engaging top national and international experts. The rationale for this project stems from the complexity of venous and lymphatic disorders, which span micro- to macrocirculation, range from minor aesthetic concerns to severe conditions such as skin ulceration, and can even include potentially life-threatening events like venous thromboembolism. Effective management therefore requires comprehensive knowledge across multiple medical disciplines. Globally, phlebology and lymphology are practiced by different specialties, with national variations in dominance, including cardiology, dermatology, internal medicine, radiology, surgery, physiatry, or general medicine.According to the world society dedicated to phlebology and lymphology, a clinical governance document for contemporary venous and lymphatic practice must integrate contributions from all relevant specialties. International oversight is also highly recommended to ensure consistency in evaluating the certainty of evidence, as well as the appropriateness and affordability of final recommendations, while respecting the national context. The Italian VALID (Vein And Lymphatic International Document) project aims to generate evidence-based, contextually relevant recommendations for the management of venous and lymphatic disorders in Italy, engaging national experts across specialties and collaborating with international authorities to identify and analyze any divergences from existing global guidelines. This document is grounded in a rigorous, objective literature review conducted in collaboration with representatives of the GRADE Group (referent: Prof. Gordon Guyatt, McMaster University, Canada) and incorporates considerations of sustainability and patient-centered feasibility. Special attention is given to Gender Medicine and Telemedicine. The work provides a foundation for prioritization strategies to optimize waiting lists and resource allocation. The project is endorsed by the International Union of Phlebology, the Venous-Lymphatic World International Network Foundation, and the Lymphatic Education & Research Network. An English version of the document has also been prepared to facilitate international dissemination and collaboration.

Methods

The two project coordinators (Prof. Sergio Gianesini and Prof. Massimo Danese), following procedural guidelines provided by the Italian National Institute of Health, identified the Development Group, composed of 15 members. Candidates were selected based on their objective scientific and clinical expertise, combining national experts (8/15) with representatives from all continents (7/15) to ensure

both a thorough review of the available literature and the national contextualization of the recommendations.

2 Proponents — Drafting Panel (15 experts) — 15 PICOs — Supervision Panel (5 experts) — 15 Statements
Drafting Groups (9 experts each from the Drafting Panel) — Supervision Panel (5 experts) — Multispecialty Assessment → 2 Top Independent Reviewers

The literature search was supervised by Prof. Gordon Guyatt (GRADE Group, McMaster University, Canada) and Dr. Joao Pedro Lobo Lima (GRADE Group, McMaster University, Canada) and was based on evaluating existing meta-analyses, as well as creating a new meta-analysis on the use of Platelet-Rich Plasma in the treatment of venous ulcers conducted by the same authors of the present document. In cases where direct evidence was lacking – even after removing publication date limits and including observational studies – indirect evidence was used to formulate Good Clinical Practice Statements, according to the five criteria established by GRADE, summarized as follows:[4]

- 1. The statement is genuinely necessary in the context of current clinical practice.
- 2. Implementing the Good Clinical Practice Statement results in a substantial net positive effect after considering all relevant outcomes and potential downstream consequences.
- 3. Collecting and summarizing the evidence would constitute a misuse of the panel's limited time, energy, and resources.
- 4. The indirect evidence is linked to a well-documented, clear, and explicit rationale.
- 5. The statement is clear and actionable.

For each of these five points, detailed contextualization was provided for every individual Good Clinical Practice Statement. A professional librarian, Rachel Couban, MA, MISt, AHIP (GRADE Group, McMaster University, Canada), was involved in designing the search strings and identifying the relevant literature. A professor of Statistics and Scientific Methodology (Prof. Danila Azzolina, University of Ferrara) contributed to the study design and project execution. The Development Group identified 15 high-priority topics using the PICO methodology, reflecting their relevance in current venous and lymphatic disease management. Following the guidelines of the Italian National Institute of Health, a Supervisory Group composed of five leading national experts evaluated the appropriateness of the proposed PICOs using a 9-point Likert Scale.[5] Subsequently, the Development Group was divided into 15 working subgroups of nine members each, each dedicated to one of the 15 PICOs, with the task of analyzing the corresponding literature and formulating recommendations. The literature search was conducted independently by two reviewers using Epistemonikos and Medline. Boolean search terms are reported in each section corresponding to the recommendations. Meta-analyses and randomized controlled trials were limited to publications in English over the last 10 years (September 1, 2014 – September 1, 2024). Detailed search strategies, inclusion and exclusion criteria, and study selection processes are provided in each recommendation section. The 2020 PRISMA guidelines were used to report search results.[6] All disagreements between reviewers (Maria Portugal, Sergio Gianesini) were resolved through discussion without the need for a third party. The Covidence software was used to manage and screen search records for potential inclusion according to predefined criteria (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). The Development Group employed the GRADE Evidence to Decision framework to generate structured and transparent recommendations following the literature review.[7] All recommendations and Good Clinical Practice Statements achieved unanimous consensus among Development Group experts. The concept of appropriateness followed Brook's definition: "The expected health benefits (*e.g.*, increased life expectancy, pain relief, reduced anxiety, improved functional capacity) outweigh the anticipated negative consequences (*e.g.*, mortality, anxiety, pain, loss of workdays) to a sufficiently large degree to justify the action, without considering economic impact."[8, 9] In line with the Italian National Institute of Health's guidelines for Good Clinical Practice, experts did not consider cost-effectiveness in formulating final recommendations due to the lack of robust data. Nevertheless, each recommendation was accompanied by a technical section developed by the Department of Economics at the University of Ferrara, providing a foundation for subsequent research projects involving institutions, patients, and insurance providers. The Supervisory Group approved all 15 recommendations. Given the multidisciplinary nature of venous and lymphatic disease, experts from 13 organizations were invited to review the entire document. Any comments received were discussed by the Development and Supervisory Groups and included in the final document if at least 70% agreement was reached among participants in both groups. Two independent reviewers (Julianne Stoughton, Harvard University; Stanley Rockson, Stanford University) reviewed the entire document to further validate its methodology and content, also analyzing potential discrepancies with

guidelines from other countries. The final commentary from these reviewers was included in a dedicated chapter.

Target users

This document aims to provide an update on current best practices, based on scientific evidence translated into principles of clinical appropriateness. Under no circumstances should the recommendations provided in this work be considered absolute; healthcare professionals must always contextualize each individual case, applying their knowledge and professional ethics, while giving the utmost attention to the patient's needs and preferences. The primary target audience of this clinical practice recommendations document includes specialists involved in the diagnosis and management of venous and lymphatic disorders of the lower limbs, such as vascular medicine and surgery, angiology, general surgery, cardiology, internal medicine, sports medicine, dietetics, physiatry, dermatology, and radiology. The document is also intended for general practitioners, as well as healthcare professionals such as nurses and physiotherapists. The document emphasizes the appropriateness of care while also highlighting aspects of sustainability, making it relevant for healthcare policymakers as well. It is useful both for analyzing the current scientific evidence – reported with an assessment of the certainty of evidence – and for identifying research areas that still require development.

The 15 recommendations and Good Clinical Practice statements provided are intended to support healthcare professionals and policymakers by guiding the identification of future appropriate diagnostic and therapeutic pathways.

Recommendations and good practice statements sum-up

Good Clinical Practice Statement 1: Swollen lower limb expert evaluation

In cases of lower limb swelling, it is appropriate to integrate a color Doppler ultrasound examination with a consultation by an experienced physician (*Good clinical practice statement based on ungraded evidence*).

Recommendation 2: Thermal tumescent *vs.* non-thermal non-tumescent procedures

2.1) For the treatment of chronic venous disease associated with great saphenous vein reflux, radiofrequency or 1470 nm laser is suggested as the first choice over other procedural techniques, in the absence of technical contraindications.
2.2) In specific cases, after careful medical evaluation including a detailed assessment of patient needs and characteristics, specific adhesives can be used to suppress great saphenous vein reflux, without significant differences in anatomical recurrence or quality of life compared to radiofrequency or 1470 nm laser.
2.3) In experienced hands and specific reflux patterns, saphenous-sparing procedures are suggested over total ablation.
2.4) Mechanochemical ablation is not suggested compared to radiofrequency, laser, or adhesive in treating great saphenous veins larger than 7 mm.
2.5) For the treatment of refluxing great saphenous veins, endovenous polidocanol microfoam is suggested over radiofrequency, laser, or surgery only in patients who are not eligible for radiofrequency, laser, or surgical treatment. In Italy, the only foam concentration currently authorized by the Italian Medicines Agency (AIFA) is 3% polidocanol, and its use is limited to the treatment of incompetent great saphenous veins with a diameter between 4 and 8 mm, following the Tessari method (Official Gazette No. 50, February 28, 2019, code 19A01287). Therefore, clinical practice is recommended to strictly adhere to AIFA indications.
2.6) Surgical treatment is suggested in cases at high risk of saphenofemoral recurrence and with significant junctional hemodynamic overload, compared to endovenous techniques.
2.7) Patients should be informed during the consent process about the presence of a foreign body following adhesive injection, potential allergic reactions, and granuloma formation.
2.8) Healthcare professionals should be aware of the varying quantity and quality of literature regarding different devices *(Weak recommendation, in favor of intervention, with very low certainty of evidence)*.

Recommendation 3: Ilio-femoral venous stenting

In patients with chronic thrombotic or non-thrombotic iliac-femoral venous stenosis, a conservative approach including graduated compression, tailored exercise, and weight control, monitored by experienced professionals for at least six months, is suggested before considering stenting, compared to immediate stent placement *(Weak recommendation, against intervention, with low certainty of evidence)*.

Good Clinical Practice Statement 4: Pelvic venous reflux multi-specialty management

In cases of pelvic venous reflux, a gynecological assessment prior to recommending vascular treatment is appro-

priate (*Good clinical practice statement based on ungraded evidence*).

Good Clinical Practice Statement 5: Varicose veins procedures thromboprophylaxis

Varicose vein interventions may be complicated by thromboembolic events. Individual risk assessment is appropriate to personalize prophylactic regimens and avoid identical administration for all patients. The Caprini score should be used to guide, but not dictate, thromboprophylaxis prescription (*Good clinical practice statement based on ungraded evidence*).

Recommendation 6: Advanced dressings for venous ulcers

Polyurethane foam dressings are suggested for exudative venous ulcers and silver-based dressings for locally infected lesions, compared to debridement and compression alone (*Weak recommendation, in favor of intervention, with low certainty of evidence*).

Recommendation 7: Venous active drugs

In cases of venous edema and/or pain in the lower limb, MPFF, calcium dobesilate, rutosides, ruscus, or sulodexide are suggested over no treatment. Healthcare professionals and patients should be aware of the varying quality of evidence for different drugs (*Weak recommendation, in favor of intervention, with certainty ranging from very low to moderate*).

Good Clinical Practice Statement 8: Compression garment prescription

Graduated compression for lower limb discomfort due to venous and/or lymphatic disorders should be prescribed by an experienced healthcare professional (*Good clinical practice statement based on ungraded evidence)*.

Good Clinical Practice Statement 9: Treatment of lymphedema

In cases of lower limb lymphedema, conservative treatment should be carried out by experienced professionals for at least three months before considering surgical intervention. Both conservative and surgical approaches should only be offered by highly specialized centers, and conservative protocols should never be interrupted, even after successful surgery (*Good clinical practice statement based on ungraded evidence*).

Recommendation 10: Treatment of lipedema

In patients with lipedema, ketogenic diet and liposuction are suggested only in selected cases with significant quality-of-life impact and after at least six months of ineffective conservative treatment at specialized centers, compared to no treatment *(Weak recommendation, against intervention, with very low certainty of evidence)*.

Good Clinical Practice Statement 11: Echo-color-Doppler for teleangectasia treatment

It is appropriate to perform venous color Doppler screening before treating lower limb venous aesthetic issues (*Good clinical practice statement based on ungraded evidence*).

Recommendation 12: Platelet rich plasma in the treatment of venous ulcers

Platelet-rich plasma (PRP) is suggested for difficult-to-heal venous ulcers, compared to debridement and compression alone (*Weak recommendation, in favor of intervention, with low certainty of evidence*).

Good Clinical Practice Statement 13: Veno-lymphatic diet

In patients with lower limb venous and lymphatic disorders, obesity and excessive thinness should be avoided, while adequate hydration is encouraged. No evidence supports specific diets, foods, or beverages significantly affecting venous-lymphatic drainage (*Good clinical practice statement based on ungraded evidence*).

Good Clinical Practice Statement 14: Weight-bearing impact on veno-lymphatic drainage

In patients with lower limb venous and lymphatic disorders, clinical assessment of postural abnormalities is recommended, with gait analysis added when diagnostic clarification is needed (*Good clinical practice statement based on ungraded evidence*).

Recommendation 15: Veno-lymphatic hydrotherapy

In patients with lower limb venous and lymphatic disorders, a structured hydrotherapy exercise protocol is suggested over dry-land exercise *(Weak recommendation, in favor of intervention, with low certainty of evidence)*.

Evidence, recommendations and statements synthesis

Good Clinical Practice Statement 1: Swollen lower limb expert evaluation

In cases of lower limb swelling, it is appropriate to integrate a color Doppler ultrasound examination with a consultation by an experienced physician (*Good clinical practice statement based on ungraded evidence*).

Rationale

Lower limb swelling is a common and nonspecific sign that can originate from heterogeneous and potentially overlapping causes, directly or indirectly involving the venous and lymphatic systems.[9] Clinical scenarios range from chronic conditions to acute medical emergencies requiring immediate intervention, such as venous thromboembolism. Color Doppler ultrasound is a fundamental diagnostic tool, with a specificity exceeding 90% for venous thrombosis and the identification of reflux.[10] The same ultrasound examination can also reveal lymphatic alterations and lipedema characteristics, which may underlie the edema.[11, 12] However, pathognomonic ultrasonographic images for both lymphedema and lipedema have not yet been identified,[13] and inter-observer variability and the accuracy of venous ultrasound should be taken into account.[14] Moreover, multiple causes of edema may act in overlapping ways, highlighting the need for appropriate clinical contextualization of the ultrasound findings. Typical examples include cardiovascular disorders, liver disease, medications, vascular malformations, previous trauma, and lifestyle factors.[15] The cost-effectiveness of vascular ultrasound has already been demonstrated in the context of deep vein thrombosis.[16, 17] However, data regarding the sustainability of the same examination for lower limb swelling, combined with an associated specialist consultation, are not yet available according to the literature reviewed in this study. At the same time, chronic lower limb edema remains a public health need that is still insufficiently addressed,[18] while venous thromboembolism continues to be one of the leading preventable causes of death, thus requiring attention from clinical governance.[19] For the reasons and evidence outlined above, this expert panel considers it appropriate to always combine a venous-lymphatic specialist consultation with the ultrasound examination for lower limb swelling. This approach allows for the early diagnosis of previously unrecognized venous-lymphatic drainage disorders or the proper therapeutic planning of an already known hemodynamic alteration. The experts in this working group also recommend the development of future research lines dedicated to evaluating the cost-effectiveness of adding a venous-lymphatic consultation to the ultrasound assessment (Table 1A, 1B).

TABLE 1A.—*Good Practice Statement checklist for Statement 1.*[4]

Process for developing good practice statement	**Supporting information**	**Verification**
Write Good Practice Statement		
Does the statement follow a PICO prioritization process?		X Yes o No
If you answered No → 1) Explain why the PICO question was not prioritized but is being addressed → avoid developing any type of actionable statement that acts as an independent response to the PICO question.		
Are the Population and Intervention components clear?		X Yes o No
If you answered No → Check whether you are developing an implementation consideration (refer to flow chart in Lotfi et al.(8))		
Items to complete	**Supporting information**	**Verification**
All the following criteria must be fulfilled *to consider the statement a GPS.*		
(1) Message is really necessary in regard to actual health care practice		This criterion has been addressed: X Yes o No
(2) Implementing the GPS results in a large net positive consequence (i.e. satisfy several evidence to decision (EtD) criteria) after consideration of all relevant outcomes and potential downstream consequences ** check the criteria considered in the development of the GPS.		This criterion has been addressed: X Yes o No **Evidence-to-Decision criteria** Importance of the problem [X] Certainty in effects [X] Variability and certainty in the importance of outcomes [X] Magnitude of resource requirements [X] Certainty of evidence of resource use [X] Cost-effectiveness [X] Equity [X] Acceptability [X] Feasibility [X]
(3) Collecting and summarizing the evidence is a poor use of a guideline panel's limited time, energy or		This criterion has been addressed: X Yes o No
resources. The opportunity cost of collecting and summarizing the evidence is large and can be avoided.		
(4) There is a well-documented clear and explicit rationale connecting the indirect evidence		This criterion has been addressed: X Yes o No
(5) Clear and actionable (This criterion should apply to any developed statement. For example, all formal recommendations are clear and actionable)		This criterion has been addressed: X Yes o No
Final judgement		
Did you answer Yes to ***all*** of the above?	X Yes Development as GPS is appropriate o No Development as GPS is ***not*** appropriate → Revisit the PICO question and the importance of addressing it.	

Economic affordability considerations

Economic sustainability considerations regarding the addition of a specialist consultation extend to the assessment of the consultation's overall sustainability. An economic impact analysis should be developed.[20] Direct costs associated with the resources required to deliver the service can be calculated using a few selected performance elements: professional time, material goods, consumables, and overhead costs. Unfortunately, most studies use billing fees as surrogates for the total cost of the service, which reflects a different concept entirely. An average consultation cost should be determined to support economic analysis. Existing literature, such as Goldberg *et al.*, reports operational costs for specific procedures, but not for consultations.[21]

Technical research notes

- **PICO question:** in patients with lower limb swelling (P), is color Doppler ultrasound followed by clinical evaluation (I) more appropriate for venous-lymphatic diagnosis than color Doppler ultrasound alone (C) (O)?
- **Search string:** (ultrasound.ti. OR ultrasound.ab.) AND (swelling.ti. OR edema.ti. OR swelling.ab. OR edema.ab.) AND (lower limb*.ti. OR leg*.ti. OR lower limb*.ab. OR leg*.ab.)
- **PRISMA:** flow chart is provided in Figure 1.

Good clinical practice statement

- 1. **The statement is truly necessary in the context of current clinical practice.**

TABLE 1B.—*Evidence to Decision Framework, Good Practice Statement 1.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with lower limb swelling (P), is color Doppler ultrasound followed by clinical evaluation (I), compared with color Doppler ultrasound alone (C), more appropriate for veno-lymphatic diagnosis (O)?	In light of the evident benefit and the absence of potential risks inherent in integrating an ultrasound examination with a specialist clinical evaluation, as well as considering the lack of targeted studies on the subject, a detailed literature search and its subsequent systematization are considered inappropriate.	In cases of lower limb swelling, it is appropriate to integrate color Doppler ultrasound with an evaluation by an experienced physician.	Placing ultrasound examination within the appropriate clinical context through specialist evaluation protects patients from both under-treatment and over-treatment, which may result from an insufficient correlation between ultrasound findings and clinical data. As this involves a non-invasive ultrasound examination combined with clinical assessment, no significant risks are present. Furthermore, an organizational healthcare benefit is achieved by avoiding additional investigations that may be potentially unnecessary and performed without specialist guidance.	Good practice statement	The present good practice statement is based on the need to place ultrasound findings within the appropriate clinical context, as such findings are not always directly correlated with the patient's symptomatic presentation. Preference is therefore given to treating the person rather than the technical data generated by the ultrasound examination.	The present work is not intended to evaluate cost-effectiveness; however, a key aspect to be addressed in future studies is cost-effectiveness and the potential positive impact on time management resulting from an appropriate specialist consultation.	The feasibility of this good practice statement is high, given the straightforward integration of ultrasound examination with specialist consultation, particularly when the ultrasound assessment itself is performed by the specialist. Acceptability is maximal and well appreciated by patients, who benefit from a more comprehensive evaluation of their clinical condition.

Patients affected by lower limb edema, in the case of an ultrasound report indicating normal veno-lymphatic drainage, are at risk of missing the identification of other possible organic or lifestyle-related causes that require specialist assessment. At the same time, in the case of a positive ultrasound report for veno-lymphatic disorder, there is a risk of overtreatment in all cases of spontaneous clinical compensation. A specialist consultation serves as a guarantee of the right to appropriate care.

• 2. **The implementation of the Good Clinical Practice Statement results, overall, in a broad and positive effect when all relevant outcomes and downstream consequences are considered.**

A specialist evaluation complementing the ultrasound examination optimizes the appropriateness of the entire clinical management pathway of lower limb edema, avoiding delays that could exacerbate the clinical picture, preventing veno-lymphatic progression, and promoting precision medicine.

• 3. **Collecting and summarizing the evidence would represent a misuse of the panel's limited time, energy, and resources.**

Given the clear benefit and the absence of inherent risks in integrating ultrasound assessment with a specialist consultation – as well as the lack of specific studies on the subject – a detailed evidence search and systematization are considered inappropriate.

• 4. **Indirect evidence is linked to a well-documented, clear, and explicit rationale.**

The well-documented diagnostic complexity of the multifactorial etiology of lower limb edema and its therapeutic approach provides a clear and explicit rationale for performing a specialist consultation to complement the ultrasound examination.

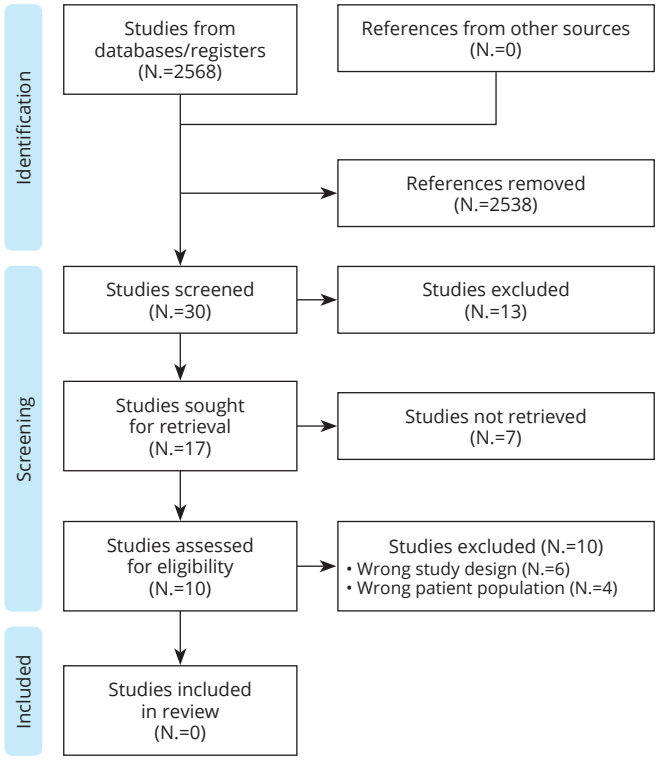

Figure 1.—PRISMA flow chart for recommendation 1.

• 5. **The statement is clear and feasible.**

The statement is clear and easily applicable, particularly when the same specialist performs the ultrasound examination.

Applicability

A) Facilitating factors

Diagnostic and specialist consultation services are already active; therefore, only a connection between the two is required. The existing General Practice service can collect both the ultrasound and specialist data for an appropriate holistic follow-up.

B) Barriers

No major barriers identified, except for the potential cost of the specialist consultation, which may be offset by improved disease management and consequent reduction of associated healthcare costs.

C) Suggestions and tools

• 1. Involvement of General Practitioners in the follow-up of patients requiring subsequent ultrasound and clinical assessments over time.

• 2. Promotion of performing the ultrasound examination by the same specialist responsible for the clinical evaluation.

TABLE 2A.—*Evidence to Decision Framework, Recommendation 2.*

PICO	Note	Evidence-to-Decision Framework Recommendation
In patients with chronic venous insufficiency (P), are tumescent thermal techniques (I) superior to non-tumescent non-thermal techniques (C) in terms of anatomical recurrence, improvement of the Venous Clinical Severity Score/CIVIQ, and reduction of complications (O)?	Studies on homogeneous populations in terms of chronic venous disease severity, hemodynamic loads, and lifestyle factors potentially influencing the risk of recurrence or disease progression are necessary before strong recommendations on this topic can be made.	2.1) For the treatment of chronic venous disease associated with great saphenous vein reflux, radiofrequency or 1470-nm laser is suggested as the first choice over other procedural techniques, in the absence of technical contraindications. 2.2) In selected cases, after careful medical evaluation, including a detailed assessment of the patient's needs and characteristics, specific medical glue may be used to suppress great saphenous vein reflux, with no significant differences in terms of anatomical recurrence and quality of life compared with radiofrequency and 1470-nm laser. 2.3) In experienced hands and in specific reflux patterns, saphenous vein–sparing procedures are suggested over total ablation. 2.4) Mechanochemical ablation is not suggested compared with radiofrequency, laser, and glue techniques in the treatment of great saphenous veins with a diameter greater than 7 mm. 2.5) In the treatment of refluxing great saphenous veins, endovenous polidocanol microfoam is suggested over radiofrequency, laser, and surgery only in patients who are not eligible for radiofrequency/laser/surgical treatment. In Italy, the only foam concentration currently authorized by the Pharma Agency (AIFA) is polidocanol 3%, limited to use in the treatment of incompetent great saphenous veins with a diameter between 4 and 8 mm, according to the Tessari method (Official Gazette No. 50 of 28 February 2019, code 19A01287). Therefore, clinical practice is recommended to strictly adhere to AIFA indications. 2.6) Venous surgery is suggested in cases with a high risk of saphenofemoral recurrence and significant junctional hemodynamic overload, compared with endovenous techniques. 2.7) It is suggested that, during the informed consent process, patients be informed about the presence of a foreign body following adhesive injection, the possible resulting allergic reactions, and granuloma formation. 2.8) It is suggested that healthcare professionals be aware of the differing quantity and quality of the scientific literature produced in the investigation of the various devices. (WEAK recommendation, IN FAVOR of the intervention, with VERY LOW certainty of evidence).

D) Potential resource implications

Increased number of specialist consultations, but reduction in overall care-related costs due to effective prevention of disease progression.

E) Monitoring indicators

• 1. Number of specialist consultations following ultrasound examination for lower limb edema.

• 2. Percentage of false-positive and false-negative ultrasound results for pathological conditions.

Recommendation 2: Thermal tumescent *vs.* non-thermal non-tumescent procedures

2.1) For the treatment of chronic venous disease associated with great saphenous vein reflux, radiofrequency or 1470 nm laser is suggested as the first choice over other procedural techniques, in the absence of technical contraindications.

2.2) In specific cases, after careful medical evaluation, including a detailed assessment of patient needs and characteristics, specific adhesives can be used to suppress great saphenous vein reflux, without significant differences in anatomical recurrence or quality of life compared to radiofrequency and 1470 nm laser.

2.3) In experienced hands and in specific reflux patterns, saphenous-sparing procedures are suggested over total ablation.

2.4) Mechanochemical ablation is not suggested compared to radiofrequency, laser, and adhesive for the treatment of great saphenous veins with a diameter greater than 7 mm.

2.5) For the treatment of refluxing great saphenous veins, endovenous polidocanol microfoam is suggested over radiofrequency, laser, and surgery only in patients who are not eligible for radiofrequency, laser, or surgery. In Italy, the only foam concentration currently authorized by the Italian Medicines Agency (AIFA) is 3% polidocanol, limited to the treatment of incompetent great saphenous veins with a diameter between 4 and 8 mm, using the Tessari method (Official Gazette No. 50, February 28, 2019, code 19A01287). Therefore, clinical practice should strictly adhere to the AIFA indications.

2.6) Venous surgery is suggested in cases at high risk of saphenofemoral recurrence and with significant junctional hemodynamic overload, compared to endovenous techniques.

2.7) Patients should be informed during the consent process about the presence of a foreign body following adhesive injection, potential allergic reactions, and granuloma formation.

2.8) Healthcare professionals should be aware of the vary-

Evidence-to-Decision Framework				
Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/acceptability
The treatment of the refluxing great saphenous vein using radiofrequency, 1470 nm laser, mechano-chemical ablation, glue, and automatically produced polidocanol endovenous microfoam has shown a high safety profile. Patients must be clearly informed that the glue represents a foreign body, potentially associated with granuloma formation and allergic reactions. The clinical benefit of the techniques described here outweighs the potential risks associated with their use.	From very low to low	This recommendation is based on the amount of literature available supporting radiofrequency and 1470 nm laser compared to other therapeutic options, as well as the lack of demonstrated superiority of other technical approaches. In eligible cases, specific types of glue are considered more appropriate than mechano-chemical ablation within the non-thermal, non-tumescent category, in light of their demonstrated performance in venous occlusion rates.	This work is not focused on cost-effectiveness evaluation: this represents a key element to be considered in future detailed clinical governance studies.	The feasibility of using all the technologies mentioned here is well documented and acceptable both for the patient and the healthcare professional. The acceptability of radiofrequency and 1470 nm laser may be limited by the need for tumescent anesthetic injections, while glue is limited by its persistence as a foreign body. The acceptability of mechano-chemical ablation is good but limited by a high rate of recanalization. Endovenous polidocanol microfoam produced automatically is feasible and generally well accepted, but still requires appropriate validation of mid-term outcomes.

ing quantity and quality of literature produced in the investigation of different devices (*Weak recommendation, in favor of the intervention, with very low certainty of evidence*).

Rationale

Many technologies are available for the treatment of the great saphenous vein affected by venous reflux. Indications for treatment are beyond the scope of this recommendation, which is instead dedicated to evaluating the evidence supporting tumescent thermal techniques (mainly radiofrequency and laser) and non-tumescent non-thermal techniques (adhesive, sclerotherapy, mechanochemical ablation). Seven meta-analyses were identified in our research covering the period 2021-2024.[22-28]

The meta-analysis by Kolluri *et al.* was extracted but did not meet the minimum acceptability criteria for a reliable systematic review: several elements required for an appropriate GRADE assessment were missing, limiting the possibility of evaluating the certainty of evidence. In particular, this review did not present detailed forest plots with individual study data, event counts, patient numbers, or study weights – elements necessary to determine inconsistency, imprecision, and risk of bias. Additionally, the work lacked funnel plots to assess publication bias and direct and indirect comparisons necessary to evaluate inconsistency. The review did not address transitivity, further complicating its assessment.[29]

A summary of the results from the seven meta-analyses is presented in Table 2A, 2B, 2C, and 2D, showing very low certainty of evidence, with only a few outcomes reaching at least low certainty. For this reason, the recommendation was classified as weak with very low certainty of evidence. Outcomes considered included venous occlusion rates, recurrence of varicose veins, Venous Clinical Severity Score (VCSS), CIVIQ-20, and adverse events.

In the comparison between radiofrequency, 1470 nm laser, and adhesive, tumescent thermal techniques are considered the first choice in light of the available literature, the lack of strong evidence supporting the superiority of adhesive, and the persistence of a foreign body associated with its use. Preliminary data suggest possible superiority of radiofrequency in terms of vessel occlusion and VCSS, but further research is required before recommending a specific technique.

Specific recommendations are included to emphasize the importance of case-by-case evaluation, including patient perspectives, particularly regarding adhesive use, where the permanent nature of the implanted foreign body and potential allergic reactions must always be specified.[30]

In 2024, an American document suggested with a 1B grade that thermal and non-thermal techniques are comparable.[31] A 2022 European document, however, suggested superiority of tumescent thermal techniques (1A). The same publication indicated that for patients with great saphenous insufficiency, adhesive may be considered (IIaA) along with mechanochemical ablation when there is a preference for a non-tumescent non-thermal technique (IIbA).[32]

In 2019, our research group highlighted the importance of a globally synergistic literature review to avoid significant discrepancies in reporting certainty of evidence.[2] While differences in appropriateness and sustainability of recommendations may exist across countries, the methodology and assessment of the quality of collected evidence should be consistent. Following the present literature review, which included a detailed analysis of certainty of evidence, we suggest refraining from issuing strong recommendations on this topic. Moreover, a clear distinction between adhesive and mechanochemical ablation should be maintained, considering different outcomes reported in the literature, particularly for large-caliber veins.

A 2023 analysis showed decreased performance of mechanochemical ablation compared to radiofrequency in terms of venous occlusion (odds ratio 4.33; 95% CI 1.15-55.54), and compared to adhesive in terms of VCSS (mean difference 0.99; 95% CI 0.22-1.77 for radiofrequency; 0.84; 95% CI 0.08-1.65 for glue). The regression model did not show statistically significant differences, but a trend of reduced efficacy of mechanochemical ablation was reported compared to radiofrequency and laser regarding great saphenous vein occlusion. Furthermore, in a three-year randomized follow-up, a decline in venous occlusion for mechanochemical ablation in veins larger than 7 mm was observed.[33]

A 2021 Canadian meta-analysis on venous occlusion reported contradictory results comparing mechanochemical ablation with radiofrequency (potentially more effective) and laser (potentially less effective), with low certainty of evidence.[22] Considering these data, the panel limited mechanochemical ablation to great saphenous veins <7 mm in selected patients at low risk of recurrence.

Venous surgery, compared to laser and radiofrequency, did not demonstrate significant benefits in VCSS, with potential improvement only in anatomical recurrence. Nonetheless, all these results showed low certainty of evidence; therefore, the weak recommendation is not to abandon venous surgery entirely, but rather consider it appropriate in specific cases with significant vein caliber and hemodynamic overload.[25]

TABLE 2B.—*Summary of Findings for recommendation 2.*

Population: Patients with incompetent great saphenous vein
Chen 2021 (trials published between inception to up to March 2020); 4 studies 968 participants
Frequentist random-effects pairwise meta-analysis

Glue *vs.* Radiofrequency

Outcome	Number of trials (participants)	OR/MD (95% CI)* Certainty of evidence	*GRADE Simple Language Summary*
Closure rate	3 studies (Not reported)	OR: 0.61 (0.18 to 2.01) VERY LOW (Due to serious risk of bias, very serious imprecision and study design)	*We are very uncertain about the effects of glue compared to radiofrequency on the proportion of closure rates.*
Venous clinical severity score (VCSS 0-30)[a]	4 studies (968 participants)	MD: -0.03 (-0.18 to 0.12) VERY LOW (Due to serious riskof bias and study design)	*We are very uncertain about the effects of glue compared to radiofrequency on the VCSS.*
Phlebitis	3 studies (625 participants)	OR: 1.22 (0.7 to 2.13) VERY LOW (Due to study design and serious risk of bias and imprecision)	*We are very uncertain about the effects of glue compared to radiofrequency on the the risk of phlebitis.*

*We were not able to calculate baseline risk as event rate in control groups were not provided.
[a] MID: 1.0. CI: confidence interval; OR: odds ratio; MD: mean difference; MID: minimally important difference.

Population: People with chronic venous insufficiency (CEAP 2–6)
Bellmunt-Montoya 2021 (trials published between Inception to up to February 2020); 6 studies including 1160 participants
Frequentist random-effects and fixed-effect pairwise meta-analysis

Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) MD (95% CI)	*GRADE Simple Language Summary*
CHIVA *vs.* stripping			
Recurrence of varicose veins[a]	5 trials (966 participants)	-100 (-207 to 77) RR: 0.74 (0.46 to 1.2) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of CHIVA compared to stripping on the risk of recurrence of varicose veins.*
CIVIQ-20 (0-100)	1 trial (126 participants)	MD: 1.80 (-3.03 to 6.63) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of CHIVA compared to stripping on CIVIQ-20.*
CHIVA *vs.* Radiofrequency			
Recurrence of varicose veins[b]	1 trial (144 participants)	74 (-19 to 328) RR: 2.02 (0.74 to 5.53) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of CHIVA compared to radiofrequency on the risk of recurrence of varicose veins.*
CIVIQ-20 (0-100)	1 trial (126 participants)	MD: 1.60 (-3.46 to 6.66) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of CHIVA compared to radiofrequency on CIVIQ-20.*
CHIVA *vs.* Laser			
Recurrence of varicose veins[c]	1 trial (100 participants)	-32 (-40 to 122) RR: 0.20 (0.01 to 4.06) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of CHIVA compared to laser on the risk of recurrence of varicose veins.*
Superficial venous thrombosis[d]	1 trial (100 participants)	-45 (-58 to 70) RR: 0.25 (0.03 to 2.16) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of CHIVA compared to laser on CIVIQ-20.*

[a] Assumed risk: 384/1000 patients (MID: 50/1000); [b] Assumed risk: 72/1000 patients (MID: 50/1000); [c] Assumed risk: 40/1000 patients (MID: 50/1000); [d] Assumed risk: 60/1000 patients (MID: 100/1000).
CEAP: Clinical-Etiology-Anatomy-Pathophisiology; CIVIQ-20: Chronic Venous Disease Quality of Life Questionnaire; CI: confidence interval; RR: risk ratio; MD: mean difference; MID: minimally important difference.

Population: Saphenous vein insufficiency in adult patients
Amshar 2022; 5 studies with 1420 patients
Frequentist fixed-effects pairwise meta-analysis

Glue (variclose, BIOLAS) *vs.* Laser

Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) OR/MD (95% CI) Certainty of evidence	*GRADE Simple Language Summary*
Anatomic closure rates[a]	2 studies (707 participants)	-22 (-88 to 16) OR: 0.71 (0.36 to 1.4) LOW (Due to serious risk of bias and imprecision)	*Glue may have little to no effect on the proportion of anatomic closure compared to laser.*
Venous clinical severity score (VCSS 0-30)[b]	3 studies (713 participants)	MD: -0.09 (-0.2 to 0.03) VERY LOW (Due to serious risk of bias and study design)	*We are very uncertain about the effects of glue compared to laser on VCSS.*

[a] Assumed risk: 942/1000 patients (MID: 50/1000); [b] MID: 1.0.
CI: confidence interval; OR: odds ratio; MD: mean difference; MID: minimally important difference.

TABLE 2C.—*Summary of Findings for recommendation 2.*

Population: Lower limb symptomatic venous insufficiency
Bontinis 2023 (studies from inception up to August 2022); 17 trials including 2156 participants
Frequentist network meta-analysis

Outcome	Number of trials (participants)	OR/MD (95% CI)* Certainty of evidence	*GRADE Simple Language Summary*
MOCA *vs.* radiofrequency			
Vein closure	2 studies (296 participants)	OR: 3.99 (1.82 to 10.53) VERY LOW (Due to study design, serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of MOCA compared to radiofrequency on vein closure rate.*
Venous clinical severity score (VCSS 0-30)[a]	2 studies (296 participants)	MD: 0.96 (0.71 to 1.20) VERY LOW (Due to study design, serious risk of bias and serious imprecision)	*We are very uncertain about the effects of MOCA compared to radiofrequency on VCSS.*
MOCA *vs.* Laser			
Vein closure	2 studies (236 participants)	OR: 3.99 (1.82 to 10.53) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of MOCA compared to laser on vein closure rate.*
Venous clinical severity score (VCSS 0-30)[a]	2 studies (236 participants)	MD: 0.94 (0.61 to 1.24) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of MOCA compared to laser on VCSS.*
MOCA *vs.* glue			
Vein closure	1 study (163 participants)	OR: 3.99 (1.82 to 10.53) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of MOCA compared to glue on vein closure rate.*
Venous clinical severity score (VCSS 0-30)[a]	1 study (163 participants)	MD: 0.89 (0.65 to 1.15) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of MOCA compared to glue on VCSS.*

[a] MID: 1.0. *We were not able to calculate baseline risk as event rate in control groups were not provided.
CI: confidence interval; RR: risk ratio; MID: minimally important difference; SMD: standardized mean difference.

Population: Patients with varicose veins
Farah 2022 (Inception to December 4th, 2020)
Frequentist random-effects pairwise meta-analysis

Outcome	Number of trials (participants)	RR/MD (95% CI)* Certainty of evidence	*GRADE Simple Language Summary*
Surgery *vs.* Laser			
Anatomic closure rates	2 studies (794 participants)	RR: 0.9 (0.83 to 0.97) LOW (Due to serious risk of bias and imprecision)	*Surgery may reduce anatomic closure rates compared to laser.*
Venous clinical severity score (VCSS 0-30)[a]	3 studies (725 participants)	MD: -0.09 (-0.27 to 0.09) LOW (Due to serious risk of bias and imprecision)	*Surgery may have little to no effect on VCSS compared to laser.*
Serious Adverse Events	12 studies (3996 participants)	RR: 0.99 (0.77 to 1.27) VERY LOW (Due to serious serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of surgery compared to laser on the risk of serious adverse events.*
Surgery *vs.* Radiofrequency			
Anatomic closure rates	1 study (217 participants)	RR: 1.15 (1.04 to 1.26) VERY LOW (Due to study design and very serious imprecision)	*We are very uncertain about the effects of surgery compared to radiofrequency on anatomic closure rates.*
Venous clinical severity score (VCSS 0-30)[a]	5 studies (652 participants)	MD: -0.04 (-0.44 to 0.36) LOW (Due to study design)	*Surgery may have little to no effect on VCSS compared to radiofrequency.*
Serious Adverse Events	10 studies (1740 participants)	RR: 1.65 (1.16 to 2.35) VERY LOW (Due to serious imprecision and study design)	*We are very uncertain about the effects of surgery compared to radiofrequency on the risk of serious adverse events.*
Radiofrequency *vs.* Glue			
Recurrece: reflux reappearence	2 studies (466 participants)	RR: 3.22 (1.07 to 9.64) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of radiofrequency compared to glue on the risk of recurrence.*
Serious Adverse Events	1 study (60 participants)	RR: 1.63 (1.13 to 2.33) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of radiofrequency compared to glue on the risk of serious adverse events.*

[a] MID: 1.0. *We were not able to calculate baseline risk as event rate in control groups were not provided.
CI: confidence interval; MD: mean difference; MID: minimally important difference.

TABLE 2D.—*Summary of Findings for recommendation 2.*

Population: Patients with venous insufficiency caused by lower extremity truncal vein incompetence **Kabnick 2024 (from between January 1, 2000 and January 31, 2023); 17 studies** **Frequentist random-effects pairwise meta-analysis**			
Outcome	Number of trials (participants)	OR (95% CI)* Certainty of evidence	*GRADE Simple Language Summary*
Polidocanol 1% endovenous microfoam (PEM) *vs.* Radiofrequency or Laser			
Closure rate	1 study (1070 participants)	OR: 0.65 (0.36 to 1.18) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PEM compared to radiofrequency or laser on closure rate.*
Deep venous thrombosis (DVT)	1 study (1070 participants)	OR: 0.64 (0.18 to 2.25) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PEM compared to radiofrequency or laser on the risk of DVT.*
Polidocanol 1% endovenous microfoam (PEM) *vs.* Surgery			
Closure rate	1 study (270 participants)	OR: 0.51 (0.27 to 0.97) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PEM compared to surgery on closure rate.*
Deep venous thrombosis (DVT)	1 study (272 participants)	OR: 1.02 (0.29 to 3.57) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PEM compared to surgery on the risk of DVT.*
Polidocanol 1% endovenous microfoam (PEM) *vs.* Physician compounded foam			
Closure rate	1 study (384 participants)	OR: 2.91 (1.58 to 5.37) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PEM compared to foam on closure rate.*
Deep venous thrombosis (DVT)	1 study (384 participants)	OR: 2.73 (0.78 to 9.61) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PEM compared to foam on the risk of DVT.*

*We were not able to calculate baseline risk as event rate in control groups were not provided. CI: confidence interval; OR: odds ratio; MID: minimally important difference.

Population: Varicose veins **Ontario Health Quality 2021 (studies from inception up to January 14, 2020); 19 studies** **Frequentist random-effects pairwise meta-analysis**			
MOCA *vs.* radiofrequency			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) Certainty of evidence	*GRADE Simple Language Summary*
Vein closure[a]	2 studies (237 participants)	RD: 150 fewer (-220 to -70) LOW (Due to very serious imprecision)	*MOCA may reduce vein closure rates compared to radiofrequency.*
MOCA *vs.* Laser			
Vein closure[b]	2 studies (226 participants)	RD: 180 more (100 to 260) LOW (Due to very serious imprecision)	*MOCA may increase vein closure rate compared to laser.*
Glue *vs.* Laser			
Vein closure[c]	2 studies (622 participants)	RD: 20 (-10 to 40) LOW (Due to very serious imprecision)	*Glue has little to no effect on vein closure rates compared to laser.*

[a] Assumed risk: 384/1000 patients (MID: 50/1000); [b] Assumed risk: 72/1000 patients (MID: 50/1000); [c] Assumed risk: 40/1000 patients (MID: 50/1000). MID: 50/1000. CI: confidence interval; RD: risk difference.

A 2024 meta-analysis focused on automatically produced polidocanol microfoam (PEM) concluded that it is not significantly different from tumescent thermal techniques in achieving occlusion of refluxing great saphenous veins and in thromboembolic risk, but superior to manually produced sclerosing foam regarding venous occlusion.[28] Given the very low certainty of evidence, the current competitiveness of PEM compared to radiofrequency, laser, surgery, and manually produced foam remains highly uncertain (Table 2A, 2B, 2C). Therefore, the recommendation limits its use to patients not eligible for radiofrequency, laser, or surgery, specifying adherence to AIFA regulations for manually produced 3% polidocanol foam.

Steam and microwave technologies lack sufficient literature support to issue a dedicated recommendation.[34] While this review focuses on technologies for treating the great saphenous vein, saphenous-sparing strategies, compared to stripping/radiofrequency/stripping ablation, have shown, albeit with very low certainty, possible improvement in anatomical recurrence, CIVIQ scores, and adverse events.[24] A 10-year follow-up randomized study suggested

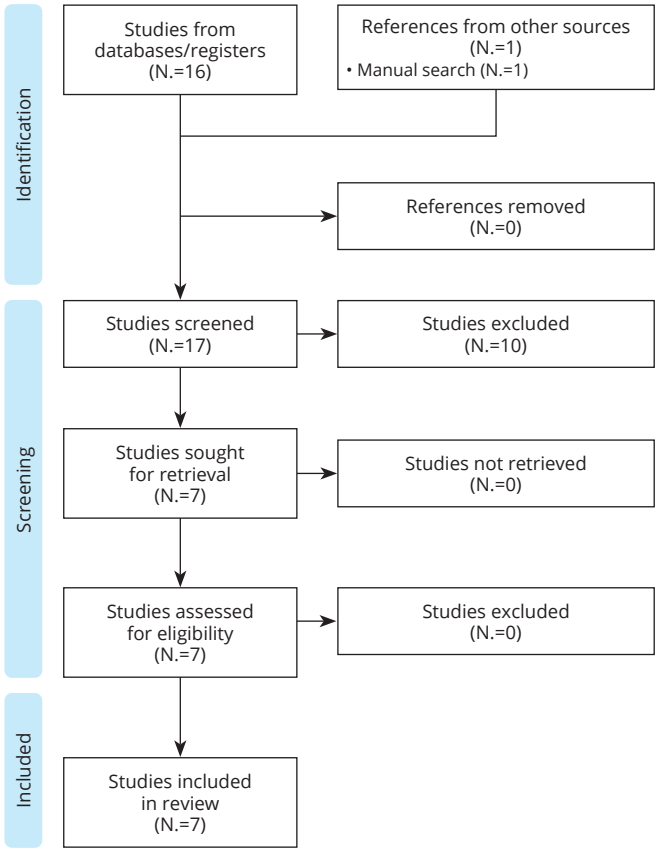

Figure 2.—PRISMA flow chart for recommendation 2.

a potential reduction in varicose vein recurrence, provided the physician is sufficiently experienced.[35, 36]

Based on the risk/benefit analysis related to the strategic choice of treatment, saphenous-sparing approaches may be appropriate in specific hemodynamic scenarios, where reflux suppression testing confirms potential efficacy.[37] It should be noted that, despite the preliminary sustainability analysis, no cost-effectiveness considerations are included in this document; future evaluations should optimize healthcare resources and promote best clinical practice. Furthermore, different technologies have generated varying amounts and quality of scientific evidence, which must be understood by both physicians and patients (Figure 2).

Economic affordability considerations

National data to determine the cost of thermal and non-thermal procedures are not available, unless professional associations are able to provide such information. A specific calculation is required. The study by Epstein *et al*.[38] reports the costs of procedures such as laser, radiofrequency, and ultrasound-guided foam sclerotherapy, calculated in the UK context, taking into account the following elements: operating room use, instrumental technology, consumables, various materials, and staff. Similarly, in the UK context, Brittenden *et al*.[39] analyze the costs of laser treatment and consider various comparators. The cost of the operating room is a resource that must be carefully considered, including its potential appropriateness in light of the procedural minimally invasive nature.

Research technical notes

- **PICO:** in patients with chronic venous insufficiency (P), are tumescent thermal techniques (I) superior to non-tumescent non-thermal techniques (C) in terms of anatomical recurrence, improvement of the Venous Clinical Severity Score/CIVIQ, and reduction of complications (O)?
- **Search string:** epistemonikos: (title:(chronic venous disease OR varicose vein*) OR abstract:(chronic venous disease OR varicose vein*)) AND (title:(laser OR radiofrequency OR microwave) OR abstract:(laser OR radiofrequency OR microwave)) AND (thermal tumescent) AND (non-thermal non tumescent). Medline: (chronic venous disease.ab. OR varicose vein*.ab.) AND (laser.ab. OR radiofrequency.ab. OR microwave.ab.).
- **Inclusion criteria:**

Study Design	Partecipants	Intervention	Results	Publication Type	Language
Meta-analysis, systematic revisions	Age: 18-65 yo	Thermal and non thermal, tumescent and not tumescent venous procedures	Anatomical recurrences, clinical severity score, quality of life, complications	Original manuscript published in an indexed journal	English
	Chronic venous disease patients undergoing endovenous procedures				

- **Exclusion criteria:** 1) populations, interventions, and comparators that are irrelevant; 2) information not within the time frame from September 2014 to September 2024; 3) non-English language studies.
- **Result:** Seven meta-analyses, published between 2020 and 2024.[22-28] Following the literature review and discussion among experts, the Development Group, together with the Surveillance Group, reached unanimous approval of the recommendation.
- **References indicating the link between evidence and recommendation:** efficacy and safety;[22-28] patient values and preferences;[22, 23, 25, 27] feasibility.[25]
- **Important and/or critical outcomes not found in the literature:** stratification of anatomical recurrence according to hemodynamic pattern.

Applicability

A) Facilitating factors

The necessary equipment indicated by the recommendation is available nationwide. The learning curve for performing these procedures is rapid.

B) Barriers

The additional cost of the equipment needed to perform the procedure must be balanced by an appropriate care setting, consistent with the minimally invasive nature of the procedure. Using an operating room represents an unnecessary cost; an outpatient setting is preferable. If the care setting is not adapted, the cost of the operating room and the equipment may become a barrier in terms of reimbursement.

C) Suggestions and tools

• Interaction between vascular experts and healthcare governance representatives aimed at optimizing management and dedicated resources for the treatment of superficial venous insufficiency of the lower limb.

• Creation of educational material for healthcare professionals and informational material for patients regarding validated and modern procedural management of superficial venous disease.

D) Potential resource implications

Optimization of procedural timings and related waiting lists through the provision of more minimally invasive procedures that can be performed in outpatient settings.

E) Monitoring indicators

Number of endovenous procedures compared to surgical ablative procedures.

Recommendation 3: Ilio-femoral venous stenting

In patients with chronic ilio-femoral venous stenosis, whether thrombotic or non-thrombotic, a conservative treatment approach is suggested. This should include graduated compression, tailored physical exercise, and weight management, all monitored by experienced healthcare professionals for at least six months before considering possible stenting, rather than proceeding immediately with stent placement (*Weak recommendation, against the intervention, with low certainty of evidence*).

Rationale

Ilio-femoral venous obstruction, whether thrombotic or non-thrombotic, can significantly impact the patient's clinical scenario and quality of life. This topic has attracted increasing interest in the medical community over the past two decades, including the appropriateness of venous stenting.[40, 41] This therapeutic approach has demonstrated feasibility, safety, and potential clinical benefits.[42-44] However, only one randomized study has compared stenting with conservative treatment, using pain scales, the Venous Clinical Severity Score, and the 36-item Short Form Health Survey, at 6 months follow-up.[45] Complications have been reported in up to 39% of cases, necessitating careful consideration of procedural indications.[46]

A recent randomized study evaluated the effectiveness of stenting in improving quality of life in iliac venous lesions, both thrombotic and non-thrombotic, but did not achieve significant results.[47] Furthermore, although expert opinions support stenting following early thrombus removal, there is no randomized evidence in the literature regarding the appropriateness of delayed stent placement.[48] A detailed literature analysis is required to understand the actual certainty of evidence on this topic, considering potential confounding factors such as different thromboprophylaxis regimens and heterogeneity in clinical severity, hemodynamics, and lifestyle.[49-51]

It must also be noted that regulatory standards for stent durability are set at 10 years. Given the typically longer life expectancy of patients with venous disease, careful risk-benefit evaluation must always accompany any stenting indication.[52] Beyond the decision to place a stent, the therapeutic plan should always include lifestyle and physical activity components, which can significantly improve the patient's clinical outcome.[53, 54]

The literature identified in this review includes only the aforementioned randomized study comparing procedural versus conservative management.[45] The certainty of evidence was low regarding stenting's ability to promote venous ulcer healing, leading to a weak recommendation against its routine use compared to a conservative approach (Table 3A). Considering the potentially favorable effect, which is not strongly supported by the literature and could lead to severe complications, the panel suggests waiting up to six months of appropriate conservative treatment before considering the procedure. The six-month period was chosen based on the average healing time for venous ulcers and the potential benefits of adequate compression therapy and rehabilitative exercise.

To our knowledge, there is no strong evidence favoring one stent model over another, with only one randomized study comparing two different products.[55] This work does not include a cost analysis of stenting, which remains a priority for future development of proper clinical governance in this medical field (Table 3A, 3B, Figure 3).

TABLE 3A.—*Evidence to Decision Framework for recommendation 3.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with chronic venous insufficiency (P), are tumescent thermal techniques (I) superior to non-tumescent non-thermal techniques (C) in terms of anatomical recurrence, improvement of the Venous Clinical Severity Score/CIVIQ, and reduction of complications (O)?	The panel highlights the lack of meta-analyses comparing ilio-femoral venous stenting with conservative treatment for ilio-femoral venous obstruction associated with ulceration and/ or symptoms. It is also important to note that it is currently not possible to conduct an appropriate cost-effectiveness assessment.	In patients with chronic ilio-femoral venous stenosis, whether thrombotic or non-thrombotic, a conservative treatment approach is suggested. This should include graduated compression, tailored physical exercise, and weight management, all monitored by experienced healthcare professionals for at least six months before considering possible stenting, rather than proceeding immediately with stent placement (weak recommendation, against the intervention, with low certainty of evidence).	The risk–benefit balance of ilio-femoral venous stenting requires further investigation. While observational literature reports feasibility, safety, and potential efficacy, high rates of complications have also been described, so extreme caution should be exercised before recommending the procedure.	Low	The panel evaluated the potential clinical benefit provided by both procedural and conservative treatments, including physical exercise and lifestyle interventions. Considering the lack of strong evidence supporting stenting and the possible short- and mid-term complications, the panel suggests maximizing the attempt at a conservative approach, with any consideration of stenting not exceeding six months, in order to avoid delays in the improvement of signs and symptoms associated with the condition.	This work does not address cost-effectiveness aspects, whose relevance is, however, of fundamental importance, especially in light of the potentially high costs generated both by the procedure and by the chronicity of the condition.	Both conservative and procedural treatments may not be immediately well tolerated by patients, considering compliance with the use of compression stockings, physical exercise, weight reduction, as well as the placement of a permanent foreign body, whose long-term performance is still largely unknown. A careful assessment of the patient's preferences and needs should be included among the key factors determining the final treatment indication.

TABLE 3B.—*Summary of Findings for statement 3.*

Rossi 2018			
Population: Patients with CVD (C3-C6 in the CEAP classification)			
Stenting + BMT *vs.* BMT Alone			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) Certainty of evidence	*GRADE Simple Language Summary*
Proportion of ulcers healed[a, b]	1 trial (34 participants)	517 more (104 to 840) LOW (due to very serious imprecision)	*Stenting + BMT may increase the proportion of ulcers healed compared to BMT Alone*

[a] Assumed risk 400/1000 (MID: 50/1000); [b] Complete epithelialization of ulcerated areas.
CVD: chronic venous disease; CI: confidence interval; MID: minimally important difference.

Economic affordability considerations

According to the study by Radaideh *et al.*, the cost of venous thromboembolism is estimated at approximately 10 billion dollars annually in the USA alone, with the main impact deriving from the long-term consequences of the disease.[56] National-level cost studies on post-thrombotic syndrome are both lacking and necessary, along with potential adaptation of reimbursement coding.

Technical research notes

• **PICO:** in patients with ilio-femoral venous obstruction (P), does immediate placement of an ilio-femoral stent (I) compared to several months of conservative treatment (C) improve venous ulcer healing, quality of life, and pain (O)?

• **Search string:** epistemonikos: (title:(deep AND venous OR vein*) OR abstract:(deep AND venous OR vein*)) AND (title:(stent*) OR abstract:(stent*)) AND (title:(thrombosis OR reflux OR obstruction) OR abstract:(thrombosis OR reflux OR obstruction)) AND (title:(conservative) OR abstract:(conservative)) (((venous stenting) OR (deep reflux)) OR (deep venous obstruction)) AND (quality of life). Medline: ((deep adj venous OR vein$).ti,ab.) AND (stent$).ti,ab. AND (thrombosis OR reflux OR obstruction).ti,ab. AND (conservative).ti,ab.

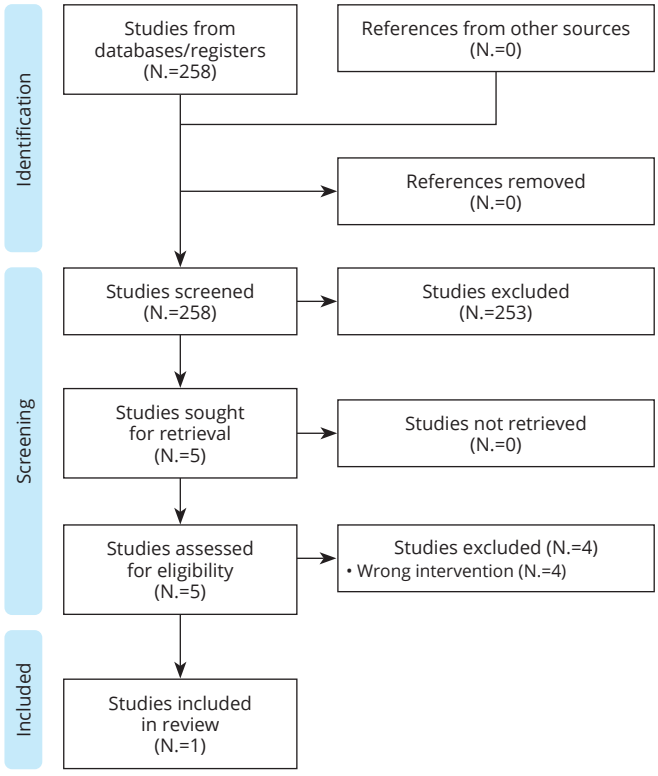

Figure 3.—PRISMA flow chart for statement 3.

- **Inclusion criteria:**

Study Design	Partecipants	Intervention	Results	Publication Type	Language
Meta-analysis, systematic revisions, randomized comparative trials	Age: 18-65 yo	Ilio-femoral venous stenting	Ulcer healing, quality of life, pain	Original manuscript published in an indexed journal	English
	Ilio-femoral obstruction				

- **Exclusion criteria:** all studies reporting: 1) populations, interventions, or comparators that are irrelevant; 2) information outside the timeframe from September 2014 to September 2024; 3) non-English language.
- **Results:** the identified literature did not allow for a meta-analysis; therefore, the recommendation was based on the only available randomized trial. Following the literature review and expert discussion, the Development Group, together with the Surveillance Group, reached unanimous approval of the recommendation.
- **References indicating the link between evidence and recommendation:** 1) efficacy and safety;[45] 2) patient values and preferences;[45] 3) feasibility.[45]
- **Important and/or critical outcomes:** not found in the literature, follow-up beyond three years.

Applicability

A) Facilitating factors

A proper conservative approach, potentially leading to clinical and especially symptomatic benefits in place of a vascular procedure, due to its non-invasive nature, facilitates the implementation of this Clinical Best Practice Recommendation.

B) Barriers

- The effectiveness of the conservative approach requires time and patient compliance.
- To date, there are no rigorously validated conservative protocols.

C) Suggestions and tools

- Collaboration between vascular experts and representatives from Sports Medicine, Dietetics, and Public Health authorities to facilitate adapted physical exercise programs and targeted dietary plans.
- Public awareness initiatives promoting healthy lifestyle habits.

D) Potential resource implications

Reduction in procedural healthcare costs, potentially decreasing the demand for stent placement procedures.

E) Monitoring indicators

Number of avoided stent placement procedures in favor of a conservative lifestyle-based approach to the pathology.

Good clinical practice statement 4: Pelvic venous reflux multi-specialty management

In cases of pelvic venous reflux, a gynecological evaluation before providing any indication for vascular treatment is appropriate (*Good clinical practice statement based on ungraded evidence quality*).

Rationale

Male varicocele represents a well-known and widely managed medical condition.[57] In contrast, the so-called *female varicocele* still lacks proper recognition both within the medical community and among the general population, thus representing a matter of healthcare equity and gender medicine. Pelvic venous disorder (PVD) has been identified as responsible for lower abdominal pain in 39-91% of cases. Similarly, pelvic venous reflux may be asymptomatic and/or present with diverse clinical manifestations.[58] Preliminary evidence also suggests a possible role of pelvic venous insufficiency in infertility, with potential resolution following appropriate embolization.[59] The true epidemiological impact of this condition is likely underestimated due to the lack of structured real-world data collection. At the same time, a paradoxical risk of overtreatment exists in less-experienced

centers.[60] Dilated and incompetent ovarian veins have been identified in at least 50% of asymptomatic women, clearly indicating that treatment should follow a detailed clinical evaluation involving both vascular and gynecologic expertise.[61] Although pelvic venous embolization has been shown to be safe and effective in experienced hands, its indication requires extreme caution, as complication rates have been reported to exceed 30% in some series.[62] Hormonal status must also be carefully evaluated, as it can influence both the clinical manifestations of venous dilation and nociceptive sensitivity.[63] All other potential causes of pelvic pain must be ruled out. Among these, the following should always be excluded: endometriosis, adenomyosis, adhesions, irritable bowel syndrome, cystitis, chronic fatigue syndrome, trauma, leiomyomas, nerve root compression, sacral cysts, cauda equina syndrome, pelvic inflammatory disease, and neoplastic conditions. Additionally, post-traumatic disorders and major depression have been associated with pelvic venous disease. A thorough multidisciplinary evaluation – including detailed anamnesis – is essential to identify the nature, severity, and triggers of symptoms.[64] The clinical indications for treatment following the identification of pelvic venous reflux are still in need of appropriate standardization and validation.[65] Today, chronic pelvic pain affects at least 26% of the female population and remains a multifactorial challenge requiring optimal multidisciplinary collaboration involving both vascular and gynecological specialists.[66] The panel strongly recommends further studies on cost-effectiveness and on the role of mandatory gynecologic consultation in the management pathway (Table 4A, 4B, Figure 4).

Economic affordability considerations

An economic evaluation of the cost associated with adding a gynecologic consultation is not currently feasible, and a dedicated study on this aspect is recommended.

TABLE 4A.—*Good Practice Statement checklist for statement 4.*[4]

Process for developing good practice statement	**Supporting information**	**Verification**
Write Good Practice Statement		
Does the statement follow a PICO prioritization process?		X Yes o No
If you answered No → 1) Explain why the PICO question was not prioritized but is being addressed → avoid developing any type of actionable statement that acts as an independent response to the PICO question.		
Are the Population and Intervention components clear?		X Yes o No
If you answered No → Check whether you are developing an implementation consideration (refer to flow chart in Lotfi et al.(8))		
Items to complete	**Supporting information**	**Verification**
All the following criteria must be fulfilled *to consider the statement a GPS.*		
(1) Message is really necessary in regard to actual health care practice		This criterion has been addressed: X Yes o No
(2) Implementing the GPS results in a large net positive consequence (i.e. satisfy several evidence to decision (EtD) criteria) after consideration of all relevant outcomes and potential downstream consequences ** check the criteria considered in the development of the GPS.		This criterion has been addressed: X Yes o No **Evidence-to-Decision criteria** Importance of the problem [X] Certainty in effects [X] Variability and certainty in the importance of outcomes [X] Magnitude of resource requirements [X] Certainty of evidence of resource use [X] Cost-effectiveness [X] Equity [X] Acceptability [X] Feasibility [X]
(3) Collecting and summarizing the evidence is a poor use of a guideline panel's limited time, energy or		This criterion has been addressed: X Yes o No
resources. The opportunity cost of collecting and summarizing the evidence is large and can be avoided.		
(4) There is a well-documented clear and explicit rationale connecting the indirect evidence		This criterion has been addressed: X Yes o No
(5) Clear and actionable (This criterion should apply to any developed statement. For example, all formal recommendations are clear and actionable)		This criterion has been addressed: X Yes o No
Final judgement		
Did you answer Yes to ***all*** of the above?	X Yes Development as GPS is appropriate	
	o No Development as GPS is ***not*** appropriate → Revisit the PICO question and the importance of addressing it.	

Technical research notes

• **PICO:** in patients with chronic pelvic pain (**P**), is the detection of pelvic venous reflux combined with a gynecological evaluation (**I**) more appropriate than the sole identification of venous reflux (**C**) in determining the etiology of pain (**O**)?

• **Search string:** (pelvic pain.ti. OR pelvic pain.ab.) OR (pelvic congestion syndrome.ti. OR pelvic congestion

TABLE 4B.—*Evidence to Decision Framework Good Practice Statement 4.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with chronic pelvic pain (P), is the detection of pelvic venous reflux combined with a gynecological evaluation (I) more appropriate than the sole identification of venous reflux (C) in determining the etiology of pain (O)?	Female pelvic pain is as potentially not appropriately diagnosed and treated.	In cases of pelvic venous reflux, a gynecological evaluation before providing any indication for vascular treatment is appropriate (good practice statement based on ungraded evidence quality).	A gynaecological consult before the indication to a pelvic venous procedure delivers the significant benefit of an accurate differential diagnosis avoiding eventual invasive procedures not useful for the clinical symptomatology resolution. As it is a diagnostic integration, no associated risks are foreseen.	Good Practice Statement	The main value is to be found in the appropriate differential diagnosis performance in front of the aspecific symptom of the pelvic pain. The preference is for the cure of the person rather of the instrumental finding.	The cost of a gynaecological consult can be easily compensated and justified by the potential saving coming from the counteraction against an overindication to embolization.	Feasibility is high considering that it deals with a gynaecological visit, easily accepted and appreciated by the patient who can perceive a holistic approach to the person.

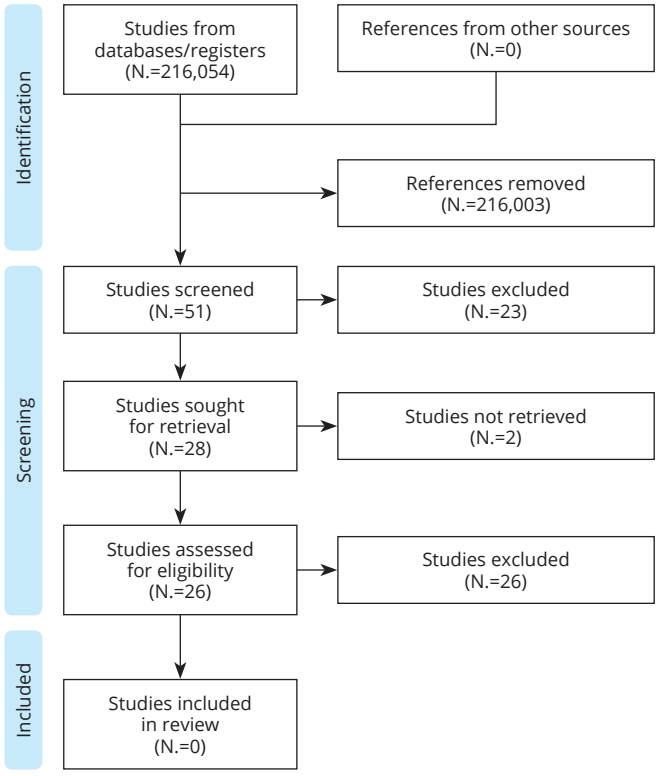

Figure 4.—PRISMA flow statement 4.

syndrome.ab.) OR (pelvic venous disorder*.ti. OR pelvic venous disorder*.ab.).

- **PRISMA:** flow chart provided in Figure 4.

Good practice statement indication

- 1. **The statement is genuinely necessary in the context of current clinical practice.**

Patients with pelvic pain are at risk both of missed diagnosis of the corresponding varicocele and of inappropriate procedural treatment following the ultrasonographic detection of venous dilation in this anatomical region. Promoting active collaboration between vascular specialists and gynecologists is extremely necessary to ensure appropriate management of this highly prevalent medical condition.

- 2. **Implementation of the Clinical Good Practice Indication has a broadly positive impact.**

A gynecological evaluation for careful differential diagnosis of pelvic pain maximizes the appropriateness of the overall clinical management of the patient, potentially avoiding inappropriate indications for embolization of varicosities unrelated to symptoms, and ensuring correct diagnostic and therapeutic framing.

- 3. **Collecting and summarizing the evidence would represent a misuse of the panel's limited time, energy, and resources.**

In light of the evident benefit and the absence of inherent risks in integrating a possible vascular procedural indication with a gynecological specialist visit, and considering the lack of targeted studies on the subject, a detailed systematic review is considered inappropriate.

- 4. **The indirect evidence is linked to a well-documented, clear, and explicit rationale.**

The well-documented diagnostic complexity of the multifactorial etiology of pelvic pain and its therapeutic approach provides a clear and explicit rationale for performing a gynecological specialist evaluation prior to any possible vascular embolization procedure.

- 5. **The statement is clear and actionable.**

The statement is clear and easily implementable, particularly if gynecological and vascular scientific societies actively promote the necessary collaboration in managing the common issue of pelvic pain.

Applicability

A) Facilitating factors

- Gynecological consultation services are already active, making it necessary only to establish a connection between the gynecological visit and the vascular specialist involved in the potential indication for pelvic venous disease treatment.
- The existing General Practice service can collect both vascular and gynecological data for the patient to ensure proper holistic follow-up.

B) Barriers

None, except for the potential cost of the specialist visit, which can potentially be offset by improved disease management and the consequent reduction of associated healthcare costs.

C) Suggestions and tools

- Involvement of General Practice for the follow-up of any gynecological and vascular controls over time.
- Promotion of differential gynecological and vascular diagnostics by the respective Scientific Societies.

D) Potential resource implications

Increase in consultation services, but reduction in treatment-associated costs due to more effective treatment indications.

E) Monitoring indicators

- Number of gynecological visits following a potential procedural indication for pelvic venous disorder.
- Percentage of potential indications for pelvic vascular

treatment where the underlying symptoms are primarily attributable to gynecological rather than venous issues.

Good clinical practice statement 5: Varicose veins procedures thromboprophylaxis

Procedures on varicose veins may be complicated by thromboembolic events; therefore, an individualized risk assessment is appropriate. Thromboprophylaxis should be personalized, avoiding a one-size-fits-all approach. The Caprini score is recommended to guide, without strictly determining, the prescription of thromboprophylaxis (*Good clinical practice statement based on unassessed quality of evidence*).

Rationale

Over the last decade, interventions for varicose veins have progressively shifted from surgery to endovenous options, while still lacking a clear protocol for post-procedural thromboembolism prevention. Both surgical and endovenous approaches have demonstrated safety and feasibility,[67] but both have also been associated with potentially severe thromboembolic events.[68]

Guidelines on this topic are limited, resulting in heterogeneous practices both nationally and internationally. An Irish survey reported that 73.3% of physicians always prescribe post-operative venous thromboprophylaxis, yet in 71.4% of cases this consisted of a single heparin injection.[69]

Evidence shows that thromboembolic risk may be elevated not only for a few days but potentially for much longer periods.[70] The use of a standardized protocol based on the Caprini score to calculate thromboembolic risk has shown potential preventive efficacy.[71] A specific subanalysis of Caprini score utilization across different procedures reported 5.6% thrombotic events in the 7-9 score range, rising to 14.7% for scores of 10 or higher.[72]

One study confirmed the correlation between the Caprini score and thrombotic risk following venous procedures, with and without anticoagulation. Without anticoagulation, thrombotic incidence was 2.6% for scores up to 6, 8.5% for scores between 7 and 10, and 33.3% for scores above 11.[73] While the Caprini score can support the initial risk assessment of patients undergoing procedures, dedicated studies specifically in the context of venous insufficiency treatment and risk stratification are needed.

A 2023 study randomized patients undergoing automated polidocanol endovenous microfoam ablation of the great saphenous vein to sapheno-femoral compression versus saline irrigation of the deep system, versus addition of apixaban 5 mg daily for 5 days. The results suggest a potential benefit in reducing thrombotic complications with the addition of apixaban to the other prophylactic measures. The certainty of evidence from this data is low, requiring further studies (Table 5A). A major bias in this study is the lack of patient risk stratification.[74]

TABLE 5A.—*Evidence to Decision Framework good practice statement 5.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In adult patients undergoing a procedure for the treatment of chronic venous insufficiency (P), is the addition of pharmacological thromboprophylaxis (I), compared to no thromboprophylaxis (C), appropriate to reduce the risk of post-procedural thromboembolism (O)?	Future studies should highlight any differences in thrombotic risk among the specific and heterogeneous minimally invasive procedures currently available as a result of technological advancements.	Procedures on varicose veins may be complicated by thromboembolic events; therefore, an individualized risk assessment is appropriate. Thromboprophylaxis should be personalized, avoiding a one-size-fits-all approach. The Caprini score is recommended to guide, without strictly determining, the prescription of thromboprophylaxis (good clinical practice recommendation based on unassessed quality of evidence).	The benefit of protection against thromboembolic risk using drugs with proven efficacy and safety, such as heparin, and/or preventive measures such as certified elastic compression, outweighs the risk of major acute thromboembolic and chronic post-thrombotic events.	Good practice statement	The primary value lies in the prevention of pulmonary embolism, the leading cause of preventable death, and of post-thrombotic syndrome, a highly debilitating condition. The preferred approach is a detailed assessment of thromboembolic risk for both the individual patient and the specific type of procedure.	Cost-efficacy evaluation about thromboprophylaxis was not in the scope of this document, but it remains as a fundamental aspect in the assessment of the affordability. This calculation will have to include the consideration of the potential cost benefit associated with the avoidance of thrombotic complication costs.	Good Practice Statement is feasible considering the self-administration of a subcutaneous injection or of the oral administration and/or of the graduated compression stocking use. Acceptability by the patient can be limited by the personal tolerance in the daily use, yet prescribed for a limited amount of time.

TABLE 5B.—*Good Practice Statement checklist for statement 5.*[4]

Process for developing good practice statement	**Supporting information**	**Verification**
Write Good Practice Statement		
Does the statement follow a PICO prioritization process?		☒ Yes ○ No
If you answered No → 1) Explain why the PICO question was not prioritized but is being addressed → avoid developing any type of actionable statement that acts as an independent response to the PICO question.		
Are the Population and Intervention components clear?		☒ Yes ○ No
If you answered No → Check whether you are developing an implementation consideration (refer to flow chart in Lotfi et al.(8))		
Items to complete	**Supporting information**	**Verification**
All the following criteria must be fulfilled *to consider the statement a GPS.*		
(1) Message is really necessary in regard to actual health care practice		This criterion has been addressed: ☒ Yes ○ No
(2) Implementing the GPS results in a large net positive consequence (i.e. satisfy several evidence to decision (EtD) criteria) after consideration of all relevant outcomes and potential downstream consequences ** check the criteria considered in the development of the GPS.		This criterion has been addressed: ☒ Yes ○ No **Evidence-to-Decision criteria** Importance of the problem ☒ Certainty in effects ☒ Variability and certainty in the importance of outcomes ☒ Magnitude of resource requirements ☒ Certainty of evidence of resource use ☒ Cost-effectiveness ☒ Equity ☒ Acceptability ☒ Feasibility ☒
(3) Collecting and summarizing the evidence is a poor use of a guideline panel's limited time, energy or		This criterion has been addressed: ☒ Yes ○ No
resources. The opportunity cost of collecting and summarizing the evidence is large and can be avoided.		
(4) There is a well-documented clear and explicit rationale connecting the indirect evidence		This criterion has been addressed: ☒ Yes ○ No
(5) Clear and actionable (This criterion should apply to any developed statement. For example, all formal recommendations are clear and actionable)		This criterion has been addressed: ☒ Yes ○ No
Final judgement		
Did you answer Yes to ***all*** of the above?	☒ Yes Development as GPS is appropriate ○ No Development as GPS is ***not*** appropriate → Revisit the PICO question and the importance of addressing it.	

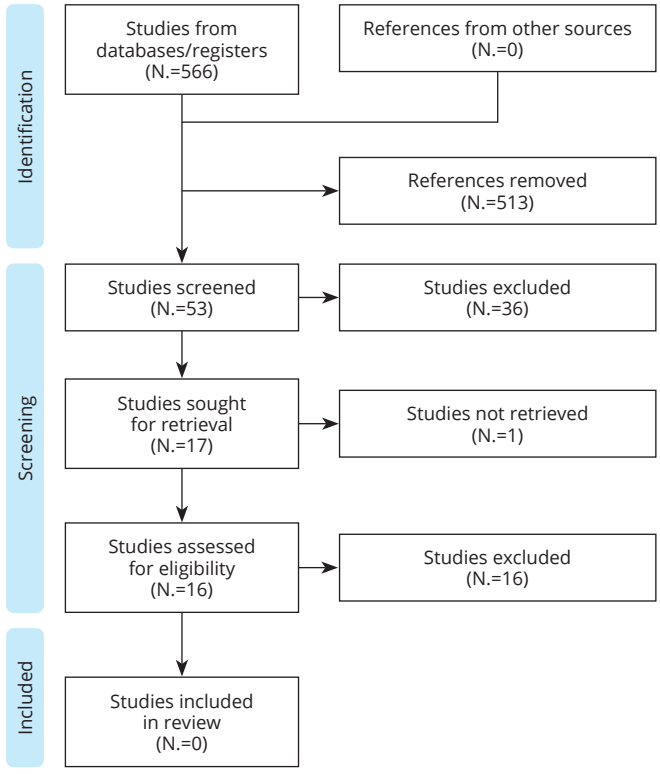

Figure 5.—PRISMA flow statement 5.

Post-procedural venous thromboprophylaxis has not shown clinically significant risks. These findings are supported by two systematic reviews from 2022 and 2023, which highlight the minimal bleeding risk and the strong need for higher-quality studies on this topic.[75-78] A one-size-fits-all prophylaxis protocol is not recommended for post-procedural venous thromboprophylaxis. Instead, a detailed assessment of both patient- and procedure-specific risk is recommended (Table 5A, 5B, Figure 5).

Economic affordability considerations

The cost of a heparin injection should be added to the cost of the personnel potentially involved in its administration. A cost-effectiveness analysis is necessary.

Technical research notes

- **PICO:** in adult patients undergoing a procedure for the treatment of chronic venous insufficiency (P), is the addition of pharmacological thromboprophylaxis (I), compared to no thromboprophylaxis (C), appropriate to reduce the risk of post-procedural thromboembolism (O)?
- **Search string:** ((thrombotic risk OR thrombosis).ti,ab.) AND ((chronic venous disease).ti,ab. OR (lymphedema).ti,ab.)
- **PRISMA:** flow chart provided in Figure 5.

Good practice statement indication

- 1. **The statement is truly necessary within the context of current clinical practice.**

Following surgical treatment for varicose veins of the lower limbs, there is marked heterogeneity in thromboprophylactic practices and in the related assessment of thromboembolic risk. Therefore, establishing a good clinical practice recommendation is of utmost necessity.

- 2. **The implementation of the Good Clinical Practice Recommendation results, overall, in a broad and positive effect, after considering all relevant outcomes and potential downstream consequences.**

Venous thromboembolism remains one of the main causes of preventable death. Implementing clinical practice focused on the appropriate management of patients undergoing extremely common procedures – such as superficial venous interventions – has a broad and positive impact, especially considering the high prevalence of the disease and the significant heterogeneity of individual (genetic and environmental) risk. Given that thrombopro-

phylactic measures are proven to be safe, the net benefit strongly supports the statement presented here.

• 3. **Collecting and summarizing the evidence would represent a misuse of the panel's limited time, energy, and resources.**

The importance of thromboprophylaxis is well established in the general post-procedural setting. Procedures targeting the venous system require even greater attention to thromboembolic risk assessment; therefore, conducting a detailed search and systematic review is considered inappropriate in this context.

• 4. **The indirect evidence is linked to a well-documented, clear, and explicit rationale.**

The significant impact of thrombotic events – both acute (pulmonary embolism) and chronic (post-thrombotic syndrome) – provides a clear and explicit rationale for applying the Good Clinical Practice Recommendation described here.

• 5. **The statement is clear and actionable.**

The statement is clear and easily implementable, particularly given the current availability of free applications that facilitate thrombotic risk assessment for both the patient and the procedure.

Applicability

A) Facilitating factors

Thromboprophylactic practice is already in place, making it highly feasible to integrate it with a standardized and reproducible assessment of individual and procedural thrombotic risk.

B) Barriers

None identified, except for the potential cost of the drug, which could be offset by better management of thromboembolic risk and the consequent reduction in costs associated with complications.

C) Suggestions and tools

• Use of clinical registries to generate data aimed at precisely identifying thrombotic risks associated with different devices used in minimally invasive treatment of superficial venous disease.

• Public education campaigns on the use of thrombotic risk scoring, potentially supported by dedicated apps.

D) Potential resource implications

Increased consumption of anticoagulants, but reduced treatment costs due to effective prevention of venous thromboembolism.

E) Monitoring indicators

Incidence of post-procedural superficial venous thromboembolism.

Recommendation 6: Advanced dressings for venous ulcers

Polyurethane foam dressings are suggested for exudative venous ulcers, and silver-based dressings for locally infected lesions, compared to debridement and compression alone (*Weak recommendation, in favor of the intervention, with low certainty of evidence*).

Rationale

The management of venous ulcers remains a major public health challenge, as over 2% of the population in industrialized countries is affected, with recurrence rates exceeding 60%.[1] An analysis from the UK estimated that

TABLE 6A.—*Evidence to Decision Framework for Statement 6.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with venous or lymphatic ulceration (P), does the use of advanced dressings (I), in addition to cleansing and compression (C), improve the healing rate (O)?	The panel emphasizes that the certainty of the evidence is low and that no cost-effectiveness analyses are available. Based on the evidence currently available, polyurethane foams may have at most a minimal effect on lesion healing, whereas silver-based dressings may promote healing.	Polyurethane foam dressings are suggested for exudative venous ulcers, and silver-based dressings for locally infected lesions, compared to debridement and compression alone (WEAK recommendation, in FAVOR of the intervention, with LOW certainty of evidence).	Foam and silver-based dressings have a high safety profile. However, foam dressings can cause maceration and excessive dryness of the ulcer bed if not used properly. Silver dressings can stimulate allergic reactions. Without considering cost-effectiveness, the risk/benefit balance favors their use.	Low	Facilitating ulcer healing is of great importance given the impact of this condition on both the patient and the healthcare system. The panel favors the use of foam and silver-based dressings, where indicated, considering the minimal benefit reported in the literature as well as empirical experience.	This work does not address cost-effectiveness evaluation. Further investigations on this topic are encouraged, particularly in homogeneous populations with similar, including complicated, lesions.	The feasibility of applying foam and silver dressings is high, as is patient acceptability. When applied correctly, these dressings are well accepted by patients, who can benefit in particular from exudate control in the case of foam and pain relief in the case of silver dressings.

TABLE 6B.—*Summary of Findings for recommendation 6.*

Population: Patients with venous leg ulcer			
O'Meara 2015 (trials published between inception to up to March 2015); 5 trials including 295 patients			
Frequentist random-effects pairwise meta-analysis			
Alginate dressings *vs.* Plain non-adherent dressing			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) RR (95% CI) Certainty of evidence	*GRADE Simple Language Summary*
Proportion of ulcers healed[a,b]	1 trial (60 participants)	64 (-112 to 288) RR: 1.08 (0.86 to 1.36) Very Low (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of alginate dressings on the proportion of ulcers healed when compared to plain nonadherent dressing.*

[a] Assumed risk: 800/1000 (MID: 50/1000); [b] Healing assessed by proportion of ulcers fully epithelialised.
CVD: chronic venous disease; CI: confidence interval; OR: odds ratio; RR: risk ratio; MID: minimally important difference

Population: people with venous leg ulcers			
Norman 2018 (trials published between inception to up to March 2018); 78 RCTs (7014 participants)			
Network meta-analysis (random-effects)			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) RR (95% CI)	*GRADE Simple Language Summary*
Alginate/sucralfate *vs.* Nonadherent dressings			
Proportion of ulcers healed[a]	1 trial (60 participants)	1404 (300 to 4767) RR: 6.80 (2.24 to 20.7) Very Low (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of alginate/ sucralfate compared to nonadherent dressings on the proprortion of ulcers healed.*
Cadexomer iodine *vs.* Nonadherent dressings			
Proportion of ulcers healed[a]	1 trial (105 participants)	0 (-148 to 378) RR: 1.0 (0.39 to 2.56) Very Low (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of cadexomer iodine compared to nonadherent dressings on the proprortion of ulcers healed.*
PMM *vs.* Nonadherent dressings			
Proportion of ulcers healed[a]	1 trial (74 participants)	102 (-48 to 365) RR: 1.42 (0.8 to 2.51) Very Low (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PMM compared to nonadherent dressings on the proprortion of ulcers healed.*
Hydrocolloid *vs.* Nonadherent dressings			
Proportion of ulcers healed[a]	7 trial (245 participants)	10 (-36 to 70) RR: 1.04 (0.85 to 1.29) Very Low (Due to serious risk of bias, inconsistency and very serious imprecision)	*We are very uncertain about the effects of hydrocolloid compared to nonadherent dressings on the proprortion of ulcers healed.*
Foam *vs.* Nonadherent dressings			
Proportion of ulcers healed[a]	1 trial (132 participants)	36 (-22 to 106) RR: 1.15 (0.91 to 1.44) Low (Due to serious risk of bias and imprecision)	*Foam may have little to no effect on the proportion of ulcers healed compared to nonadherent dressings.*

[a] Assumed risk: 242/1000 (MID: 50/1000). Healing defined as complete epithelialisation.
CEAP: Clinical-Etiology-Anatomy-Pathophisiology; CIVIQ-20: Chronic Venous Disease Quality of Life Questionnaire; CVD: chronic venous disease; CI: confidence interval; OR: odds ratio; RR: risk ratio; MID: minimally important difference.

Population: Adults with venous leg ulcers managed in any care setting			
Zhao 2020 (trials published between inception to up to May 2019); 8 studies, including 1057 patients			
Frequentist random-effects pairwise meta-analysis			
Silver-containing dressings (various types) *vs.* Traditional dressings			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) Certainty of evidence	*GRADE Simple Language Summary*
Proportion of ulcers healed[a]	6 trials (812 participants)	70 more (0 to 150) Low (Due to serious risk of bias and imprecision)	*Silver-containing dressings may increase the proportion of ulcers healed when compared to traditional dressings.*

[a] Healing assessed by proportion of ulcers fully epithelialised.
CVD: chronic venous disease; CI: confidence interval; OR: odds ratio; RD: risk difference.

Population: Adults with venous leg ulcers managed in any care setting			
Ribeiro 2022 (trials published between inception to up to May 2021); 1 trials including 60 patients			
Frequentist random-effects pairwise meta-analysis			
Hydrogel *vs.* Gauze + saline			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) RR/MD (95% CI) Certainty of evidence	*GRADE Simple Language Summary*
Proportion of ulcers healed[a,b]	1 trial (60 participants)	433 (73 to 1542) RR: 5.33 (1.73 to 16.42) Very Low (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of Hydrogel on the proportion of ulcers healed when compared to gauze +saline.*
Changes in ulcer size from baseline (in cm)	1 trial (60 participants)	MD: -1.50 (-1.86 to -1.14) Low (Due to serious risk of bias and imprecision)	*Hydrogel may decrease ulcer size compared to gauze +saline*

[a] Assumed risk: 100/1000 (MID: 50/1000); [b] healing assessed by proportion of ulcers fully epithelialised.
CI: confidence interval; RR: risk ratio; MID: minimally important difference; MD: mean difference.

the costs associated with this condition amount to 1.2% of the national health budget, partly related to the use of advanced dressings.[2] For this reason, awareness regarding the validation of these products is of great importance.

The review conducted here included four meta-analyses published between 2015 and 2022, reporting certainty of evidence ranging from very low to low.[3-6] Only polyurethane foams and silver-based dressings reached at least a low level of evidence certainty, whereas alginates, cadexomer, protease modulators, hydrocolloids, and hydrogels remained at a very low level. All these studies emphasize the need for further high-quality publications, highlighting the frequent methodological weaknesses in research addressing this highly debilitating condition.[7]

A 2022 review including 43 randomized studies confirmed the lack of strong evidence supporting topical products for the treatment of venous ulcers.[8] Similarly, a 2022 Cochrane review demonstrated that even for ulcer cleansing there is a lack of evidence, particularly regarding polyhexamethylene biguanide *versus* saline solution, hydrogen peroxide versus sterile water, propylbetain and polyhexanide *versus* saline solution, or octenidine hydrochloride-phenoxyethanol *versus* Ringer's solution.[9]

Considering the literature cited above and the risk/benefit ratio, the panel recommends the use of polyurethane foams for exudative venous lesions and silver-based dressings for locally infected ulcers. The low certainty of evidence leads to a weak recommendation, specifically for lesions that are difficult to heal, defined as those that fail to resolve after six months of appropriate treatment.[10]

This work does not address the cost-effectiveness of advanced dressings. Future research on this topic is strongly encouraged, particularly in homogeneous populations with similar lesion types, including more complex cases (Table 6A, 6B, Figure 6).

Economic affordability considerations

Various dressings are available for venous ulceration, with variable efficacy. Cost-effectiveness data are both limited and necessary. In this assessment, the number of dressing changes is a critical factor. Thomas and Young, for example, compared Biatain Silicone with two alternative dressings. Biatain Silicone demonstrated better exudate management, reducing the frequency of dressing changes and consequently lowering the weekly cost per lesion.[79] The cost of ulcer management should include the average cost of a single intervention multiplied by the number of interventions. From the payer's perspective, this cost encompasses the dressing, related materials, and staff time (including travel costs in the case of home care). Cheng *et al.* provided an example of such a calculation in the Australian context.[80] A similar study in the Italian context is highly desirable.

Technical research notes

• **PICO:** in patients with venous or lymphatic ulceration (P), does the use of advanced dressings (I), in addition to cleansing and compression (C), improve the healing rate (O)?

• **Search string:** epistemonikos: title:(venous OR lymphatic) OR abstract:(venous OR lymphatic)) AND (title:(ulcer) OR abstract:(ulcer)) AND (title:(dressing) OR abstract:(dressing)) AND (title:(healing percentage OR time) OR abstract:(healing percentage OR time)). Medline via Ovid: ((venous or lymphatic).ti,ab.) AND (ulcer.ti,ab.) AND (dressing.ti,ab.) AND ("healing percentage".ti,ab. OR time.ti,ab.)

• **Inclusion criteria:**

Study Design	Partecipants	Intervention	Results	Publication Type	Language
Meta-analysis, systematic revisions	Age: 18-65 yo	Advanced dressings	Ulcer healing percentage	Original manuscript published in an indexed journal	English
	Venous-lymphatic ulcer				

• **Exclusion criteria:** all studies reporting: 1) populations, interventions, or comparators that are irrelevant; 2) data outside the time frame from September 2014 to September 2024; 3) language other than English.

• **Results:** four meta-analyses were identified, published between 2015 and 2022.[81-84] Following the literature review and expert discussion, the Development Group, together with the Surveillance Group, reached unanimous approval of the recommendation.

• **References indicating the link between evidence and recommendation:** 1) efficacy and Safety;[81-84] 2) patient values and preferences;[82] 3) feasibility.[81-84]

• **Important and/or critical outcomes not found in the literature:** healing rate in complicated lesions and related cost-effectiveness.[85-88]

Applicability

A) Facilitating factors

The use of advanced polyurethane and silver-based dressings is already established, making their application for specific indications, as recommended, highly feasible.

B) Barriers

None identified, except for the potential cost of the dressing, which may be offset by better ulcer management

and the consequent reduction in costs associated with the condition.

C) Suggestions and tools

Collaboration with scientific societies to promote both healthcare professional and public education regarding proper venous ulcer management.

D) Potential resource implications

• Increased use of advanced dressings, but reduced overall treatment costs due to effective ulcer management.

• Reduced workload for healthcare staff dedicated to ulcer care thanks to faster wound healing.

E) Monitoring indicators

• Consumption of advanced dressings

• Healing rates of skin lesions

Recommendation 7: Venous active drugs

In cases of venous-origin lower limb edema and/or pain, the use of MPFF, calcium dobesilate, rutosides, ruscus, or sulodexide is suggested compared to no treatment. The differing quality of evidence available for each drug should be acknowledged by both the physician and the patient (*Weak recommendation, in favor of the intervention, with certainty of evidence ranging from very low to moderate*).

Rationale

Modern venous-lymphatic practice based on scientific evidence must contend with a constantly growing market, including over-the-counter products that are not always properly validated, in line with the steady growth of the chronic venous insufficiency supplement business, with a projected compound annual growth rate of 9.5% by 2034.[89] Analgesics are among the most common OTC products (49.1%), particularly among women, younger individuals with limited education, and middle-to-lower socioeconomic urban populations.[90] In this context, analyzing the evidence related to products dedicated to venous and lymphatic disease becomes an ethical and sci-

TABLE 7A.—*Results of meta-analyses on the effect of venoactive drugs on lower limb pain control, compared with placebo.*

PAIN							
ref.	Bignamini 2020						Certainty of evidence range
Sulodexide			SMD 2.51 (1.2 to 3.82) VERY LOW (Due to study design, and risk of bias)	*We are very uncertain about the effects of suloxide compared to placebo on pain.*			Very low
ref.	Kakkos 2018		Martinez-Zapata 2020		Pompilio 2021		Certainty of evidence range
MPFF	SMD: -0.25 (-0.38 to -0.11) VERY LOW (Due to study design, serious risk of bias and imprecision)	We are very uncertain about the effects of MPFF compared to placebo on pain.	SMD: -0.23 (-0.41 to -0.05) MODERATE (Due to serious risk of bias)	*Diosmine, Hidrosmine probably have little to no difference on the risk of treatment failure compared to placebo*	MD: -6.10 (-119.06 to 90.70) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of MPFF compared to placebo on pain.*	Very low to moderate
ref.			Martinez-Zapata 2020		Pompilio 2021		Certainty of evidence range
Calcium dobesilate			SMD: -0.15 (-0.34 to 0.05) LOW (Due to serious risk of bias and imprecision)	*Calcium dobesilate may have little to no difference on the risk of treatment failure compared to placebo*	MD: 2.04 (-4.48 to 8.53) LOW (Due to serious risk of bias)	*Calcium dobesilate may have little to no difference on pain relief when compared to placebo.*	Low
ref.			Martinez-Zapata 2020		Pompilio 2021		Certainty of evidence range
Rutosides			SMD: -0.71 (-1.23 to -0.19) MODERATE (Due to serious risk of bias)	*Rutosides probably have little to no difference on the risk of adverse events compared to placebo*	MD: -1.35 (-98.64 to 63.02) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of Rutosides compared to placebo on pain.*	Very low to moderate
ref.					Pompilio 2021		Certainty of evidence range
Ruscus					MD: -1.51 (-22.51 to 19.08) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of Ruscus+HMC+VitC compared to placebo on pain.*	Very low

TABLE 7B.—*Results of meta-analyses on the effect of venoactive drugs on lower limb edema control, compared with placebo.*

EDEMA									
ref.	Bignamini 2020								Certainty of evidence range
Sulodexide			SMD 1.54 (0.97 to 2.1) VERY LOW (Due to study design, and risk of bias)	*We are very uncertain about the effects of suloxide compared to placebo on oedema*					very low
ref.	Kakkos 2018		Martinez-Zapata 2020		Pompilio 2021		Rabe 2023		Certainty of evidence range
MPFF	SMD: -0.59 (-1.15 to -0.02) VERY LOW (Due to study design, serious risk of bias and inconsistency)	*We are very uncertain about the effects of MPFF compared to placebo on ankle circumference.*	MD: -5.98 (-7.78 to -4.18) MODERATE (Due to serious risk of bias)	*Diosmine, Hidrosmine probably reduce ankle circumference compared to placebo.*	MD: -3.36 (-38.11 to 35.85) LOW (Due to serious risk of bias and imprecision)	*MPFF may reduce ankle circumference compared to placebo.*	MD: 6.7 (3.6 to 9.9) MODERATE (Due to serious risk of bias)	*MPFF probably reduces ankle circumference compared to placebo.*	very low to moderate
ref.	Martinez-Zapata 2020								Certainty of evidence range
Calcium dobesilate			MD: -1.69 (-4.84 to 1.47) MODERATE (Due to serious imprecision)	*Calcium dobesilate probably reduce anklw circumference compared to placebo*					moderate (one meta-analysis)
ref.	Martinez-Zapata 2020				Pompilio 2021				Certainty of evidence range
Rutosides			MD: -2.45 (-5.06 to 0.15) LOW (Due to serious risk of bias and imprecision)	*Rutosides may reduce ankle circumference compared to placebo.*	MD: -0.79 (-6.52 to 4.91) VERY LOW (Due to serious risk of bias, inconsistency and imprecision)	*We are very uncertain about the effects of rutosides compared to placebo on ankle circumference.*			very low/low
ref.	Pompilio 2021								Certainty of evidence range
Ruscus					MD: -2.43 (-5.29 to 0.27) LOW (Due to serious risk of bias and imprecision)	*Ruscus+HMC+VitC may reduce ankle circumference compared to placebo.*			low

entific duty.[91] For this reason, the panel focused on the effects of venoactive drugs (VADs) in terms of pain and edema control, leaving the analysis of their impact on other symptoms and signs, including venous skin ulceration, to another specifically designed work. A summary of the results found in the different sub-analyses is reported in Table 7A. MPFF, calcium dobesilate, ruscus, rutosides, and sulodexide were considered in light of the retrieved literature. The certainty of evidence regarding the drugs mentioned above in controlling pain and edema ranges from very low to moderate, clearly showing the need for studies with higher methodological quality to reach strong recommendations. This is also suggested by the significant discrepancies in evidence certainty reported for separate meta-analyses published even within a single year (Table 7A, 7B).[92, 93] No direct comparison between the different drugs can be performed, so all results are compared with placebo. Considering the sub-analysis of different drugs used for edema, MPFF was included in two meta-analyses with moderate certainty of evidence, in 2020 and 2023,[92, 94] one with low certainty in 2021,[93] and one with very low certainty in 2019.[95] Calcium dobesilate showed moderate certainty of evidence in edema control but was reported in only one meta-analysis.[92] Rutosides were included in two meta-analyses on edema, showing low and very low levels of evidence certainty in 2020 and 2021, respectively. The reduction in evidence certainty within a single year between publications confirms the need for methodological improvement for future investigations.[92, 93] Ruscus was evaluated for edema control in a 2021 meta-analysis reporting low certainty of evidence.[93] Sulodexide's effect on edema was reported in a 2020 meta-analysis with very low certainty of evidence.[96] In conclusion, all the drugs mentioned

Table 7C.—*Evidence to Decision Framework for Statement 7.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with venous-lymphatic disorders (P), are venoactive drugs (I) more effective than placebo (C) in controlling venous-origin edema and pain (O)?	The panel emphasizes that there are no specific protocols regarding dosage and duration of prescription for the various venoactive drugs that have demonstrated clinical superiority. Prescribers should tailor treatment to each individual case.	In cases of venous-origin lower limb edema and/or pain, the use of MPFF, calcium dobesilate, rutosides, ruscus, or sulodexide is suggested compared to no treatment. The differing quality of evidence available for each drug should be acknowledged by both the physician and the patient (WEAK recommendation, in FAVOR of the intervention, with certainty of evidence ranging from VERY LOW to MODERATE).	MPFF, calcium dobesilate, rutoside, ruscus, and sulodexide have demonstrated strong safety profiles along with potential clinical benefits.	Very low to moderate	Targeting the microcirculation is clinically important in the management of chronic venous disease. Promoting good clinical practice in this context is also essential to counteract products that, although available on the market, are not adequately scientifically validated.	This work does not consider cost-effectiveness. Venoactive drugs are currently not covered by the National Health Service. Cost-effectiveness evaluations are strongly encouraged.	The use of venoactive drugs is feasible and accepted by appropriately educated patients, also considering the minimal side effects and the potential clinical benefits.

Table 7D.—*Summary of Findings for recommendation 7.*

Population: Patients with CVD at any disease stage **Bignamini 2020 (trials published between inception to up to 30 April 2019); 13 trials** **Frequentist random-effects pairwise meta-analysis**			
Sulodexide *vs.* Control (heparan sulfate and placebo)			
Outcome [subgroup]	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) RR/SMD(95% CI) Certainty of evidence	*GRADE Simple Language Summary*
Pain*	1 study (927 participants)	SMD 2.51 (1.2 to 3.82) VERY LOW (Due to study design, and risk of bias)	*We are very uncertain about the effects of suloxide compared to placebo on pain.*
Edema (volume)*	4 study (1005 participants)	SMD 1.54 (0.97 to 2.1) VERY LOW (Due to study design, and risk of bias)	*We are very uncertain about the effects of suloxide compared to placebo on oedema.*
Adverse events[a]	2 trials (270 participants)	41 (-34 to 173) RR: 1.31 (0.74 to 2.32) LOW (Due to serious risk of bias and imprecision)	*Suloxide may have little to no difference on the risk of adverse events when compared to control group.*

[a] 131/1000 (MID: 100/1000).
*Meta-analyses t of overall proportion from studies reporting a single proportion.
CVD: chronic venous disease; CI: confidence interval; OR: odds ratio; RR: risk ratio; MID: minimally important difference.

above showed a potential effect on venous edema, with MPFF reporting the most abundant literature, confirmed by two meta-analyses of moderate certainty of evidence *versus* placebo.[92, 94] Calcium dobesilate probably reduces edema compared with placebo, being included in a single meta-analysis with moderate certainty of evidence.[92] Ruscus may reduce edema according to a single meta-analysis with low certainty of evidence,[93] while rutosides showed contradictory results, requiring future investigations.[92, 93] Similarly, considering the very low certainty of evidence for sulodexide's effect on edema, further studies are recommended to strengthen the recommendation (Table 7B).[93] Regarding pain control, MPFF was included in two meta-analyses showing very low certainty of evidence, in 2018 and 2021,[93, 95] as well as in a meta-analysis with moderate certainty in 2020.[92] Rutosides were included in two meta-analyses, showing moderate certainty in 2020 and very low in 2021, respectively. Again, the reduction in evidence certainty over a single year highlights the need for methodological improvement in future research.[92, 93] Ruscus was evaluated in 2021 in a meta-analysis with very low certainty of evidence.[93] Sulodexide's effect on pain was reported in a 2020 meta-analysis with very low certainty.[96] As with edema management, all the drugs mentioned above show a potential effect on pain associated with chronic venous insufficiency, with MPFF and

TABLE 7E.—*Summary of Findings for recommendation 7.*

Population: Patients with CVD in CEAP C6 class or C1-C5 classes **Pompilio 2021 (trials published between inception to up to February 2020); 45 trials and 18 observational studies** **Network meta-analysis**			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) MD (95% CI)	*GRADE Simple Language Summary*
Micronized purified flavonoid fraction (MPFF) *vs.* Placebo			
Pain VAS (0-100)	1 trial (592 participants)	MD: -6.10 (-119.06 to 90.70) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of MPFF compared to placebo on pain.*
Ankle circumference, in centimeters	4 trials (451 participants)	MD: -1.86 (-4.84 to 0.98) VERY LOW (Due to serious risk of bias, inconsistency and imprecision)	*We are very uncertain about the effects of MPFF compared to placebo on ankle circumference.*
CIVIQ-20 (0-100)	1 trial (592 participants)	MD: -3.36 (-38.11 to 35.85) LOW (Due to serious risk of bias and imprecision)	*MPFF may reduce ankle circumference compared to placebo.*
Ruscus extract combined with hesperidin methyl chalcone and vitamin C (Ruscus+HMC+VitC) *vs.* Placebo			
Pain VAS (0-100)	1 trial (148 participants)	MD: -1.51 (-22.51 to 19.08) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of Ruscus+HMC+VitC compared to placebo on pain.*
Ankle circumference, in centimeters	5 trials (324 participants)	MD: -2.43 (-5.29 to 0.27) LOW (Due to serious risk of bias and imprecision)	*Ruscus+HMC+VitC may reduce ankle circumference compared to placebo.*
Hydroxyethyl-rutosides (HR) *vs.* Placebo			
Pain VAS (0-100)	1 trial (35 participants)	MD: -1.35 (-98.64 to 63.02) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of HR compared to placebo on pain.*
Ankle circumference, in centimeters	1 trial (104 participants)	MD: -0.79 (-6.52 to 4.91) VERY LOW (Due to serious risk of bias, inconsistency and imprecision)	*We are very uncertain about the effects of HR compared to placebo on ankle circumference.*
Calcium dobesilate *vs.* Placebo			
Pain VAS (0-100)	2 trials (765 participants)	MD: 2.04 (-4.48 to 8.53) LOW (Due to serious risk of bias)	*Calcium dobesilate have little to no difference on pain relief when compared to placebo.*
CIVIQ-20 (0-100)	3 trials (1116 participants)	MD: 0.99 (-4.97 to 2.96) LOW (Due to serious risk of bias and imprecision)	*Calcium dobesilate may increase ankle circumference compared to placebo.*

Pain VAS (0-199) - MID 15.
Ankle circumference and CIVIQ-20: No MID was used for raing imprecision.
CEAP: Clinical-Etiology-Anatomy-Pathophisiology; CIVIQ-20: Chronic Venous Disease Quality of Life Questionnaire; CVD: chronic venous disease; CI: confidence interval; OR: odds ratio; RR: risk ratio; MID: minimally important difference.

TABLE 7F.—*Summary of Findings for recommendation 7.*

Population: Patients with venous leg ulcer **Sun 2024 (trials from 1990 to 12 June 2021); 13 trials** **Frequentist fixed-effects pairwise meta-analysis**			
Pentoxifylline *vs.* Placebo			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) OR (95% CI)	*GRADE Simple Language Summary*
Adverse events - gastrointestinal disturbances[a, b]	4 trials (421 participants)	49 (2 to 139) OR: 2.29 (1.04 to 5.03) LOW (Due to very serious imprecision)	*Pentoxifylline may have little to no difference on the risk of adverse evetns when compared to placebo.*

[a] Assumed risk: 42/1000 patients (MID: 100/1000); [b] healing assessed by proportion of ulcers fully epithelialised.
CI: confidence interval; OR: odds ratio; MID: minimally important difference.

rutosides reporting moderate certainty of evidence *versus* placebo.[92] At the same time, two other meta-analyses with very low certainty on MPFF[95] and rutosides[93] limited the related recommendation. Calcium dobesilate may reduce venous pain according to two meta-analyses with low certainty of evidence.[92, 93] Ruscus[93] and sulodexide[96] showed very low certainty in a single meta-analysis, so further research is recommended (Table 7C). All these drugs have

TABLE 7G.—*Summary of Findings for recommendation 7.*

Population: Patients with CVD **Kakkos 2018 (studies from inception up to December 14th, 2017)** **Frequentist fixed- and random-effects pairwise meta-analysis**			
Micronized purified flavonoid fraction (MPFF) *vs.* Placebo			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) RR (95% CI)	*GRADE Simple Language Summary*
Pain	1 trial 2 observational studies (839 participants)	SMD: -0.25 (-0.38 to -0.11) VERY LOW (Due to study design, serious risk of bias and imprecision)	*We are very uncertain about the effects of MPFF compared to placebo on pain.*
Ankle circumference, in centimeters	1 trial 2 observational studies (282 participants)	SMD: -0.59 (-1.15 to -0.02) VERY LOW (Due to study design, serious risk of bias and inconsistency)	*We are very uncertain about the effects of MPFF compared to placebo on ankle circumference.*
CI: confidence interval; RR: risk ratio; MID: minimally important difference; SMD: standardized mean difference			

Population:patients with chronic venous disease (CVD) **Rabe 2023 (Inception to April 2022); 8 studies involving 1635 patient** **Frequentist random-effects pairwise meta-analysis**			
Micronized purified flavonoid fraction (MPFF) *vs.* Placebo			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) RR (95% CI)	*GRADE Simple Language Summary*
Ankle circumference, in milimeters	4 trials (1274 participants)	MD: 6.7 (3.6 to 9.9) MODERATE (Due to serious risk of bias)	*MPFF probably reduces ankle circumference compared to placebo.*
Ankle circumference: no MID was used for imprecision rating. CI: confidence interval; MD: mean difference; MID: minimally important difference.			

demonstrated high safety profiles. Without considering cost-effectiveness and related sustainability aspects, the panel considered the potential benefits on edema and pain to outweigh the risks for all the drugs mentioned above, formulating a weak recommendation and highlighting that the certainty of evidence reaches at most a moderate value (Table 7A, 7B, 7C, 7D, 7E, 7F, 7G, 7H, Figure 7).

Economic affordability considerations

Venoactive drugs are often used in patients with lower limb drainage disorders. The study by Kalin highlights the need to identify the appropriate duration of prescription, taking into account the patient's status and the underlying need for a personalized approach.[97] There is a strong need for a high-quality randomized trial to improve both the baseline evidence and the potential reimbursement of validated products.

TECHNICAL RESEARCH NOTES

- **PICO:** in patients with venous-lymphatic disorders (P), are venoactive drugs (I) more effective than placebo (C) in controlling venous-origin edema and pain (O)?
- **Search string:** epistemonikos: (title:(chronic venous disease) OR abstract:(chronic venous disease)) AND (title:(lymphedema) OR abstract:(lymphedema)) OR (title:(venous active drugs) OR abstract:(venous active drugs)) (((venous) AND (active)) AND (drugs))) OR phlebotonics ((((mpff) OR (sulodexide)) OR (calicium dobesilate)) OR (ruthosides)) OR (horse chestnut) OR (Pentoxifylline). Medline via Ovid: ((chronic venous disease).ti,ab. and (lymphedema).ti,ab.) or (venous active drugs).ti,ab. ((venous and active and drugs).ti,ab.) or phlebotonics.ti,ab. (mpff or sulodexide or calcium dobesilate or ruthosides or horse chestnut or pentoxifylline).ti,ab.
- **Inclusion criteria:**

Study Design	Partecipants	Intervention	Results	Publication Type	Language
Meta-analysis, systematic revisions	Age: 18-65 yo	Venous active drugs	Edema	Original manuscript published in an indexed journal	English
	Venous-lymphatic disorder		Pain		

- **Exclusion criteria:** all studies reporting: 1) irrelevant populations, interventions, and comparators; 2) information not falling within the time frame between September 2014 and September 2024; 3) non-English language.
- **Result:** five meta-analyses, published between 2018 and 2023, were identified through the search.[92-96] Following the literature review and expert discussion, the Development Group, together with the Surveillance Group, unanimously approved the recommendation.

TABLE 7H.—*Summary of Findings for recommendation 7.*

Population: patients with venous insufficiency Martinez-Zapata 2020 (from inception to November 2019); 56 studies (7690 participants) Frequentist fixed- and random-effects pairwise meta-analysis			
Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) Point estimate (95% CI)	*GRADE Simple Language Summary*
Calcium dobesilate *vs.* Placebo			
Ankle circumference, in milimeters	3 trials (1475 participants)	MD: -1.69 (-4.84 to 1.47) MODERATE (Due to serious imprecision)	*Calcium dobesilate probably reduce ankle circumference compared to placebo.*
Pain	8 trials (10662 participants)	SMD: -0.15 (-0.34 to 0.05) LOW (Due to serious risk of bias and imprecision)	*Calcium dobesilate may have little to no difference on the risk of treatment failure compared to placebo.*
Adverse events[a]	4 trials (9108 participants)	23 (0 to 52) RR: 1.22 (1 to 1.49) MODERATE (Due to serious risk of bias)	*Calcium dobesilate probably have little to no difference on the risk of adverse events compared to placebo.*
Diosmine, Hidrosmine *vs.* Placebo			
Ankle circumference, in milimeters	3 trials (286 participants)	MD: -5.98 (-7.78 to -4.18) MODERATE (Due to serious risk of bias)	*Diosmine, Hidrosmine probably reduce ankle circumference compared to placebo.*
Pain	3 trials (846 participants)	SMD: -0.23 (-0.41 to -0.05) MODERATE (Due to serious risk of bias)	*Diosmine, Hidrosmine probably have little to no difference on the risk of adverse events compared to placebo.*
Adverse events[b]	9 trials (1429 participants)	-8 (-32 to 21) RR: 0.93 (0.72 to 1.19) MODERATE (Due to serious risk of bias)	*Diosmine, Hidrosmine probably have little to no difference on the risk of adverse events compared to placebo.*
Rutosides *vs.* Placebo			
Ankle circumference, in milimeters	7 trials (602 participants)	MD: -2.45 (-5.06 to 0.15) LOW (Due to serious risk of bias and imprecision)	*Rutosides may reduce ankle circumference compared to placebo.*
Pain	3 trials (219 participants)	SMD: -0.71 (-1.23 to -0.19) MODERATE (Due to serious risk of bias)	*Rutosides probably have little to no difference on the risk of adverse events compared to placebo.*
Adverse events[c]	14 trials (1329 participants)	31 (2 to 68) RR: 1.34 (1.02 to 1.76) MODERATE (Due to serious risk of bias)	*Rutosides probably have little to no difference on the risk of adverse events compared to placebo.*
Treatment failure[j] [5-10 years]	8 trials (62 participants)	153 (-34 to 662) RR: 2.07 (0.76 to 5.63) Low (Due to very serious imprecision)	*Short duration may increase the risk of treatment failure compared to longer duration.*
Aminaftone *vs.* Placebo			
Adverse events[d]	1 trial (79 participants)	-19 (-44 to 247) RR: 0.6 (0.06 to 6.32) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of aminaftone compared to placebo on adverse events.*
Centella asiatica *vs.* Placebo			
Adverse events[e]	1 trial (94 participants)	38 (-115 to 335) RR: 1.14 (0.58 to 2.23) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of Centella asiatica compared to placebo on adverse events*
Grape seed extract *vs.* Placebo			
Adverse events[f]	1 trial (75 participants)	-86 (-162 to 148) RR: 0.57 (0.19 to 1.74) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of grape seed extract compared to placebo on adverse events.*
French maritime pine bark *vs.* Placebo			
Pain	1 trial (40 participants)	SMD: -1.39 (-2.09 to -0.69) VERY LOW (Due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of French maritime pine bark compared to placebo on pain.*

[a] 105/1000 (MID: 50/1000); [b] 113/1000 (MID: 100/1000); [c] 90/1000 (MID: 100/1000); [d] 47/1000 (MID: 100/1000); [e] 273/1000 (MID: 100/1000); f 200/1000 (MID: 100/1000).
Ankle circumference: no MID was used for imprecision rating.
CI: confidence interval; RR: risk ratio; MD: mean difference; MID: minimally important difference; SMD: standardized mean difference.

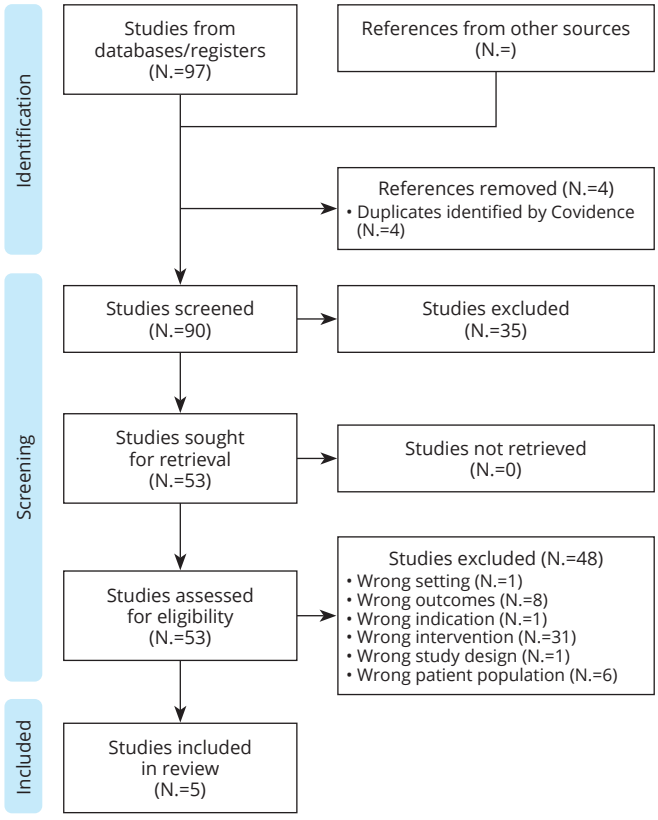

Figure 7.—PRISMA flow chart for recommendation 7.

• **References linking evidence to recommendation:** efficacy and safety;[92-96] patients' values and preferences;[92, 93] feasibility.[92, 93]

• **Important and/or critical outcomes not found in the literature:** subgroup analysis of edema control and venous leg pain across different ethnicities.[98, 99]

Applicability

A) Facilitating factors

The use of venoactive drugs is already common practice, although often accompanied by the use of substances not solidly validated by science. To promote the correct use of the most appropriate substances, it is useful to create targeted educational campaigns for both healthcare professionals and the general population.

B) Barriers

None, except for the potential cost of the drug, which could be offset by better management of venous disease and the consequent reduction in disease-associated costs.

C) Suggestions and tools

Collaboration with scientific societies to promote education for both healthcare professionals and the general population regarding the proper management of venous disease.

D) Potential resource implications

• Increased use of venoactive drugs but reduced costs associated with treatment due to effective management of venous disease.

• Decrease in the number of patients requiring venous surgical intervention.

E) Monitoring indicators

Consumption of venoactive drugs and the percentage of venous procedures avoided as a result of their effective administration.

Good clinical practice statement 8: Compression garment prescription

It is appropriate that graduated compression for discomfort of the lower limb due to venous and/or lymphatic disorder be prescribed by an experienced healthcare professional (*Good clinical practice recommendation based on unassessed quality of evidence*).

Rationale

Certified graduated compression is of primary importance in the management of venous and lymphatic disease. However, its effectiveness is influenced by patient compliance and proper prescription in general.[100] Appropriate compression must meet specific characteristics, including safety, correct microenvironment between skin and tissue, odor management, desired pressure gradient, and fit.[101] Unfortunately, the market also contains non-certified products that can confuse both prescribers and consumers.[102] A joint effort involving healthcare professionals, patients, institutions, and educators is necessary to achieve the full benefits of proper compression. In this regard, it has been shown that appropriate healthcare prescription of compression devices can improve patient compliance by up to 33%.[103] Another reason for non-compliance with validated products is the associated cost.[104] However, dedicated studies should highlight the overall cost of the disease and the potential cost control achievable through proper compression compared with non-certified products.[105] A survey involving 5070 healthcare professionals demonstrated that education on this topic can positively influence knowledge, attitudes, and practice regarding correct prescription and use of compression.[106] The literature clearly shows that not only prescription but also accurate sizing requires expertise, aimed at identifying the right product for the specific patient.[107] In Italy, compression products are considered Class I medical devices under

European regulation 2017/745, and the professional figure authorized to prescribe them is not clearly defined.[108] This represents a significant regulatory gap, considering that while compression is generally safe, it can also have potential contraindications and adverse effects if prescribed incorrectly.[109, 110] At the same time, what has traditionally been considered a contraindication may, in specific circumstances, represent an appropriate indication – for example, the use of a compression stocking specifically designed for a patient with arterial disease.[111] For all the reasons described above, scientific societies and institutions should highlight both the prescription and training requirements for those prescribing these products. Both healthcare professionals and consumers should be properly informed about the significant variability in product quality available on the market, as well as the necessity of consulting experienced professionals to avoid unnecessary – or even potentially harmful – compression, in favor of certified devices that can provide substantial benefits for both patients and the healthcare system (Table 8A, 8B, Figure 8).[1, 110]

Economic affordability considerations

Our research group has previously published on the cost-effectiveness of compression in healthy subjects exposed to prolonged orthostatism, reporting an annual benefit of € 1510 associated with reduced disease-related costs.[103] Similar scientific studies are needed to highlight the economic impact of proper compression in the context of venous and lymphatic disease.

TABLE 8A.—*Good Practice Statement for statement 8.*[4]

Process for developing good practice statement	**Supporting information**	**Verification**
Write Good Practice Statement		
Does the statement follow a PICO prioritization process?		X Yes o No
If you answered No → 1) Explain why the PICO question was not prioritized but is being addressed → avoid developing any type of actionable statement that acts as an independent response to the PICO question.		
Are the Population and Intervention components clear?		X Yes o No
If you answered No → Check whether you are developing an implementation consideration (refer to flow chart in Lotfi et al.(8))		
Items to complete	**Supporting information**	**Verification**
All the following criteria must be fulfilled *to consider the statement a GPS.*		
(1) Message is really necessary in regard to actual health care practice		This criterion has been addressed: X Yes o No
(2) Implementing the GPS results in a large net positive consequence (i.e. satisfy several evidence to decision (EtD) criteria) after consideration of all relevant outcomes and potential downstream consequences ** check the criteria considered in the development of the GPS.		This criterion has been addressed: X Yes o No **Evidence-to-Decision criteria** Importance of the problem [X] Certainty in effects [X] Variability and certainty in the importance of outcomes [X] Magnitude of resource requirements [X] Certainty of evidence of resource use [X] Cost-effectiveness [X] Equity [X] Acceptability [X] Feasibility [X]
(3) Collecting and summarizing the evidence is a poor use of a guideline panel's limited time, energy or		This criterion has been addressed: X Yes o No
resources. The opportunity cost of collecting and summarizing the evidence is large and can be avoided.		
(4) There is a well-documented clear and explicit rationale connecting the indirect evidence		This criterion has been addressed: X Yes o No
(5) Clear and actionable (This criterion should apply to any developed statement. For example, all formal recommendations are clear and actionable)		This criterion has been addressed: X Yes o No
Final judgement		
Did you answer Yes to ***all*** of the above?	X Yes Development as GPS is appropriate	
	o No Development as GPS is ***not*** appropriate → Revisit the PICO question and the importance of addressing it.	

Research technical notes

• **PICO:** in patients with venous-lymphatic insufficiency of the lower limb (P), is the prescription of compression stockings by a non-expert (I) less effective than

TABLE 8B.—*Evidence to Decision Framework, good practice statement 8.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/acceptability
In patients with venous-lymphatic insufficiency of the lower limb (P), is the prescription of compression stockings by a non-expert (I) less effective than that indicated by a specialist (C) for the improvement of discomfort (O)?	The venous-lymphatic patient is currently exposed to unclear prescription of lower limb compression supports and, consequently, to the risk of purchasing inadequate materials.	It is appropriate that graduated compression for discomfort of the lower limb due to venous and/or lymphatic disorder be prescribed by an experienced healthcare professional (good clinical practice recommendation based on unassessed quality of evidence).	The benefits of proper elastic compression in venous-lymphatic patients extend to the entire symptomatic spectrum of venous and lymphatic disease, as well as to the improvement of any associated edema. The only risks are related to inadequate prescription, not to the device itself.	Good practice statement	The primary value lies in the therapeutic efficacy associated with the certified graduated pressure delivered by a validated compression stocking. The preference is to protect the patient from products with unvalidated clinical performance.	This document does not address cost-effectiveness evaluations. However, the significant and positive clinical impact of adequate compression makes it reasonable to invest in its use in order to contain costs associated with disease progression.	Feasibility is high, considering the easy availability of certified compression products. An information campaign is necessary to distinguish between validated and non-validated products. Acceptability is high when prescribing healthcare personnel are well trained in selecting the appropriate type and size of stocking for each specific patient.

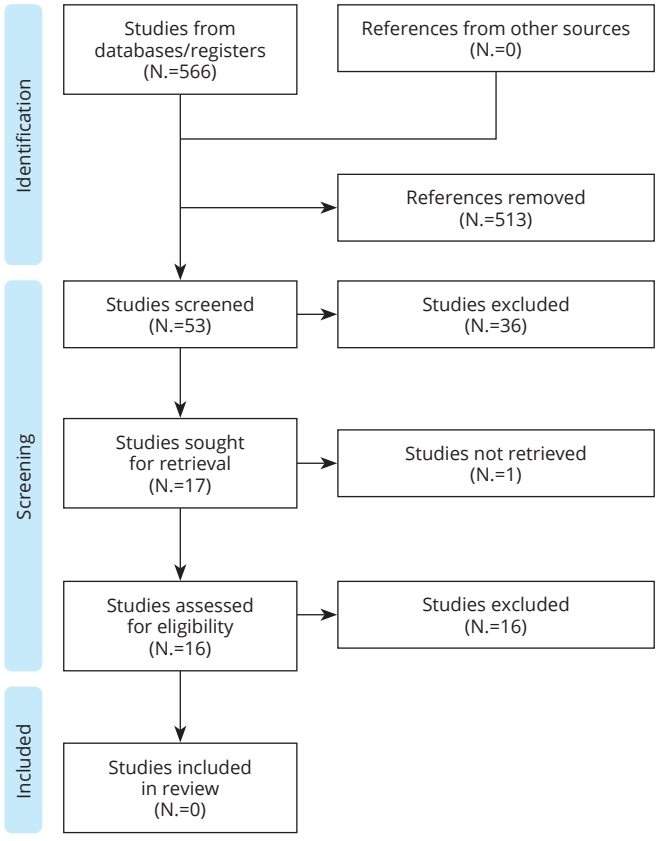

Figure 8.—PRISMA flow chart for statement 8.

that indicated by a specialist (C) for the improvement of discomfort (O)?

- **Search string:** ((compression stocking$).ti,ab. AND prescri$.ti,ab.) OR ((non-healthcare professional$ OR non healthcare professional$).ti,ab.)
- **PRISMA:** flow chart provided in Figure 8.

Good clinical practice recommendation

- 1. **The statement is genuinely necessary in the context of current clinical practice.**

The current context shows significant confusion in the prescription of compression devices, leading to the purchase of non-certified and clinically inadequate stockings. It is essential to draw healthcare and public attention to the importance of correct prescription of properly manufactured compression supports, rather than allowing the proliferation of an unethical market for inadequately validated stockings.

- 2. **Implementation of the Good Clinical Practice Recommendation results in a broad and positive effect, considering all relevant outcomes and potential downstream consequences.**

The correct use of validated compression significantly impacts both the clinical course and costs of venous and superficial disease, while the risk of complications is minimal and primarily associated with inadequate prescription.

- 3. **Collecting and summarizing the evidence would constitute a misuse of the panel's limited time, energy, and resources.**

The importance of adequate elastic compression for positive clinical impact, compared to non-validated stockings with graduated compression values, is evident from the pathophysiological rationale of venous and lymphatic disorders. Therefore, a detailed research and systematic review are considered inappropriate given the panel's limited time, energy, and resources.

- 4. **The indirect evidence is connected to a well-documented, clear, and explicit rationale.**

Evidence of the positive clinical impact of correct compression prescription for venous-lymphatic patients represents a clear and explicit rationale for the application of the Good Clinical Practice Recommendation presented here.

- 5. **The statement is clear and actionable.**

The statement is clear and implementable if collaboration is established with scientific societies, institutions, and healthcare providers involved in the sale of these products, ensuring both medical and public education on the topic.

Applicability

A) Facilitating factors

Validated compression devices are easily available throughout the country.

B) Barriers

There is a significant lack of healthcare and public education regarding the proper certification of scientifically validated compression devices. Information programs need to be implemented in this context.

C) Suggestions and tools

Establish a training requirement for healthcare personnel responsible for prescriptions to ensure patients are guided to the correct elastic support.

D) Potential resource implications

Reduction in costs related to the diagnosis and treatment of venous and lymphatic disease due to the positive clinical effect of proper elastic compression.

E) Monitoring indicators

Number of prescriptions for certified elastic supports compared to non-certified ones.

Good clinical practice statement 9: Treatment of lymphedema

In cases of lower limb lymphedema, it is appropriate that conservative treatment be carried out by experienced professionals for at least three months before considering a surgical approach. Both conservative and surgical approaches should be offered only by highly specialized centers, without ever discontinuing conservative protocols, even after a successful surgical procedure (*Good clinical practice statement based on unassessed quality of evidence*).

Rationale

Lymphedema remains a hidden epidemic requiring utmost attention to improve its management globally. Appropriate physical therapy – including compression, skin care, exercise, and manual lymphatic drainage – remains the cornerstone of treatment. Preventing fibrotic progression of fluid accumulation, as well as advancement to more severe stages, is of fundamental importance for both the patient and for controlling the impact on the healthcare system. Surgical options are available, with the two main procedures being lymphaticovenous anastomosis and vascularized lymph node transfer. The literature shows potential positive outcomes of lymphatic surgery in terms of lower limb volume control, improved quality of life, and a preventive effect on cellulitis.[111] However, these studies are primarily case reports and observational studies, without randomization against isolated conservative treatment.[112] The only comparative study identified in the literature was published by Mihara *et al.*, analyzing the addition of lymphaticovenous anastomosis after three months of conservative treatment versus continuation of conservative therapy alone. The study demonstrates potential surgical benefits in preventing cellulitis, but only at six months of follow-up, with no differences in limb circumference or pain. Thigh induration, however, was improved.[113] The certainty of evidence for this study was very low, making the related Good Clinical Practice Recommendation weak. Medium- to long-term follow-up of lymphaticovenous anastomosis is needed, considering the current evidence reporting 75% patency at 12 months and 36% at 24 months after surgery.[114] Furthermore, randomized trials comparing the surgical gold standard with conservative treatment are necessary to achieve a strong level of recommendation, not only regarding treatment indication but also concerning its timing. Currently, there is a high need to increase the certainty of evidence related to surgical treatment of lymphedema.[115] Based on the data above, the Good Clinical Practice Recommendation favors appropriately delivered conservative treatment: only in case of failure after at least three months should surgical intervention be considered. It must also be clearly stated that surgical procedures do not replace conservative treatment, considering the chronic nature of lymphedema. The three-month timeframe was identified to promptly interrupt the vicious cycle leading to fibrosis[116] and is supported by the data from Mihara *et al.*[113] Only highly specialized, high-volume centers should manage these patients, given the extreme expertise required for appropriate management, both conservative and surgical (Table 9A, 9B, Figure 9).[117]

Economic affordability evaluation

The cost of lymphedema was analyzed by Gutknecht *et al.* in 348 patients from the metropolitan area of Hamburg, Germany. The total cost was € 5784 per patient per year, with € 4445 (76.9%) for direct costs and € 1338 for indirect costs. The main expenditure items were manual lymphatic drainage massage and disability-related costs.[118] An analysis of costs at the Italian level is highly desirable, considering both conservative and surgical approaches.

Research technical notes

- **PICO:** in patients with lymphedema (P), does immediate surgical treatment (I) compared to an initial three-

TABLE 9A.—*Good practice statement checklist 9.*[4]

Process for developing good practice statement	**Supporting information**	**Verification**
Write Good Practice Statement		
Does the statement follow a PICO prioritization process?		☒ Yes ○ No
If you answered No → 1) Explain why the PICO question was not prioritized but is being addressed → avoid developing any type of actionable statement that acts as an independent response to the PICO question.		
Are the Population and Intervention components clear?		☒ Yes ○ No
If you answered No → Check whether you are developing an implementation consideration (refer to flow chart in Lotfi et al.(8))		
Items to complete	**Supporting information**	**Verification**
All the following criteria must be fulfilled *to consider the statement a GPS.*		
(1) Message is really necessary in regard to actual health care practice		This criterion has been addressed: ☒ Yes ○ No
(2) Implementing the GPS results in a large net positive consequence (i.e. satisfy several evidence to decision (EtD) criteria) after consideration of all relevant outcomes and potential downstream consequences ** check the criteria considered in the development of the GPS.		This criterion has been addressed: ☒ Yes ○ No **Evidence-to-Decision criteria** Importance of the problem ☒ Certainty in effects ☒ Variability and certainty in the importance of outcomes ☒ Magnitude of resource requirements ☒ Certainty of evidence of resource use ☒ Cost-effectiveness ☒ Equity ☒ Acceptability ☒ Feasibility ☒
(3) Collecting and summarizing the evidence is a poor use of a guideline panel's limited time, energy or		This criterion has been addressed: ☒ Yes ○ No
resources. The opportunity cost of collecting and summarizing the evidence is large and can be avoided.		
(4) There is a well-documented clear and explicit rationale connecting the indirect evidence		This criterion has been addressed: ☒ Yes ○ No
(5) Clear and actionable (This criterion should apply to any developed statement. For example, all formal recommendations are clear and actionable)		This criterion has been addressed: ☒ Yes ○ No
Final judgement		
Did you answer Yes to ***all*** of the above?	☒ Yes Development as GPS is appropriate	
	○ No Development as GPS is ***not*** appropriate → Revisit the PICO question and the importance of addressing it.	

TABLE 9B.—*Evidence to Decision Framework for Statement 9.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with lymphedema (P), does immediate surgical treatment (I) compared to an initial three-month conservative approach (C) lead to improvement in edema or a reduction in disease-related adverse events (O)?	A significant lack of randomized studies on the subject leads to the weakness of the present recommendation. It is mandatory to specify that only highly specialized centers can appropriately manage these patients, both surgically and conservatively.	In cases of lower limb lymphedema, it is appropriate that conservative treatment be carried out by experienced professionals for at least three months before considering a surgical approach. Both conservative and surgical approaches should be offered only by highly specialized centers, without ever discontinuing conservative protocols, even after a successful surgical procedure (good clinical practice recommendation based on unassessed quality of evidence).	The risk-benefit ratio of lymphatic surgery must be carefully evaluated, as strong evidence of its benefit is currently lacking.	good practice statement	The value conveyed by this recommendation balances the need to avoid overtreatment, particularly surgical, while at the same time ensuring the maximum benefit of care for a debilitating condition such as lymphedema. For this reason, a limited period of exclusively conservative treatment is recommended.	This work does not include cost-effectiveness analyses. Both the conservative and the surgical approaches entail significant costs, particularly considering the chronic nature of the condition.	The feasibility of lymphatic surgery is limited by the required highly specialized expertise, as well as by various anatomical and hemodynamic factors. Patient acceptability is generally good in light of the minimally invasive nature of the surgical procedure. Compliance with conservative treatment can be optimized through appropriate patient education.

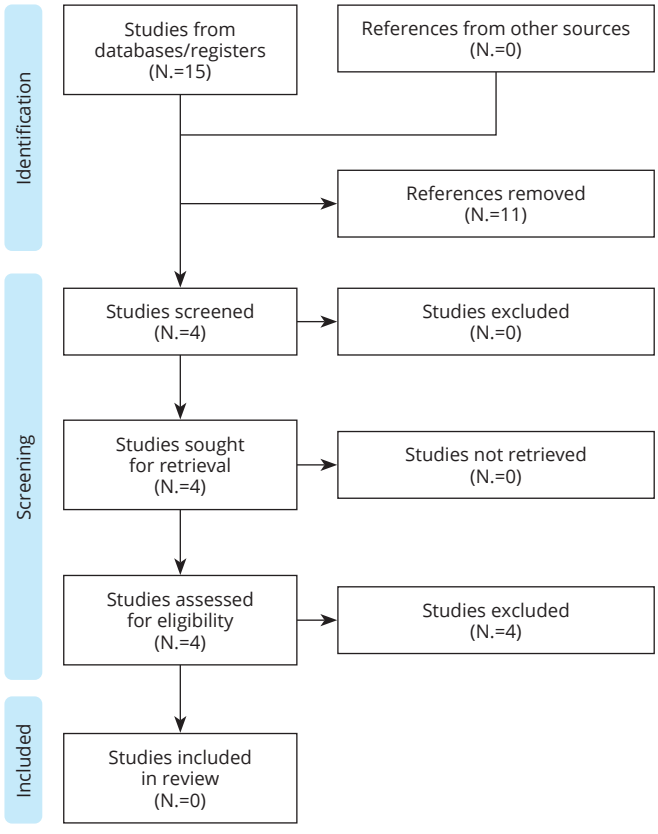

Figure 9.—PRISMA flow chart for statement 9.

month conservative approach (C) lead to improvement in edema or a reduction in disease-related adverse events (O)?

- **Search string:** (lymphedema).ti,ab. AND (lymphatic surgery).ti,ab. AND (conservative).ti,ab.
- **PRISMA:** flow chart provided in Figure 9.

Good clinical practice recommendation

- 1. **The statement is genuinely necessary in the context of current clinical practice.**

This recommendation is absolutely necessary given the current clinical context, characterized by a lack of appropriate highly specialized conservative management prior to potential surgical indication. It is also a priority to emphasize the importance of involving only highly specialized centers, considering the current risk of patients undergoing unnecessary or inappropriate surgery.

- 2. **Implementation of the Good Clinical Practice Recommendation results in a broad and positive effect, considering all relevant outcomes and potential downstream consequences.**

A proper highly specialized assessment with the possible implementation of an appropriate conservative therapeutic plan can reduce the eventual need for surgery, leading to a broad and positive effect for both patients and the national healthcare system.

• 3. **Collecting and summarizing the evidence would constitute a misuse of the panel's limited time, energy, and resources.**

Since lymphedema is a chronic condition, adding three months of evaluation and conservative management by highly specialized personnel represents an absolute benefit, potentially reducing the number of cases necessarily directed to surgery. Therefore, a detailed systematic review is considered inappropriate given the panel's limited time, energy, and resources.

• 4. **The indirect evidence is connected to a well-documented, clear, and explicit rationale.**

Evidence of the positive clinical impact of an adequate conservative approach to lymphedema, along with the lack of strong evidence supporting surgical intervention, represents a clear and explicit rationale for the application of the Good Clinical Practice Recommendation presented here.

• 5. **The statement is clear and actionable.**

The statement is clear and implementable when collaborating with scientific societies and institutions to increase healthcare and public education regarding the necessity of following standardized conservative care protocols rather than proceeding directly to surgical intervention.

Applicability

A) Facilitating factors

Conservative care protocols for lymphedema are already established and implementable nationwide. It is essential to promote their standardized adoption prior to any potential surgical indication.

B) Barriers

Lymphatic practice requires high specialization, making it necessary to enhance the expertise of healthcare personnel in this field.

C) Suggestions and tools

Establish training requirements for healthcare personnel dedicated to lymphedema management.

D) Potential resource implications

Increase in workload for personnel dedicated to lymphedema care, but also a reduction in healthcare costs associated with the condition, both due to slower disease progression and by limiting surgical indications.

E) Monitoring indicators

Number of patients no longer eligible for surgery after 3 months of appropriate conservative management.

Recommendation 10: Treatment of lipedema

In patients with lipedema, a ketogenic diet and liposuction are suggested only in selected cases, characterized by a significant impact on quality of life and after at least six months of ineffective conservative treatment by specialized centers, compared to no treatment (*Weak recommendation, against surgery, with very low certainty of evidence*).

Rationale

Lower limb lipedema is an abnormal inflammatory deposition of adipose tissue, presenting with easy bruising, pain, and physical and psychological disability.[119] Current therapeutic cornerstones include compression, physical therapy, exercise, diet, and, in selected cases, surgery.[119] The evidence regarding the specific type of compression to be used is limited, although a general benefit from compression in lymphedema has been reported.[120] Specific protocols for physical exercise and physical therapies are likewise lacking. Many types of diets have been proposed over the years, but none have demonstrated specific benefits. A meta-analysis on a ketogenic diet targeted at lipedema reported a potential benefit regarding body composition and anthropometric measures.[121] However, the certainty of evidence was very low, making it highly uncertain which type of diet should be recommended to patients with lipedema. In general, avoiding overweight is beneficial, although there is no clear correlation between lipedema and obesity. The surgical option is liposuction (dry, wet, super-wet, tumescent, laser-assisted, or megaliposuction).[122] Observational studies have demonstrated safety, feasibility, and persistent results up to 8 years of follow-up, but no investigation has demonstrated the superiority of surgical treatment over conservative treatment in randomized studies.[123, 124] A 2024 meta-analysis evaluated different liposuction techniques, highlighting that tumescent, power-assisted, and water-jet options may improve bruising, swelling, pressure sensitivity, and aesthetic outcomes. Water-jet liposuction was found to be more effective in reducing tissue tension and the overall impact of the condition, but there was significant heterogeneity across all outcomes and no comparison with conservative approaches. All studies in this meta-analysis were retrospective.[125] A potential role for shockwave therapy has been described, emphasizing the associated release of lipid peroxidation products from edematous dermis and a possible preventive effect on lipedematous sclerosis.[126] However, more data are needed before a formal recommendation can be made. Another 2024 meta-analysis analyzed liposuction without comparisons to other therapeutic approaches, focusing instead on pre- and post-intervention data. The certainty of evidence was very low, preventing conclu-

sions regarding the effects of liposuction on edema, pain, bruising, mobility, and quality of life (Table 10A).[121] This limitation is primarily due to methodological issues in the systematic reviews conducted by Amato, which reported data and differences within intervention groups without providing comparators. The absence of comparison groups is a critical limitation, as it prevents evaluation of the intervention effect relative to alternatives or controls. Without a comparator, it is impossible to determine whether the observed results are attributable to the intervention itself or confounding factors. Consequently, the findings lack the contextual rigor necessary to draw definitive conclusions regarding the true effect of the intervention. In light of the data above, the recommendation is to wait at least six months of appropriate conservative care before considering a ketogenic diet and/or liposuction surgery. Management of these patients should be conducted only in highly specialized centers (Table 10A, 10B, Figure 10).

Economic affordability considerations

To our knowledge, cost-effectiveness data on lipedema and its management are not available. Studies on this topic, including both direct and indirect costs, are strongly recommended.

Technical research notes

- **PICO:** in patients with lipedema (P), are immediate surgical procedures or a specific diet (I) superior to con-

Table 10A.—*Summary of Findings for recommendation 10.*

Population: Women diagnosed with lipedema based on the manifestation of typical clinical signs **Amato 2024 (studies published between inception up to January 15, 2024); 7 studies** **Frequentist random-effects pairwise meta-analysis**			
Low-carbohydrate, high-fat (LCHF) ketogenic diets (pre- and post-intervetion)			
Outcome	Number of trials (participants)	MD (95% CI)* Certainty of evidence	*GRADE Simple Language Summary*
Lean Body Mass (Kg)	3 studies (151 participants)	MD: -2.1 (-0.61 to -3.59) VERY LOW (Due to study design and serious risk of bias)	*We are very uncertain about the effects of Low-carbohydrate, high-fat (LCHF) ketogenic diets on LBM.*
Waist/Hip ratio	4 studies (121 participants)	0 (0.01 to -0.01) VERY LOW (Due to study design, serious risk of bias and imprecision)	*We are very uncertain about the effects of Low-carbohydrate, high-fat (LCHF) ketogenic diets on waist/hip ratio.*
Pain sensitivity (VAS 0-10)	4 studies (102 participants)	MD: -1.12 (-0.44 to -1.79) VERY LOW (Due to study design and serious risk of bias)	*We are very uncertain about the effects of Low-carbohydrate, high-fat (LCHF) ketogenic diets on pain sensitivity.*
*Mean difference pre- and post-intervention. CI: confidence interval; MD: mean difference			

Population: People with chronic venous insufficiency (CEAP 2–6) **Amato 2024 (trials published between inception to up to August 2024); 7 studies** **Frequentist random-effects pairwise meta-analysis**			
Outcome	Number of trials (participants)	MD (95% CI)* Certainty of evidence	*GRADE Simple Language Summary*
Liposuction for lipoedema (pre- and post-intervetion)			
Pain (VAS 0-10)	4 studies (224 participants)	MD:-4.73 (-3.68 to -5.77) VERY LOW (Due to study design and serious risk of bias)	*We are very uncertain about the effects of liposuction on pain.*
Edema (VAS 0-10)	1 study (63 participants)	MD: -5.23 (-4.51 to -5.95) VERY LOW (Due to study design and serious risk of bias)	*We are very uncertain about the effects of liposuction on edema.*
Bruising (VAS 0-10)	2 studies (88 participants)	MD:-3.54 (-1.18 to -5.9) VERY LOW (Due to study design and serious risk of bias and inconsistency)	*We are very uncertain about the effects of liposuction on bruising.*
Mobility impairment (VAS 0-10)	1 study (63 participants)	MD: -4.68 (-3.88 to -5.48) VERY LOW (Due to study design and serious risk of bias)	*We are very uncertain about the effects of liposuction on mobility.*
Quality of Life (VAS 0-10)[c]	1 study (50 participants)	MD:-4.1 (-2.26 to -5.94) VERY LOW (Due to study design and serious risk of bias)	*We are very uncertain about the effects of liposuction on quality of life.*
CI: confidence interval; MD: mean difference.			

TABLE 10B.—*Evidence to Decision Framework for Statement 10.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with lipedema (P), are immediate surgical procedures or a specific diet (I) superior to conservative treatment (C) in reducing pain, edema, bruising, improving quality of life, anthropometric parameters, and mobility (O)?	While liposuction has demonstrated safety and feasibility in expert hands and when following appropriate indications, no comparative study has analyzed its outcomes versus conservative management. The same applies to a ketogenic diet for patients with lipedema.	In patients with lipedema, a ketogenic diet and liposuction are suggested only in selected cases, characterized by a significant impact on quality of life and after at least six months of ineffective conservative treatment by specialized centers, compared to no treatment (WEAK recommendation, AGAINST surgery, with VERY LOW certainty of evidence).	The benefit of liposuction and/or a ketogenic diet in the context of lipedema is unclear. Considering that both practices may lead to adverse events, extreme caution must be exercised in their indication.	Very low	The key values emphasized by this recommendation consist of promoting the most effective conservative approach to lipedema, while also considering the persistence of the pathological condition even after potential surgical or dietary interventions.	This work did not include a cost-effectiveness assessment, the execution of which is recommended, particularly in the surgical context.	Both liposuction and a ketogenic diet have demonstrated feasibility. Acceptability may be limited by the invasive nature of surgery and by patient compliance with the diet.

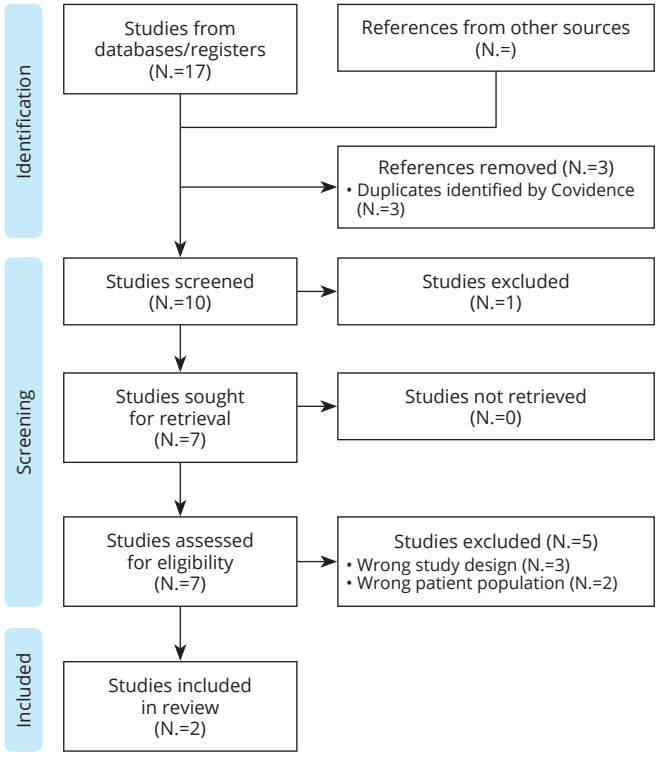

Figure 10.—PRISMA flow chart for recommendation 10.

servative treatment (C) in reducing pain, edema, bruising, improving quality of life, anthropometric parameters, and mobility (O)?

• **Search string:** epistemonikos: (title:(lipedema) OR abstract:(lipedema)) AND (title:(treatment) OR abstract:(treatment)). Medline: (lipedema).ti,ab. AND (treatment).ti,ab.

• **Inclusion criteria:**

Study Design	Partecipants	Intervention	Results	Publication Type	Language
Meta-analysis, systematic revisions	Age: 18-65 yo	Lipedema surgery	Pain, edema, hematoma, quality of life, anthropometric parameters, mobility	Original manuscript published in an indexed journal	English
	Lipedema	Diet	Pain		

• **Exclusion criteria:** all studies reporting: 1) populations, interventions, or comparators that are irrelevant; 2) information outside the time frame from September 2014 to September 2024; 3) languages other than English.

• **Results:** two meta-analyses were identified and evaluated.[121]

• **References linking evidence to recommendation:** 1) efficacy and safety;[121] 2) patient values and preferences;[121] 3) feasibility.[121]

• **Important and/or critical outcomes not found in the literature:** subanalysis of post-procedural control across different stages of lipedema.

Applicability

A) Facilitating factors

Recommended treatment protocols are already available nationwide. Dissemination of correct principles and

appropriate care timelines would facilitate immediate implementation of the recommendation.

B) Barriers

Dedicated diagnostic and therapeutic care pathways are still lacking, which would allow organized and facilitated access to treatment.

C) Suggestions and tools

• 1. Collaboration between scientific societies and institutions to increase professional health education on the topic, as well as public awareness of the lipedema issue.

• 2. Creation of a dedicated diagnostic-therapeutic care pathway, including lifestyle aspects along with precise procedural indications.

D) Potential resource implications

Increase in workload for personnel dedicated to lipedema care, but also a reduction in healthcare costs associated with the condition, both due to slower disease progression and limitation of surgical indications.

E) Monitoring indicators

Number of patients no longer eligible for surgery after 6 months of appropriate conservative management.

Good clinical practice statement 11: Echo-color-Doppler for teleangectasia treatment

It is appropriate to perform a venous color Doppler ultrasound screening before treating venous aesthetic conditions of the lower limb (teleangectasia and reticular veins) (*Good clinical practice statement based on evidence of unassessed quality*).

Rationale

A constant increase in the demand for aesthetic treatments has been reported, partly associated with the widespread use of social media.[127] This trend includes lower limb telangiectasias, with an estimated compound annual growth rate of 8.2% from 2023 to 2031.[128] While these venous procedures are typically performed for aesthetic purposes, an underlying pathological alteration of venous drainage may go unrecognized in the absence of proper ultrasound screening. This is consistent with findings showing that 26% of telangiectasias present underlying pathological reflux,[129] and that 65% of cases are directly fed by an incompetent perforating vein.[130] Inadequate treatment of these patients not only prevents the achievement of satisfactory aesthetic results but may also worsen venous drainage in the limb. Moreover, the treatment of telangiectasias usually requires multiple sessions, the strategic planning of which demands both clinical and ultrasound assessment. The latter is also essential for evaluating previous treatments and identifying possible complications, including thrombosis of non-targeted vessels.[131] Unfortunately, an "infodemic" is present on social media and other communication platforms, exposing patients to poorly delivered procedures often performed without appropriate evaluation of limb drainage. The Good Clinical Practice Recommendation to always perform a color Doppler ultrasound screening before any aesthetic telangiectasia treatment underscores the ethical principles of aesthetic medicine, as emphasized in a dedicated publication from 2024 (Table 11A, 11B, Figure 11).[132]

Economic affordability considerations

An evaluation of the cost of the ultrasound procedure is both lacking in the literature and necessary to determine the public sustainability of the related Good Clinical Practice Recommendation.

Technical research notes

• **PICO:** in patients with lower limb venous aesthetic disorders (P), is ultrasound identification and treatment of any underlying reflux (I), compared to treatment of the telangiectasia alone (C), more effective in reducing recurrence (O)?

TABLE 11A.—*Good practice statement checklist, statement 11.*[4]

Process for developing good practice statement	**Supporting information**	**Verification**
Write Good Practice Statement		
Does the statement follow a PICO prioritization process?		X Yes o No
If you answered No → 1) Explain why the PICO question was not prioritized but is being addressed → avoid developing any type of actionable statement that acts as an independent response to the PICO question.		
Are the Population and Intervention components clear?		X Yes o No
If you answered No → Check whether you are developing an implementation consideration (refer to flow chart in Lotfi et al.(8))		
Items to complete	**Supporting information**	**Verification**
All the following criteria must be fulfilled *to consider the statement a GPS.*		
(1) Message is really necessary in regard to actual health care practice		This criterion has been addressed: X Yes o No
(2) Implementing the GPS results in a large net positive consequence (i.e. satisfy several evidence to decision (EtD) criteria) after consideration of all relevant outcomes and potential downstream consequences ** check the criteria considered in the development of the GPS.		This criterion has been addressed: X Yes o No **Evidence-to-Decision criteria** Importance of the problem [X] Certainty in effects [X] Variability and certainty in the importance of outcomes [X] Magnitude of resource requirements [X] Certainty of evidence of resource use [X] Cost-effectiveness [X] Equity [X] Acceptability [X] Feasibility [X]
(3) Collecting and summarizing the evidence is a poor use of a guideline panel's limited time, energy or		This criterion has been addressed: X Yes o No
resources. The opportunity cost of collecting and summarizing the evidence is large and can be avoided.		
(4) There is a well-documented clear and explicit rationale connecting the indirect evidence		This criterion has been addressed: X Yes o No
(5) Clear and actionable (This criterion should apply to any developed statement. For example, all formal recommendations are clear and actionable)		This criterion has been addressed: X Yes o No
Final judgement		
Did you answer Yes to ***all*** of the above?	X Yes Development as GPS is appropriate	
	o No Development as GPS is ***not*** appropriate → Revisit the PICO question and the importance of addressing it.	

TABLE 11B.—*Evidence to Decision Framework for Statement 11.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with venous aesthetic disorders of the lower limb (P), is ultrasound identification and treatment of any underlying reflux (I), compared with treatment of telangiectasia alone (C), more appropriate for reducing recurrences (O)?	Sub-analyses related to different cutaneous phenotypes are necessary for an accurate evaluation of populations of different ethnicities.	It is appropriate to perform venous color Doppler ultrasound screening before treating venous aesthetic disorders of the lower limb.	The benefit is observed mainly in the optimization of aesthetic outcomes and in the reduction of recurrences. The risks are minimal and are more associated with medical inexperience than with the procedure itself, which is inherently extremely safe.	Good Practice Statement	The value lies in promoting a procedure that addresses both the aesthetic and therapeutic aspects associated with the cosmetic disorder itself. Preference is given to an aesthetic approach that is durable and consistent in its results, not only in the short term.	The sustainability assessment falls outside the scope of this document; however, the cost of adding an evaluation and possible treatment of the feeder veins supplying the capillary cosmetic disorders is easily offset by the cost of alternatively repeating more superficial aesthetic sessions.	The addition of ultrasound examination and possible treatment of the veins supplying the capillaries is extremely feasible considering the wide availability of Doppler equipment and treatment instruments. Acceptability is high considering the minimally invasive nature of the procedure.

• **Search string:** (ultrasound).ti,ab. AND ((teleangiectasia OR spider vein$).ti,ab.)
• **PRISMA:** flow chart provided in Figure 11.

Good clinical practice recommendation

• 1. **Necessity of the Statement in Current Clinical Practice.**

The statement is absolutely necessary given the current clinical context, which is characterized by a trend toward treating superficial capillary aesthetic defects without prior assessment of any underlying pathological venous circulation.

• 2. **Expected Impact of Implementing the Recommendation.**

Proper evaluation of the circulation underlying superficial capillary blemishes leads to a significant positive outcome, allowing the identification and management of any underlying pathology and reducing the likelihood of aesthetic recurrence.

• 3. **Feasibility of Evidence Collection.**

Based on the pathophysiological principle that capillary blemishes arise from underlying venous hypertension, the appropriateness of correctly assessing and, if necessary, treating the feeding veins of these telangiectasias is evident. For this reason, a detailed systematic review or extensive evidence collection is considered inappropriate given the panel's limited time, energy, and resources.

• 4. **Rationale Supported by Indirect Evidence.**

Evidence of telangiectasia recurrence due to persistent underlying venous sources provides clear, explicit, and well-documented indirect support for the rationale of this Good Clinical Practice Recommendation.

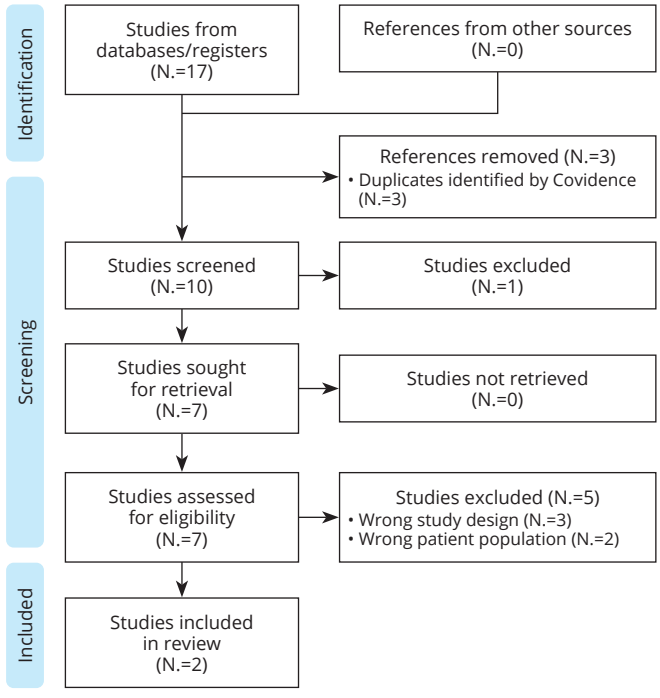

Figure 11.—PRISMA flow chart for statement 11.

• 5. **Clarity and Implementability.**

The recommendation is clear and feasible, given the ready availability of ultrasound assessment and the instruments necessary for treatment.

Applicability

A) Facilitating Factors

Ultrasound assessment and the instruments necessary

for the treatment of any feeding vein are and form part of the standard equipment in phlebology clinics.

B) Barriers

Ultrasound-guided treatments require a higher level of professional expertise than simple direct injections, so physicians interested in this practice must receive appropriate training.

C) Recommendations and Tools

Development of training requirements for healthcare personnel dedicated to the management of venous aesthetic blemishes.

D) Potential Resource Implications

Since this concerns an aesthetic matter, there is no need for significant involvement of public healthcare resources. Instead, it is recommended to implement campaigns to prevent superficial treatments performed without adequate experience or awareness of the underlying venous health.

E) Monitoring Indicators

Number of screening venous ultrasound assessments performed prior to aesthetic treatment.

Recommendation 12: Platelet-rich plasma in the treatment of venous ulcers

Platelet-rich plasma (PRP) is suggested for venous ulcers that are difficult to heal, compared to debridement and compression alone (*Weak recommendation, in favor of the intervention, with low certainty of evidence*).

Rationale

PRP, along with the broader field of regenerative medicine, has gained increasing interest within the medical community due to its potential clinical benefits.[133] PRP consists of plasma with a platelet concentration higher than that found in human blood. Its content of growth factors and anti-inflammatory mediators has the potential to positively affect the inflammatory processes and protease imbalances typical of venous ulcer beds.[134] A concentration-dependent effect has not been demonstrated; in fact, concentrations greater than 2.5 times baseline may have inhibitory effects.[135] No meta-analysis specifically dedicated to PRP in the context of veno-lymphatic ulcers is currently available in the literature; therefore, our research group conducted one. Our analysis included seven randomized controlled trials published between 2016 and 2021. The evaluation compared PRP versus control, platelet gel *versus* control, and PRP *versus* platelet gel. The control group included compression therapy and advanced dressings.[136-142] The meta-analysis showed that PRP may reduce ulcer size compared with control, but with low certainty of evidence. With very low certainty of evidence, PRP may also promote ulcer healing compared with both control and platelet gel. Similar results were found when comparing platelet gel to control (Table 12B). Based on the data above, it is not possible to make strong recommendations regarding the use of PRP in the treatment of venous ulcers. However, considering its potential to accelerate tissue regeneration of the ulcer bed, PRP may represent a valid option for difficult-to-heal lesions. It is essential to plan cost-effectiveness studies, particularly in light of the potential time savings in the management of ulcerative disease (Table 12A, 12B, Figure 12). The detailed meta-analysis is reported in the Appendix 1.

Economic affordability considerations

A meta-analysis explored the cost-effectiveness of PRP in venous ulcers, reporting a possible but uncertain benefit.[143] Further research on the topic is needed, including the cost of facilities and personnel over multiple visits.

Table 12A.—*Evidence to Decision: statement 12.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with veno-lymphatic ulceration (P), does PRP (I) improve the healing rate (O) compared with standard treatment (C)?	The recommendation does not address cost-effectiveness or the optimal concentration of PRP. Further research is needed to analyze homogeneous ulcer populations and clinically complex cases.	Platelet-Rich Plasma (PRP) is suggested for venous ulcers that are difficult to heal, compared to debridement and compression alone (WEAK recommendation, IN FAVOR of the intervention, with LOW certainty of evidence).	Considering the demonstrated safety profile of PRP and the need to improve the management of ulcerative disease, the addition of PRP after several months of unsuccessful treatment of venous ulcers is deemed appropriate.	Low	The value considered is based on the impact of venous ulcer disease on both the patient and the healthcare system, particularly regarding hard-to-heal venous ulcers.	This work does not consider cost-effectiveness. Future research on this topic is of primary importance.	PRP preparation is quick and easy to perform, with minimal impact on traditional clinical practice and patient acceptability.

TABLE 12B.—*Summary of findings for statement 12.*

Population: Patients with vein or lymphatic ulcers 7 trials (304 participants) Bayesian Network meta-analysis			
Outcome	Number of trials (participants)	Absolute risk per 1000 (95%CI) OR/MD (95% CI) Certainty of evidence	*GRADE Simple Language Summary*
PRP *vs.* Control			
Healing rate[a]	5 trials (252 participants)	280 more (123 fewer to 471 more) OR: 3.41 (0.6, 19.52) VERY LOW (due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PRP compared to control on healing rate.*
Ulcer size (cm)[c]	3 trials (222 participants)	MD: -4.42 (-7.06, -1.94) LOW (due to risk of bias and inconsistency)	*PRP may reduce ulcer size compared to control.*
Platelet Gel *vs.* Control			
Healing rate[a]	1 trial (40 participants)	105 fewer (475 fewer to 459 more) OR: 0.65 (0.02, 15.64) VERY LOW (due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of Platelet gel compared to control on healing rate.*
Ulcer size (cm)[c]	1 trial (40 participants)	MD: -3.19 (-8.03, 1.38) VERY LOW (due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of Platelet gel compared to control on ulcer size.*
PRP *vs.* Platelet Gel			
Healing rate[b]	1 trial (40 participants)	354 more (303 fewer to 518 more) OR: 5.35 (0.23, 148.62) (due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PRP compared to platelet gel on healing rate.*
Ulcer size (cm)[c]	1 trial (40 participants)	MD: -1.23 (-5.54, 3.27) (due to serious risk of bias and very serious imprecision)	*We are very uncertain about the effects of PRP compared to platelet gel on ulcer size.*

[a] Assumed risk: 475/1000 (MID 50/1000); [b] assumed risk: 800/1000 (MID 50/1000); [c] MID: 1 cm.
CI: confidence interval; OR: odds ratio; MD: mean difference.

Technical research notes

• **PICO:** in patients with veno-lymphatic ulceration (P), does PRP (I) improve the healing rate (O) compared with standard treatment (C)?

• **Search string:** epistemonikos: **(**title:(regenerative) OR abstract:(regenerative)) AND (title:(ulcer) OR abstract:(ulcer)). Medline: **(**regenerative).ti,ab. AND (ulcer).ti,ab.

• **Inclusion criteria:**

Study Design	Partecipants	Intervention	Results	Publication Type	Language
Meta-analysis, systematic revisions	Age: 18-65 yo	Platelet rich plasma treatment	Ulcer healing percentage	Original manuscript published in an indexed journal	English
	Venous-lymphatic ulcer				

• **Exclusion criteria:** all studies reporting: 1) populations, interventions, or comparators deemed irrelevant; 2) information outside the time frame between September 2014 and September 2024; 3) languages other than English.

• **Result:** the identified articles enabled the production of a new meta-analysis, reported in the appendix, from which the "Evidence to Decision Framework" was devel-

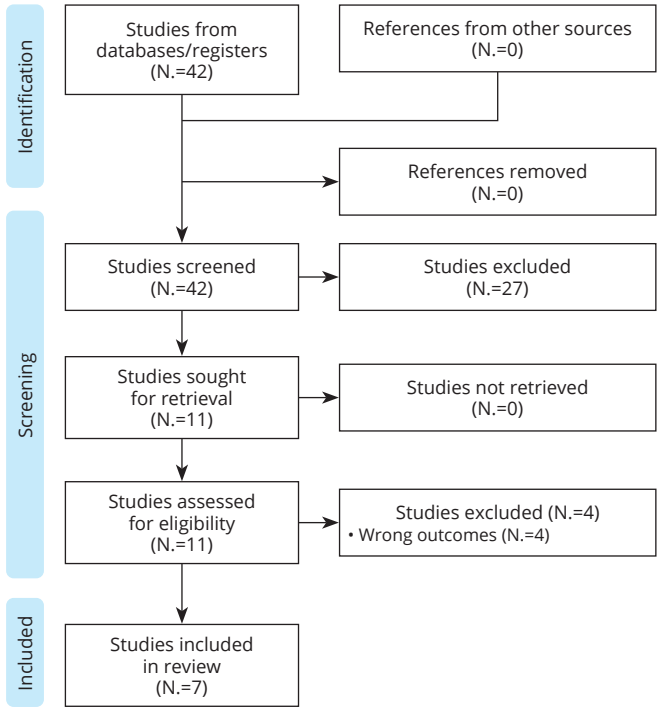

Figure 12.—PRISMA flow chart for Statement 12.

oped (Table 12A). Following the literature review and expert discussion, the Development Group, together with the Surveillance Group, reached unanimous approval of the recommendation.

• **References linking evidence to recommendation:** 1) efficacy and safety;[136-142] 2) patient values and preferences;[138-140] 3) feasibility.[138, 139]

• **Important and/or critical outcomes not found in the literature:** healing rate of complicated veno-lymphatic ulcers.

Applicability

A) Facilitating factors

The established use of PRP in various medical fields nationwide facilitates its application in the context of veno-lymphatic ulcers.

B) Barriers

The use of PRP requires training of healthcare personnel to identify appropriate patients and treatment protocols.

C) Suggestions and tools

Collaboration between scientific societies and institutions to disseminate knowledge on the correct use of PRP in the context of veno-lymphatic ulcers.

D) Potential resource implications

Possible reduction in the impact on resources currently devoted to the treatment of veno-lymphatic ulcers, due to the relatively low cost and significant efficacy of PRP in this care setting.

E) Monitoring indicators

Number of PRP treatments performed for veno-lymphatic skin lesions.

Good clinical practice statement 13: Veno-lymphatic diet

In patients with veno-lymphatic disorders of the lower limbs, it is advisable to avoid both obesity and excessive thinness, while promoting adequate hydration. There is no evidence supporting specific diets, foods, or beverages that have a significant impact on venous-lymphatic drainage (*Good clinical practice statement based on unassessed quality of evidence*).

Rationale

Diet and weight management are of great importance for general health, but specific evidence in the veno-lymphatic context is lacking. Obesity is a well-known risk factor for venous disease of the lower limbs.[144] Diets leading to obesity have also been associated with the development of lymphedema.[145] At the same time, evidence shows that pelvic venous reflux is favored by thinness.[146] Maintaining a normal weight is therefore very important, not only for veno-lymphatic disorders but also in the context of lipedema. Regarding lipedema, weight reduction has demonstrated a positive impact on quality of life, while low-carbohydrate dietary regimens have been associated with pain reduction.[147] A 2024 meta-analysis highlighted a possible positive role of the ketogenic diet in lipedema management.[121] Additionally, the use of dietary fiber to counteract constipation has been associated with a reduced risk of developing varicose veins in a large male population. However, this finding was not confirmed in women, and in general, in Western populations, no correlations have been identified between fiber intake, constipation, and venous risk.[148] Conversely, a recent Taiwanese study, therefore limited to the Asian population, suggested that vegetarian men – but not women – are more prone to developing varicosities. In the same study, women showed a higher risk of developing varicosities compared with men, regardless of diet type.[149] A systematic review highlighted that fish consumption does not alter thromboembolic risk.[150] Similarly, intermittent fasting diets should be approached with caution to avoid potential complications: a recent study emphasized the need to monitor dehydration associated with diet and the consequent thromboembolic risk.[151] The same focus on diet and thromboembolic risk was highlighted during the COVID-19 pandemic.[152] A systematic review demonstrated that limiting vitamin K intake does not alter the effect of anticoagulants antagonizing this vitamin.[153] Conversely, in patients with chronic venous insufficiency not taking vitamin K antagonists, a potential effect on coagulation has been hypothesized for vitamin E.[154] Preliminary evidence suggests that specific elements, such as vitamin D and folic acid, may promote ulcer healing (Table 13A, 13B, Figure 13).[155]

In conclusion, specific dietary regimens cannot be recommended for the management of venous and lymphatic disorders due to the significant lack of solid scientific literature. Based on the literature review, the panel considers it appropriate in these patients to promote adequate hydration while maintaining a body mass index that is neither too high nor too low.[156, 157]

Economic sustainability considerations

Indirectly, the cost-effectiveness of diet and exercise on obesity could be considered in light of obesity as an intrinsic venous risk factor; however, conclusive data are not currently available. Future investigations on this topic are strongly recommended.

TABLE 13A.—*Good Practice Statement checklist for statement 13.*[4]

Process for developing good practice statement	Supporting information	Verification
Write Good Practice Statement		
Does the statement follow a PICO prioritization process?		☒ Yes ○ No
If you answered No → 1) Explain why the PICO question was not prioritized but is being addressed → avoid developing any type of actionable statement that acts as an independent response to the PICO question.		
Are the Population and Intervention components clear?		☒ Yes ○ No
If you answered No → Check whether you are developing an implementation consideration (refer to flow chart in Lotfi et al.(8))		
Items to complete	**Supporting information**	**Verification**
All the following criteria must be fulfilled *to consider the statement a GPS.*		
(1) Message is really necessary in regard to actual health care practice		This criterion has been addressed: ☒ Yes ○ No
(2) Implementing the GPS results in a large net positive consequence (i.e. satisfy several evidence to decision (EtD) criteria) after consideration of all relevant outcomes and potential downstream consequences ** check the criteria considered in the development of the GPS.		This criterion has been addressed: ☒ Yes ○ No **Evidence-to-Decision criteria** Importance of the problem ☒ Certainty in effects ☒ Variability and certainty in the importance of outcomes ☒ Magnitude of resource requirements ☒ Certainty of evidence of resource use ☒ Cost-effectiveness ☒ Equity ☒ Acceptability ☒ Feasibility ☒
(3) Collecting and summarizing the evidence is a poor use of a guideline panel's limited time, energy or		This criterion has been addressed: ☒ Yes ○ No
resources. The opportunity cost of collecting and summarizing the evidence is large and can be avoided.		
(4) There is a well-documented clear and explicit rationale connecting the indirect evidence		This criterion has been addressed: ☒ Yes ○ No
(5) Clear and actionable (This criterion should apply to any developed statement. For example, all formal recommendations are clear and actionable)		This criterion has been addressed: ☒ Yes ○ No
Final judgement		
Did you answer Yes to ***all*** of the above?	☒ Yes Development as GPS is appropriate	
	○ No Development as GPS is ***not*** appropriate → Revisit the PICO question and the importance of addressing it.	

Technical research notes

- **PICO:** in patients with veno-lymphatic insufficiency (P), are specific diets (I) appropriate for improving lower limb discomfort (O) compared with a free diet regimen (C)?
- **Search string:** (diet).ti,ab. AND ((vein$ OR lymphatic).ti,ab.)
- **PRISMA:** flow chart is provided in Figure 13.

Good practice statement

- 1. **The statement is truly necessary in the context of current clinical practice.**

The statement is absolutely necessary in light of the current clinical context, which is characterized by numerous commercial claims regarding foods promoting venous-lymphatic health, in the absence of corresponding scientific evidence.

- 2. **Implementation of the Good Clinical Practice Recommendation has a broadly positive effect, considering all relevant outcomes and potential downstream consequences.**

Focusing on weight control and hydration has a significant positive impact on managing risk factors for chronic venous disease, pelvic venous disorder, and venous thrombosis, while simultaneously countering misinformation and disinformation promoting foods that have not demonstrated benefits for the venous-lymphatic system.

- 3. **Collecting and summarizing the evidence would represent a misuse of the panel's limited time, energy, and resources.**

Based on the pathophysiological principle that overweight is a risk factor for venous hypertension, similarly to excessive thinness for pelvic venous disorder, and dehydration for thrombosis, a detailed literature search and systematic review are considered inappropriate given the panel's limited time, energy, and resources.

- 4. **Indirect evidence is connected to a well-documented, clear, and explicit rationale.**

Evidence on the risk factors of weight and dehydration for the development of venous and lymphatic disease represents clear and explicit indirect proof of the rationale

TABLE 13B.—*Evidence to Decision Framework for Statement 13.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with veno-lymphatic insufficiency (P), are specific diets (I) appropriate for improving lower limb discomfort (O) compared with a free diet regimen (C)?	Sub-analyses across different ethnicities with homogeneous lifestyles should be conducted to make the statement a truly global good clinical practice recommendation.	In patients with veno-lymphatic disorders of the lower limbs, it is advisable to avoid both obesity and excessive thinness, while promoting adequate hydration. There is no evidence supporting specific diets, foods, or beverages that have a significant impact on venous-lymphatic drainage	The benefits of maintaining a normal weight at the venous-lymphatic level are well known. Specific dietary regimens have not demonstrated significant advantages to date and could, in fact, lead to undesirable nutritional imbalances.	Good practice statement	The key values focus on venous-lymphatic pathophysiology, whereby both excess and deficient body weight represent risk factors for venous hypertension and pelvic venous disorder, respectively. Preferences are centered on hydration status, also considering its protective role against thrombotic risk.	The assessment of sustainability falls outside the scope of this document. The potential dietary impact, including from a cost-effectiveness perspective, certainly warrants a dedicated scientific investigation.	The numerous weight management programs and proper hydration are readily accessible nationwide, making the good clinical practice recommendation both feasible and acceptable to patients.

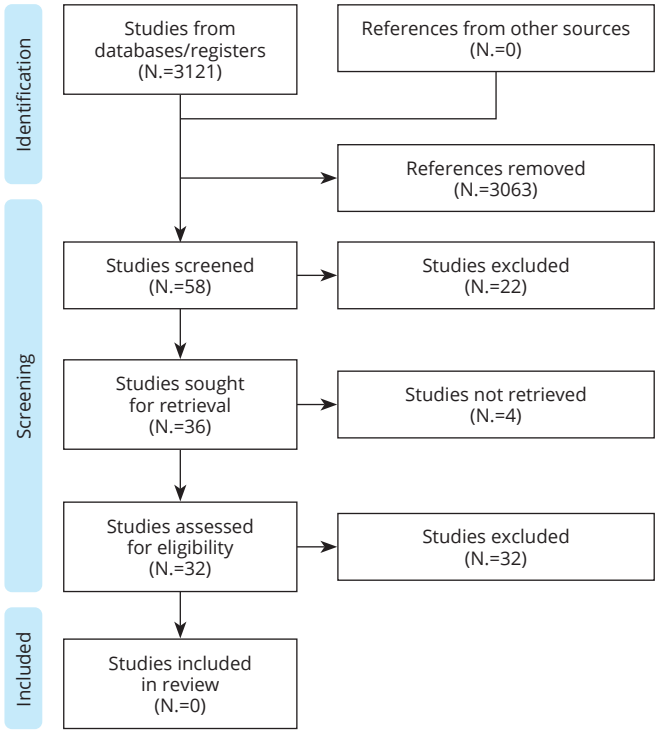

Figure 13.—PRISMA flow chart for statement 13.

underlying this Good Clinical Practice Recommendation.

• 5. **The statement is clear and implementable.**

The statement is clear and implementable, given the ready availability of weight management programs and adequate nutrition and hydration.

Applicability

A) Facilitating factors

Tools for weight management and proper nutrition are already available nationwide. Dedicated educational campaigns in the veno-lymphatic context could certainly facilitate the implementation of this good clinical practice.

B) Barriers

The current increase in sedentary lifestyles may hinder the application of this good clinical practice.

C) Suggestions and tools

Development of synergies between dietetic and phlebo-lymphology scientific societies to identify nutritional plans tailored to veno-lymphatic patients.

D) Potential resource implications

The clinical impact of proper nutrition could lead to significant improvements in the management of veno-lymphatic disorders, including from a cost-effectiveness perspective.

E) Monitoring indicators

Development of nutritional plans tailored to veno-lymphatic patients.

Good clinical practice statement 14: Weight-bearing impact on veno-lymphatic drainage

In patients with veno-lymphatic disorders of the lower limbs, it is advisable to clinically assess any postural disturbances, adding a gait analysis if there is doubt or a need for further diagnostic evaluation (*Good clinical practice statement based on unassessed quality of evidence*).

Rationale

The musculoskeletal system, together with the thoracic pump, represents the main driver of venous return, to the extent that it is considered the "peripheral heart."[158] Similarly, the plantar arch functions as a venous pump, positioned in series with the calf, thus significantly contributing to limb drainage.[159] The way this plantar pump is engaged during standing and walking can significantly influence venous return, representing a well-known risk factor for the development of chronic venous disease.[160]

Scientific data show that the type of plantar arch may represent not only a risk factor for disease onset but also for disease progression. Specifically, this has been observed in cases of increased dorsiflexion of the foot, leading to the hypothesis of an etiological basis that is both mechanical and histological, related respectively to altered hemodynamics and tissue laxity.[161] These findings highlight the need for further dedicated research, considering that, conversely, other studies have directly correlated increased joint range of motion with improved venous drainage function.[162]

The importance of appropriate posture for venous drainage has also been demonstrated in specific contexts, such as postpartum thromboembolism prevention.[163] While the significance of proper activation of the "veno-muscular pump" has been recognized for decades, specific studies aimed at identifying the best postural screening protocol are still lacking.[164]

In light of the above considerations, in veno-lymphatic patients, it is appropriate to clinically assess posture, adding a podobarostatic examination and gait analysis if there is doubt or a need for further diagnostic evaluation (Table 14A, 14B, Figure 14).

Sustainability consideration

No data have been reported on this topic. A dedicated study calculating the cost-effectiveness of postural assessment in the phlebo-lymphology context is desirable.

TABLE 14A.—*Good Practice Statement checklist for statement 14.*[4]

Process for developing good practice statement	Supporting information	Verification
Write Good Practice Statement		
Does the statement follow a PICO prioritization process?		[X] Yes [ ] No
If you answered No → 1) Explain why the PICO question was not prioritized but is being addressed → avoid developing any type of actionable statement that acts as an independent response to the PICO question.		
Are the Population and Intervention components clear?		[X] Yes [ ] No
If you answered No → Check whether you are developing an implementation consideration (refer to flow chart in Lotfi et al.(8))		
Items to complete	**Supporting information**	**Verification**
All the following criteria must be fulfilled *to consider the statement a GPS.*		
(1) Message is really necessary in regard to actual health care practice		This criterion has been addressed: [X] Yes [ ] No
(2) Implementing the GPS results in a large net positive consequence (i.e. satisfy several evidence to decision (EtD) criteria) after consideration of all relevant outcomes and potential downstream consequences ** check the criteria considered in the development of the GPS.		This criterion has been addressed: [X] Yes [ ] No Evidence-to-Decision criteria: Importance of the problem [X]; Certainty in effects [X]; Variability and certainty in the importance of outcomes [X]; Magnitude of resource requirements [X]; Certainty of evidence of resource use [X]; Cost-effectiveness [X]; Equity [X]; Acceptability [X]; Feasibility [X]
(3) Collecting and summarizing the evidence is a poor use of a guideline panel's limited time, energy or		This criterion has been addressed: [X] Yes [ ] No
resources. The opportunity cost of collecting and summarizing the evidence is large and can be avoided.		
(4) There is a well-documented clear and explicit rationale connecting the indirect evidence		This criterion has been addressed: [X] Yes [ ] No
(5) Clear and actionable (This criterion should apply to any developed statement. For example, all formal recommendations are clear and actionable)		This criterion has been addressed: [X] Yes [ ] No
Final judgement		
Did you answer Yes to ***all*** of the above?	[X] Yes Development as GPS is appropriate	
	[ ] No Development as GPS is ***not*** appropriate → Revisit the PICO question and the importance of addressing it.	

Technical research notes

- **PICO:** in patients with veno-lymphatic disorders (P), is it appropriate to treat postural disturbances (I) versus ignoring them (C) to improve the risk of development and/or progression of veno-lymphatic disease (O)?
- **Search string: (**postur$).ti,ab. AND ((venous OR lymph$).ti,ab.)
- **PRISMA:** flow chart provided in Figure 14.

Clinical practice statement

- 1. **The statement is genuinely necessary in the context of current clinical practice.**

The statement is absolutely necessary in light of the current clinical context, which is characterized by a general lack of attention to the postural component during vascular examinations, despite its potential significant impact on phlebo-lymphatic clinical outcomes.

- 2. **The implementation of the Clinical Good Practice Recommendation results in a broad and positive effect, considering all relevant outcomes and potential downstream consequences.**

A proper postural assessment has the significant effect of improving the management of venolymphatic conditions, potentially even preventing recurrence.

- 3. **Collecting and summarizing evidence would constitute a misuse of the panel's limited time, energy, and resources.**

Based on the pathophysiological principle that activation of the plantar arch and calf muscles is a key moment for venolymphatic drainage propulsion, proper functioning of these structures is a well-established element in the effective management of the condition. For this reason, a detailed literature search and systematic review are considered inappropriate given the panel's limited time, energy, and resources.

- 4. **Indirect evidence is connected to a well-documented, clear, and explicit rationale.**

Evidence of increased venous hypertension risk associated with inadequate posture represents clear and explicit indirect evidence supporting the rationale underlying this Clinical Good Practice Recommendation.

TABLE 14B.—*Evidence to Decision Framework for Statement 14.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with veno-lymphatic disorders (P), is it appropriate to treat postural disturbances (I) versus ignoring them (C) to improve the risk of development and/or progression of veno-lymphatic disease (O)?	Sub-analyses of the impact of different types of postural disturbances on venous-lymphatic drainage are necessary.	In patients with veno-lymphatic disorders of the lower limbs, it is advisable to clinically assess any postural disturbances, adding a gait analysis if there is doubt or a need for further diagnostic evaluation (good clinical practice recommendation based on unassessed quality of evidence).	Correction of postural disturbances is associated with improved venous-lymphatic drainage without introducing additional associated risks.	Good practice recommendation	The value lies in the improvement of venolymphatic drainage resulting from the correction of postural disorders. Preference is given to a holistic approach to venolymphatic care.	The sustainability study falls outside the scope of this document. However, it is conceivable that the cost of postural assessment and correction can be easily justified by the savings on the cost of the venolymphatic condition itself.	The statement of good practice is highly feasible, as postural assessment and correction are readily available throughout the country. Being a non-invasive examination and intervention, acceptability is high.

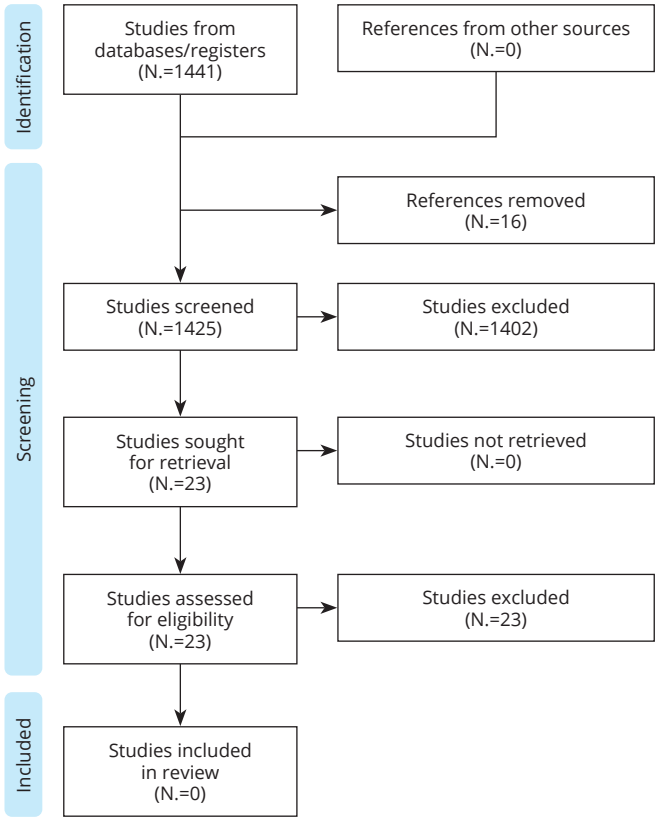

Figure 14.—PRISMA flow chart for statement 14.

• 5. **The statement is clear and implementable.**

The statement is clear and implementable due to the ready availability and low cost of postural assessment, which is already accessible nationwide.

Applicability

A) Facilitating factors

Postural assessment and correction are already readily available nationwide and can be performed quickly at a low cost.

B) Barriers

No clear parameters have been identified for the severity of postural disorders in relation to their associated impact on the venolymphatic system.

C) Suggestions and tools

• Promotion of scientific studies specifically focused on this topic.

• Provision of podobarometric scales in phlebo-lymphological clinics.

D) Potential resource implications

The expenditure of personnel and equipment for the assessment and treatment of postural disorders can be easily offset by the reduction in costs associated with venolymphatic pathology.

E) Monitoring indicators

Number of postural assessments performed on venolymphatic patients.

Recommendation 15: Veno-lymphatic hydrotherapy

In patients with veno-lymphatic disorders of the lower limbs, a specific hydrokinetic exercise protocol is suggested over dry-land exercise (*Weak recommendation, in favor of the intervention, with low certainty of evidence*).

Rationale

The aquatic environment offers physical, biochemical, and thermal benefits that have been empirically used for centuries in various fields of medicine, including phlebology and lymphology.[165] Nevertheless, the literature specifically addressing the benefits of standardized aquatic activity for venolymphatic patients is extremely limited. A 2019 meta-analysis dedicated to balneotherapy was reviewed by our group for the assessment of certainty of evidence, reporting a possible improvement in disease-specific quality of life (CIVIQ) and skin pigmentation (**low certainty of evidence**).[166] Other outcomes, such as the impact on the venous clinical severity score, risk of erysipelas, and edema, showed very low certainty of evidence (Table 15A). Specifically for edema, the beneficial effect of a specific aquatic exercise protocol was documented in the only available randomized study on the topic.[167] To our knowledge, this is the only study that compared the same physical activity in aquatic versus dry-land environments, demonstrating specific benefits for venolymphatic patients in terms of edema, joint mobility, subcutaneous thickness, and quality of life. The study was conducted in thermal water at 32 °C.[168] No studies were found in the literature documenting the effects of different water temperatures or chemical compositions, highlighting the need for further scientific investigation. Each centimeter of water corresponds to 0.7 mmHg; according to Stevin's Law, this results in a graded pressure of approximately 70 mmHg on a body immersed at 100 cm depth. This observation, combined with the very low certainty of evidence regarding the effect of the aquatic environment on edema, underscores the need for appropriate scientific research to avoid weakening the recommendation due to bias, imprecision, or inconsistency. Based on the above considerations, the use of a specific standardized exercise protocol is recommended for venolymphatic patients, preferably in thermal water (Table 15A, 15B, Figure 15).[169, 170]

Economic affordability considerations

No data on this topic were available. Future studies should focus on the cost-effectiveness of this practice, which could positively impact both the health of venolymphatic patients and reduce the costs associated with the pathology itself.

TABLE 15A.—*Evidence to Decision Framework for statement 15.*

PICO	Note	Evidence-to-Decision Framework					
		Recommendation	Benefits & Risks	Certainty of Evidence	Values & Preferences	Affordability	Feasibility/ acceptability
In patients with venolymphatic insufficiency (P), does a validated aquatic exercise protocol (I) improve edema control and quality of life (O) compared to dry-land physical activity (C)?	The recommendation is based on data obtained from the use of a specific standardized hydrokinetic exercise protocol, and not from random activity. The standardization and reproducibility of aquatic activity are of primary importance for an objective evaluation of potential benefits.	In patients with venolymphatic disorders of the lower limbs, a specific hydrokinetic exercise protocol is suggested over dry-land exercise (WEAK recommendation, in FAVOR of the intervention, with LOW certainty of evidence).	Considering the inherently low risk of complications in the aquatic environment, the potential benefits outweigh the risks.	Low	The value of calf-pump activity in an aquatic environment with reduced gravity and high graduated compression supports the recommendation to use a targeted hydrokinetic exercise protocol for venolymphatic patients.	This study does not address cost-effectiveness issues. Studies in this regard are strongly recommended, also considering the potential reduction in disease-related costs through appropriate phlebolymphologic hydrokinetic therapy.	Aquatic activity is easily performed, even by elderly, overweight, or hypomobile patients. A small group of patients may feel apprehensive about the aquatic environment. It should be noted, however, that the protocol does not involve head immersion or swimming.

TABLE 15B.—*Summary of Findings for recommendation 15.*

Population: Patients with chronic venous insufficiency
de Moraes Silva 2019 (studies from inception up to August 7th, 2018); 7 trials with 891 participants
Frequentist random-effects pairwise meta-analysis

Balneotherapy *vs.* No balneotherapy

Outcome	Number of trials (participants)	Absolute risk difference per 1000 patients (95% CI) OR/MD (95% CI)	*GRADE Simple Language Summary*
VCSS (0-27)[a]	2 trials (484 participants)	MD:-1.66 (-4.14 to 0.83) VERY LOW (due to serious risk of bias, inconsistency and imprecision)	*We are very uncertain about the effect of balneotherapy compared to no balneotherapy on VCSS.*
CIVIQ (20-100)	2 trials (149 participants)	MD: -9.38 (-18.1 to -0.57) LOW (due to serious risk of bias and inconsistency)	*Balneotherapy may reduce CIVIQ compared to no balneotherapy.*
Erysipela[b]	2 trials (519 participants)	24 (-5 to 124) OR: 2.58 (0.65 to 10.22) VERY LOW (Due to serious serious risk of bias and very serious imprecision)	*We are very uncertain about the effect of balneotherapy compared to no balneotherapy on the risk of erysipela.*
Thromboembolic event[c]	3 trials (584 participants)	-26 (-36 to 16) OR: 0.35 (0.09 to 1.42) LOW (Due to serious risk of bias and imprecision)	*Balneotherapy may have little to no effect on the risk of thromboembolic event compared to no balneotherapy.*
Palpitations[d]	3 trials (59 participants)	-22 (-33 to 192) OR: 0.33 (0.01 to 8.52) VERY LOW (Due to serious serious risk of bias and very serious imprecision)	*We are very uncertain about the effect of balneotherapy compared to no balneotherapy on the risk of palpitations.*
Pain VAS (0-10)[e]	1 trial (390 participants)	MD: -1.23 (-1.33 to -1.13) MODERATE (due to serious risk of bias)	*Balneotherapy likley have little to no effect on pain compared to no balneotherapy.*
Edema (in mL)	2 trials (153 participants)	MD: 91.46 (-0.65 to 183.58) VERY LOW (due to serious risk of bias, inconsistency and imprecision)	*We are very uncertain about the effect of balneotherapy compared to no balneotherapy on the edema volume.*
Incidence of leg ulcer[f]	2 trials (449 participants)	36 (-10 to 118) OR: 1.69 (0.82 to 3.48) LOW (Due to serious risk of bias and imprecision)	*Balneotherapy may have little to no effect on the incidence of leg ulcer compared to no balneotherapy.*
Skin pigmentation (color index)	1 trial (59 participants)	MD: -3.59 (-4.02 to -3.16) LOW (due to serious risk of bias and imprecision)	*Balneotherapy may reduce skin pigmentation compared to no balneotherapy.*

[a] MID: 1.0; [b] 16/1000 (MID:100/1000); [c] 40/1000 (MID:100/1000); [d] 33/1000 (MID:100/1000); [e] MID: 1.5; [f] 58/1000 (MID: 100/1000).
CI: confidence interval; OR: odds ratio; MID: minimally important difference; MD: mean difference; VCSS: Venous Clinical Severity Score; VAS: Visual Analogue Scale.

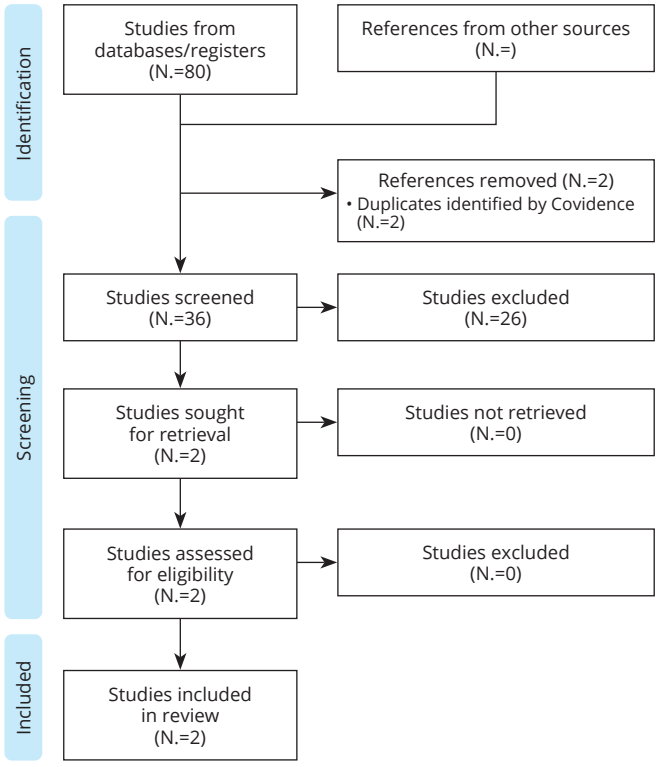

Figure 15.—PRISMA flow chart for recommendation 15.

Technical research notes

• **PICO:** In patients with venolymphatic insufficiency (P), does a validated aquatic exercise protocol (I) improve edema control and quality of life (O) compared to dry-land physical activity (C)?

• **Search strings:** Epistemonikos: (title:(aquatic OR hydro*) OR abstract:(aquatic OR hydro*)) AND (title:(vein OR lymphatic) OR abstract:(vein OR lymphatic)). Medline: (aquatic OR hydro$).ti,ab AND (vein$ OR lymphatic).ti,ab

• **Inclusion criteria:**

Study Design	Partecipants	Intervention	Results	Publication Type	Language
Meta-analysis, systematic revisions	Age: 18-65 yo	Aquatic exercise protocol	Edema	Original manuscript published in an indexed journal	English
	Venous-lymphatic patients		Quality of life		

• **Exclusion criteria:** all studies reporting: 1) irrelevant populations, interventions, or comparators; 2) information outside the time frame between September 2014 and September 2024; 3) non-English language.

• **Results:** one meta-analysis from 2019[166] and one randomized trial from 2021.[167]

Following the literature review and expert discussion, the Development Group, together with the Oversight Group, reached unanimous approval of the recommendation.

Applicability

A) Facilitating factors

Aquatic centers are readily available throughout the country.

B) Barriers

An adequate educational campaign for healthcare personnel must be implemented to convey the hydrokinetic protocol dedicated to venolymphatic patients.

C) Suggestions and tools

Development of educational materials for healthcare personnel and the general population aimed at optimizing the benefits of the aquatic environment for venolymphatic patients.

D) Potential resource implications

Potential significant reduction in venolymphatic costs in light of the substantial impact of the hydrokinetic protocol on phlebolymphologic patients.

E) Monitoring indicators

Number of hydrokinetic sessions performed for venolymphatic patients.

Conclusions

The review of the available literature on topics of primary importance in daily phlebo-lymphologic practice has revealed a scarcity of solid evidence and a low, if not very low, degree of certainty in the data. Out of 15 PICO questions of primary relevance, 8 resulted in statements of good clinical practice. Another 6 showed a level of evidence certainty ranging from very low to low. A single PICO showed sufficient data to allow the execution of a new meta-analysis, although still leading to a low certainty of evidence. Venous and lymphatic disorders, including lipedema and pelvic venous disorders, represent a true emergency in terms of clinical governance: all these drainage disorders have a significant impact on both the population and the national healthcare economy. This work does not include cost-effectiveness analyses, focusing instead on clinical appropriateness and leaving sustainability to a subsequent project phase. In this first part of the V.A.L.I.D. project, alignment among leading national and international experts was achieved to determine the most appropriate management of the main aspects of venous and lymphatic disorders. The results demonstrated the need for further efforts in the medical-scientific field, involving top experts from various specialties, methodologists, statisticians,

health economists, and patient representatives. International scientific societies should serve as hubs to globalize evidence while simultaneously nationalizing recommendations, in order to avoid discrepancies in guidelines that currently arise not from proper sustainability analyses, but from incorrect methodological applications. Considering the sub-specialized nature of phlebology and lymphology, future guidelines should include authors with objective experience in the various fields to ensure the most validated, appropriate, and holistic care.

Furthermore, given the absence of a dedicated specialty for venous and lymphatic disorders, efforts should be made to establish an academic certification of the training pathway that can appropriately identify true experts in phlebology and lymphology. Only in this way will it be possible to guarantee the right to proper care for disorders of the venous and lymphatic system of the lower limbs and pelvis, currently affecting such a large number of patients.[1]

International independent reviewers' final considerations

Prof. Julianne Stoughton

Harvard University, USA

Venous disease is highly prevalent, yet its causes and optimal management have remained elusive for years. The condition encompasses a broad spectrum, from pelvic to pelvic venous disorders, leading to chronic pain, thrombosis, or skin ulcers caused by the underlying venous insufficiency. Additionally, many individuals experience frequent and potentially debilitating symptoms such as fatigue, heaviness, swelling, and pain. Therapeutic approaches are not always well-defined or standardized, and preventive measures are often inconsistently applied and supported by limited evidence. I am excited to witness how this work will contribute to standardizing guidelines based on the best global evidence. This will also aid future research in areas where solid evidence is lacking.

Prof. Stanley Rockson

Stanford University, USA

Chronic edema is insidious, common, and impactful, generating pain, loss of mobility, psychosocial involvement, and at times even dramatic consequences. In health, the venous and lymphatic systems are components of the circulation that work together to minimize or eliminate the potential causes of onset and maintenance of edema. It is an honor for me to participate in this compelling work of clinical governance, aimed at establishing standards for good clinical practices, also intended to guide and improve the management of chronic edema in the context of human health and disease.

Patient representation considerations

Anna Maisetti

Anna Maisetti manages a community of 27,000 individuals dedicated to raising awareness of venous-lymphatic drainage disorders. The vision is to provide reliable, accessible, and acceptable knowledge about lower limb health to all segments of the population. Having personally faced secondary oncologic lymphedema, she combines her experience in the fashion sector with her firsthand testimony and currently serves as a hub for an average of two patients per day, 365 days a year. Her work allows her to have a comprehensive view of the patient perspective, including the acceptability of the recommendations presented here. The document was shared and discussed with her so that she could provide population feedback for each recommendation and good clinical practice indication.

Good clinical practice statement 1: Swollen lower limb expert evaluation

"This is a fundamental topic as we have encountered countless patients with edema who underwent ultrasound examinations that were negative, yet subsequent expert evaluation identified a venous-lymphatic disorder. Color-Doppler ultrasound is of fundamental importance, but it must be combined with an assessment by an expert physician."

Recommendation 2: Thermal tumescent *vs.* non-thermal tumescent endovenous procedures

"A significant portion of patients with venous and lymphatic disorders are unaware of the connection between the venous and lymphatic systems. Promoting this knowledge is crucial, also regarding the various technologies available for venous treatments today, to ensure that the lymphatic system is not damaged by the venous procedure. It is not clear to us whether one phlebological technique may have more or less impact on the lymphatics than another."

Recommendation 3: Ilio-femoral venous stenting + Good clinical practice statement 4: Pelvic venous reflux multispecialty management

"There is an almost complete lack of patient awareness regarding the deep and pelvic venous system and the re-

lated good clinical practices, making it easy to mislead patients with false promises of immediate results. While patients must not be under-diagnosed, they should also not be over-treated. Understanding how to identify a properly equipped center and professional is very difficult. Furthermore, pelvic symptoms can cause embarrassment during history-taking, so dedicated educational campaigns should be promoted to also prevent cases of silence or omission."

Good clinical practice statement 5: Varicose vein procedures thromboprophylaxis

"The concept of thrombosis is partially known to patients, but there is almost no knowledge of the thrombotic risk associated with venous procedures or the differences between techniques. Moreover, patients are generally unaware of any thrombotic risk associated with lymphedema. Currently, patients can only blindly trust their physician."

Recommendation 6: Advanced dressings for venous ulcers

"Venous-lymphatic ulceration is among the patients' greatest concerns. Nevertheless, significant confusion is generated by sometimes overhyped claims regarding dedicated products, which may sometimes amount to outright misinformation. Access to specialized centers is not easy, due to both lack of dedicated services and objective quality certifications. This often leads to a significant loss of time and financial resources."

Recommendation 7: Venous active drugs

"There is considerable distrust among patients regarding active venous-lymphatic drugs, especially those claiming benefits for leg drainage. The market is broad, and unfortunately both healthcare professionals and pharmacists often rely more on personal preferences than on solid scientific evidence. Advertising, particularly on television, exacerbates this phenomenon, leaving patients in real need of scientific proof."

Good clinical practice statement 8: Compression garment prescription

"Questions regarding the prescription of compression stockings and related clarifications are the most frequent. At least two patients per day, every day of the year, ask us about this. This results from overly vague medical prescriptions and the use of "denier" (yarn weight) instead of millimeters of mercury (applied pressure). Patient tolerance to compression begins with education for both the physician and the patient. More attention should be given to this topic, involving institutions as well."

Good clinical practice statement 9: Treatment of lymphedema + Recommendation 10: Treatment of lipedema

"Surgery for lymphatic disorders and lymphedema may be an option to improve conservative treatment, but sensationalism must be avoided, as many patients continue to receive false promises of miraculous results, often without waiting for several months of properly executed conservative therapy. Appropriate patient information is necessary to clarify that surgery is not the definitive solution and that conservative treatment must still be maintained. Moreover, the fact that the intervention is rarely available in the national healthcare system exposes patients to significant financial burden and uncertain outcomes. We hope that the scientific community and institutions align with patient representation to optimize therapeutic options for these debilitating yet common conditions."

Good clinical practice statement 11: Echo-color Doppler for telangiectasias treatment

"Telangiectasias are considered merely an aesthetic issue, easy to treat but also prone to recurrence, not requiring special expertise. Raising awareness of possible underlying pathologies is important, including careful analysis of potential benefits or risks that such treatments may have on the lymphatics."

Recommendation 12: Platelet-rich plasma in the treatment of venous ulcers

"Platelet-rich plasma is too specific a topic for patients. At the same time, regenerative medicine is frequently mentioned by the public, but it encompasses various medical activities and has become trendy even if not well understood or supported by accessible evidence. More scientific solidity is needed on this topic, or at least better patient education."

Good clinical practice statement 13: Veno-lymphatic diet

"While patients underestimate the importance of a proper diet, they are exposed to a vast market of products with claimed but potentially unreliable benefits. On the other hand, healthcare professionals too often recommend weight loss without specifying foods that are helpful or harmful for the specific venous/lymphatic/lipedematous condition. We hope that dedicated institutions can provide clarity on this matter."

Good clinical practice statement 14: Weight-becoming impact on veno-lymphatic drainage

"While the impact of posture on the venous and lymphatic system is beginning to be recognized in the context of medical events relevant to patient representation, this is not the case among the general population and even most healthcare professionals, who typically focus on the vascular system and overlook musculoskeletal aspects. Obtaining a postural assessment is not particularly difficult, but obtaining expert opinion on the actual need to correct posture in a specific venous-lymphatic patient remains more challenging. We hope for synergy between the vascular and postural fields in the near future."

Recommendation 15: Veno-lymphatic hydrotherapy

"Water activities and spas are heavily commercially promoted, easily capturing attention and encouraging the expenditure of time and resources. At the same time, there seems to be more empirical than scientific basis, with a lack of validated protocols for venous-lymphatic patients. There is a need to move from traditional 'water aerobics' to evidence-based activities. There is also significant confusion about water types and temperatures to be used. We hope that institutions and scientific representatives can work together to propose validated protocols specifically designed for phlebo-lymphatic patients, demonstrating the true benefits of aquatic activities versus dry-land alternatives."

APPENDIX 1

Meta-analysis produced by the research group on Statement 12. Bayesian Network Meta-Analysis Report

Statistical analysis

The statistical analysis was performed using Bayesian approaches to assess the effectiveness of different treatments on healing rates and ulcer size. Using a network meta-analysis (NMA) framework allowed for evaluating multiple interventions, by considering both direct and indirect evidence from the included studies. The analysis employed random-effects models and Bayesian hierarchical models, considering model priors, convergence diagnostics, and adjustments for study-specific covariates such as follow-up time.

For the analysis of dichotomous outcomes, treatment effects were estimated using a random-effects model. Odds ratios (ORs) were calculated along with their corresponding 95% confidence intervals, capturing the variability between studies. To improve the interpretability of the results and provide a probabilistic assessment of treatment superiority, a Bayesian hierarchical model was also employed. In this Bayesian framework, the treatment effect was modeled using beta-binomial likelihoods. Specifically, for the event probabilities in each treatment arm, non-informative priors were used.

The posterior probabilities of treatment superiority were estimated using Monte Carlo simulations with 1,000 posterior samples drawn for each treatment comparison. If the probability of one treatment being superior to another exceeded 0.95, this was interpreted as strong evidence of superiority. The network linking all interventions was created, and Bayesian inference was conducted . A random-effects framework was incorporated into the Bayesian model through the use of hierarchical priors on the treatment effects. For the between-study variance (heterogeneity parameter), a **uniform prior, U(0,2)**, was specified, reflecting a reasonable range of plausible heterogeneity values without over-constraining the model.

Markov Chain Monte Carlo (MCMC) simulations were used to estimate the posterior distributions of treatment effects. The simulations were run across four independent chains, each with 100,000 iterations. To ensure stable parameter estimation, an adaptation phase of 5,000 iterations was included as burn-in, and a thinning interval of 10 was applied to reduce autocorrelation in the chains. Convergence was assessed using trace plots, and autocorrelation plots.

For continuous outcomes, such as ulcer size reduction, mean differences (MDs) were estimated using a random-effects normal likelihood model. Priors were again chosen to reflect the characteristics of the data. The standard deviations of treatment effects were assigned a **uniform prior, U(0,2)**, consistent with the Bayesian treatment of heterogeneity in the dichotomous outcomes. The treatment means were modeled with non-informative priors, assuming no strong prior belief about their relative values. The posterior distributions of the treatment means were sampled using the same MCMC framework as the dichotomous outcomes, with similar chain settings and convergence diagnostics.

A meta-regression analysis was conducted to explore the influence of follow-up time on treatment effects. In this analysis, follow-up time was included as a covariate in the network meta-analysis model using. The regression coefficient associated with follow-up time was assigned a weakly informative normal prior, **N(0,10)**, reflecting the belief that follow-up time could have a modest effect on

treatment outcomes while allowing the data to determine the direction and magnitude of the effect. MCMC simulations were run to estimate the posterior distribution of the regression coefficient, and the probability of follow-up time having an effect on treatment outcomes was assessed using the posterior probability of direction. To validate the results, the model's consistency and robustness were evaluated. The network consistency was assessed to test for discrepancies between direct and indirect comparisons. Heterogeneity across studies was quantified and incorporated into the model through the random-effects structure. The results were summarized with forest plots for pooled effects and league tables for pairwise comparisons. Treatments were ranked using Surface Under the Cumulative Ranking Curve (SUCRA) values, providing a probabilistic ranking of their effectiveness. A SUCRA plot was generated, visualizing the hierarchy of treatments with annotations to aid interpretation.

The analysis also accounted for potential publication bias by generating funnel plots, which were inspected for asymmetry indicative of missing studies or selective reporting.

Analyses were performed with R 3.4.2 and gemtc package.

Results

The funnel plots assess potential publication bias and heterogeneity in studies evaluating healing rate and ulcer size reduction. In Figure S1, Panel A, the distribution of studies comparing Platelet Gel and PRP versus Control for healing rate appears somewhat asymmetric, suggesting possible small-study effects or publication bias. The spread of data points indicates substantial heterogeneity, meaning study results vary significantly. similarly, Figure S1 Panel B, for ulcer size, shows an uneven distribution of studies for ulcer size reduction, particularly for PRP, hinting at potential reporting bias or study variability. The wide range of standard errors further suggests differences in study designs or patient populations. All the effects are within the funnel bounds indicating no substantial publication bias.

The network meta-analysis for healing rate compares Platelet Gel, PRP, and Control (Figure S2). The network plot (Panel A) shows the connections between treatments, with PRP and Platelet Gel linked to Control. The forest plot (Panel B) presents odds ratios for healing, with PRP showing a point estimate above 1, suggesting potential improvement over Control, while Platelet Gel has a wider confidence interval crossing 1, indicating uncertainty in its effect. The league table (Panel C) quantifies these effects, with PRP showing an odds ratio of 3.41 (95% CI: 0.6-19.52) compared to Control, and Platelet Gel at 0.65 (95% CI: 0.02-15.64), suggesting variability and wide uncertainty. The SUCRA plot (Panel D) ranks PRP as the most effective treatment (SUCRA = 0.892), followed by Control (0.345), and Platelet Gel (0.263), indicating that PRP has the highest probability of being the best option for improving the healing rate. However, the wide confidence intervals suggest the need for further evidence to confirm these findings.

The network meta-analysis evaluates the effect of PRP

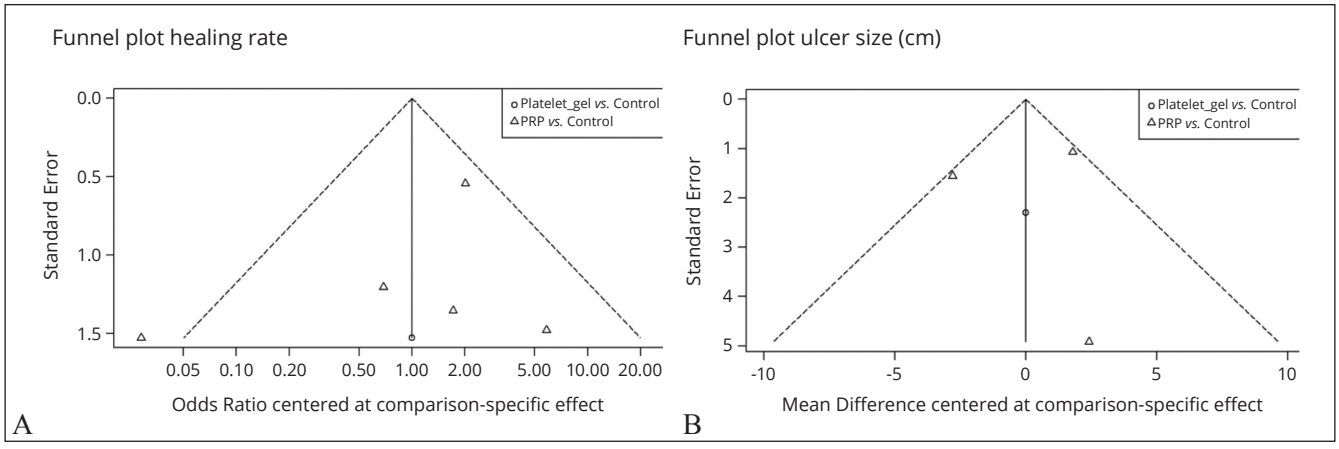

Figure S1.—Funnel plots assessing publication bias for healing rate and ulcer size reduction. A) Funnel plot for the healing rate, displaying the odds ratio (centered at the comparison-specific effect) against the standard error. The plot assesses potential publication bias in studies comparing Platelet Gel and PRP *versus* Control. B) Funnel plot for ulcer size reduction, showing the mean difference (centered at the comparison-specific effect) against the standard error. It evaluates the distribution of studies comparing Platelet Gel and PRP *versus* Control.

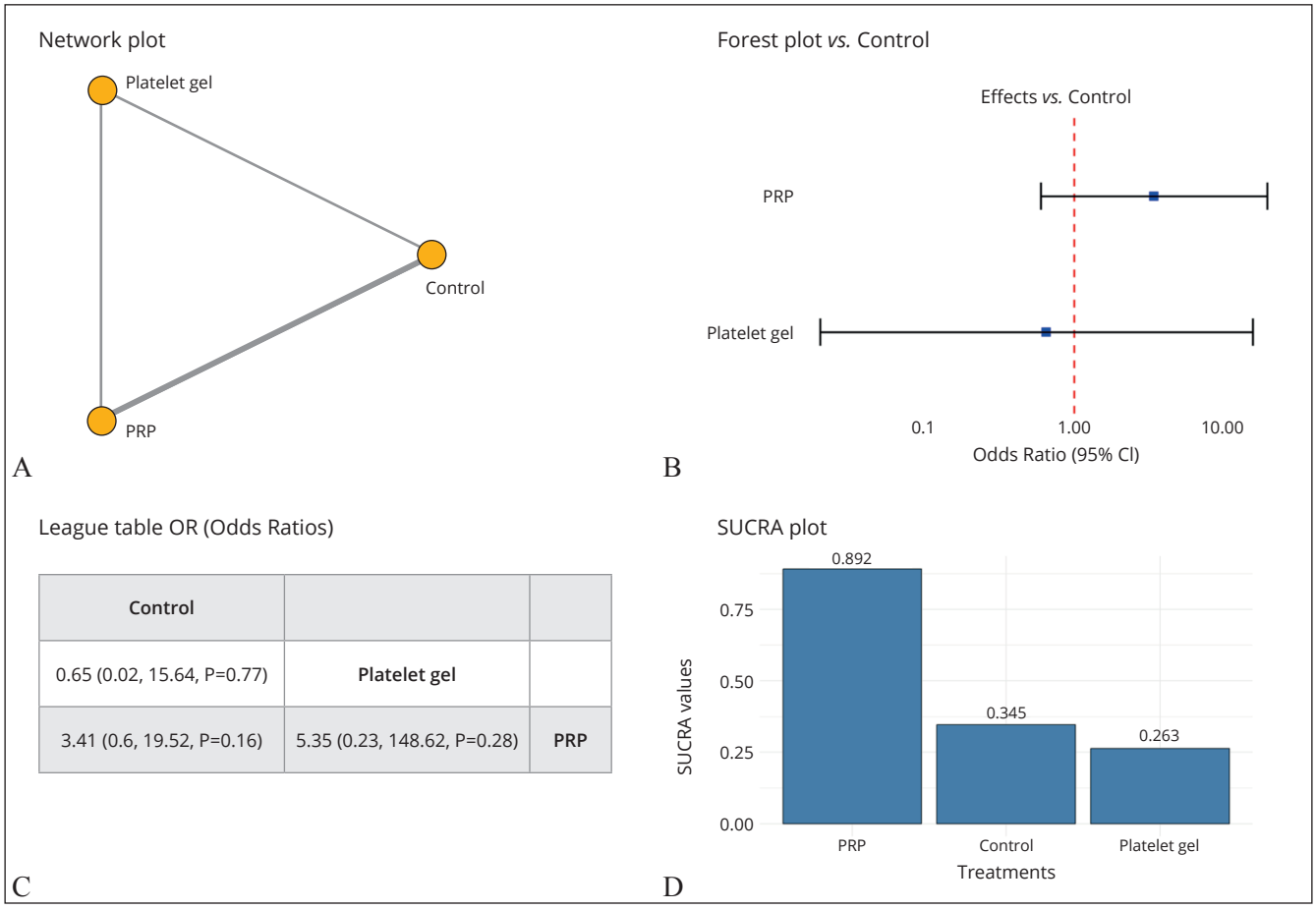

Figure S2.—Network meta-analysis of healing rate: a comparison of PRP, platelet gel, and control. A) Network plot showing the connections between treatments (PRP, Platelet Gel, and Control). B) Forest plot displaying odds ratios (95% CI) for healing rate compared to control. C) League table with odds ratios (95% CI) comparing all treatments. P is the Bayesian-P value defined as 1-the probability of effect (P Direction). D) SUCRA (Surface Under Cumulative Ranking Curve) plot ranking treatments based on healing rate probability.

and Platelet Gel on ulcer size reduction compared to Control (Figure S3). The network plot (Panel A) illustrates the connections between treatments, showing that both PRP and Platelet Gel are directly compared to Control. The forest plot (Panel B) presents the mean differences, with PRP showing a reduction in ulcer size compared to Control, while Platelet Gel has a wider confidence interval crossing zero, indicating uncertainty in its effectiveness. The league table (Panel C) quantifies these differences. PRP shows the greatest reduction in ulcer size with a mean difference of -4.42 (95% CI: -7.06, -1.94) compared to Control, while Platelet Gel has a mean difference of -3.19 (95% CI: -8.03, 1.38), suggesting a more uncertain effect. The SUCRA plot (Panel D) ranks PRP as the most effective treatment (SUCRA = 0.855), followed by Platelet Gel (0.602), with the Control ranking lowest (0.043). These results suggest that PRP has the highest probability of being the best treatment for ulcer size reduction, but the wide confidence intervals indicate variability among studies.

Figure S4 presents the Bayesian Probability of Direction (PD) for the meta-regression effect of follow-up time on healing rate and ulcer size reduction. In Panel A, the posterior distribution for the effect of follow-up time on healing rate has a median estimate of 0.35 with a 95% credible interval (CI) from -3.25 to 3.99 and a PD of 58.75%. The distribution is centered around zero, with a nearly equal probability of positive and negative effects, indicating a high level of uncertainty regarding the influence of follow-up time on the healing rate. In Panel B, the effect of follow-up time on ulcer size reduction shows a posterior median of 2.98, with a 95% CI ranging from -6.56 to 11.59, and a PD of 77.63%. The uncertainty in

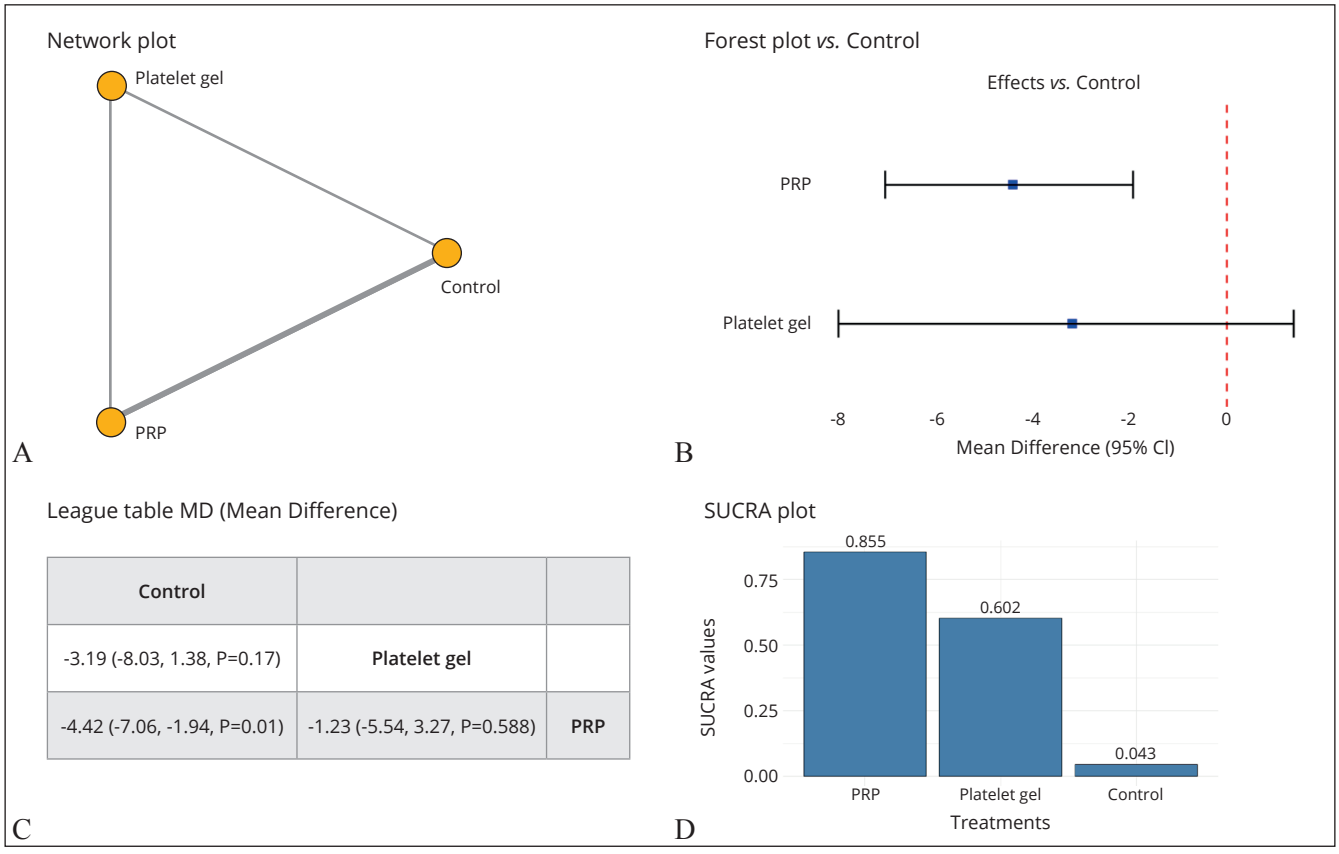

Figure S3.—Network meta-analysis of ulcer size (cm): a comparison of PRP, platelet gel, and control. A) Network plot showing the connections between treatments (PRP, Platelet Gel, and Control). B) Forest plot displaying odds ratios (95% CI) for healing rate compared to control. C) League table with odds ratios (95% CI) comparing all treatments. P is the Bayesian-P value defined as 1-the probability of effect (P Direction). D) SUCRA (Surface Under Cumulative Ranking Curve) plot ranking treatments based on healing rate probability.

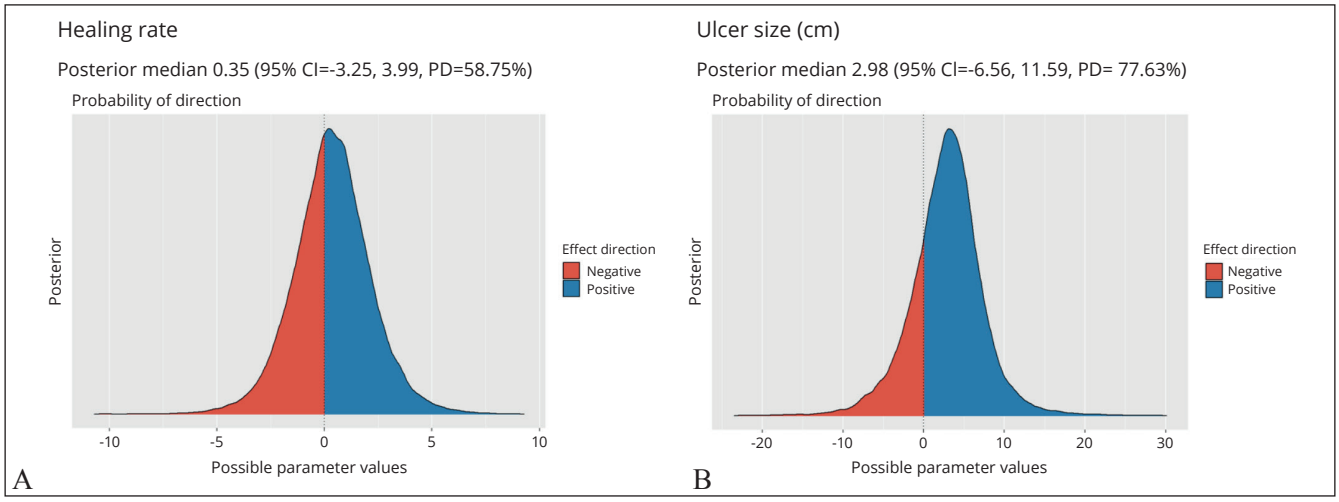

Figure S4.—Bayesian probability of direction for meta-regression effect of follow-up time. A: Posterior distribution for the effect of follow-up time on healing rate, with a posterior median of 0.35 (95% CI: -3.25 to 3.99) and a probability of direction (PD) of 58.75%. B: Posterior distribution for the effect of follow-up time on ulcer size reduction, with a posterior median of 2.98 (95% CI: -6.56 to 11.59) and a PD of 77.63%.

both estimates remains high indicating a not significant follow up-time effect.

Heterogeneity and consistency

For the healing rate endpoint, the comparison between Control and Platelet Gel is based on a single trial, preventing any meaningful evaluation of heterogeneity or consistency. This lack of direct evidence means that conclusions rely heavily on indirect comparisons within the network. In contrast, the Control *vs*. PRP comparison has more robust direct evidence, with a low pairwise heterogeneity (I^2=11.07%) indicating minimal variability among studies. However, the consistency measure (I^2=31.40%) suggests some moderate discrepancies between direct and indirect evidence, though still within an acceptable range. This implies that while PRP's effect on healing rate is relatively well-supported, minor inconsistencies across studies should be considered. Similarly, the Platelet Gel *vs*. PRP comparison is limited to a single direct trial, meaning that its interpretation is largely driven by indirect network-based inferences rather than solid head-to-head data.

For the ulcer size endpoint, the Control vs. Platelet Gel comparison mirrors the issue seen in healing rate, with only one trial providing direct evidence. This limits confidence in its findings and forces reliance on indirect comparisons, which may introduce additional uncertainty. The Control vs. PRP comparison reveals a more complex picture, with high heterogeneity (I^2=65.70%) and inconsistency (I^2=65.95%), indicating substantial variability in direct evidence and further discrepancies when indirect evidence is incorporated. This suggests that differences in study designs, patient populations, or treatment applications may be contributing to these inconsistencies, making it difficult to integrate findings into a coherent network analysis. Lastly, for Platelet Gel *vs*. PRP, the repeated lack of multiple direct comparisons across both endpoints highlights a significant gap in evidence. This means that conclusions about their relative effectiveness depend heavily on network-wide inferences, likely leading to less precise and more uncertain estimates.

These findings underscore the need for more direct head-to-head trials, particularly for Platelet Gel *vs*. PRP, to strengthen the reliability of conclusions drawn from network meta-analysis.

Convergence assessment

The trace plots in Figure S5 assess the convergence of Bayesian Markov Chain Monte Carlo (MCMC) sampling for healing rate (Panel A) and ulcer size (Panel B). Each panel displays multiple chains (colored lines) tracking parameter estimates across iterations. In Panel A (healing rate), the trace plots for the comparisons between Platelet Gel and PRP versus Control, as well as the standard deviation parameter show well-mixed chains with stable oscillations over iterations. There are no signs of divergence or trend shifts, suggesting good mixing and convergence.

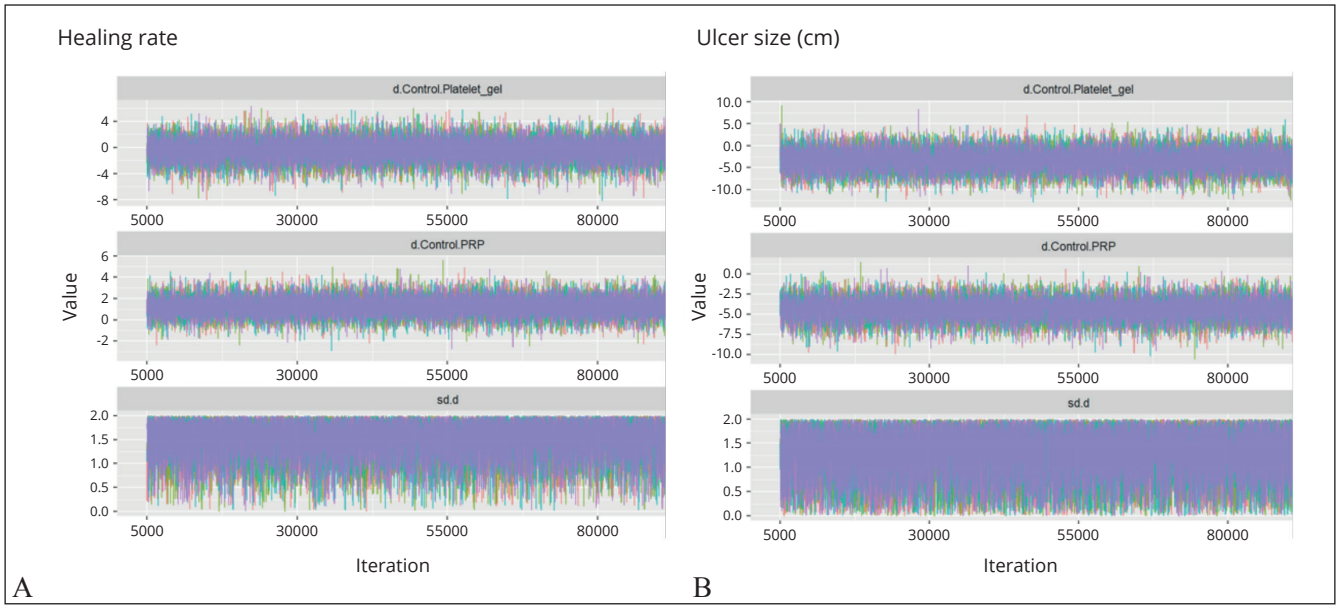

Figure S5.—Trace plots for Bayesian model convergence in healing rate and ulcer size analysis.

Similarly, Panel B (ulcer size) shows the trace plots for the same parameters, with all chains overlapping and exploring the parameter space consistently. The absence of drift or separation between chains further indicates stable sampling behavior. These plots confirm that the MCMC algorithm has likely reached convergence.

APPENDIX 2

Gender medicine in vein-lymphatic care

Gender medicine investigates how diseases differ between men and women in the context of prevention, clinical manifestations, therapeutic strategies, prognosis, psycho-social impact.[171] For more than 10 years now, the scientific community was reached out by the most authoritative journals with the aim of raising awareness toward the importance of integrating gender insights in all the different sectors of medicine.[172] Gender and sex indicators are of paramount importance in the evaluation of health/disease status, as they can influence the clinical manifestation and severity, the treatment effectiveness, the quality of the cure, as well as the general healthcare performance. The need of developing right and appropriate indicators is well reported in the scientific literature, highlighting how, if on one side genetic/epigenetic/hormonal biological sex factors can influence the physiology and the pathological expression of the disease, on the other side the economic context, the development programs, the social politics related to gender can influence the community behavior, determining the disease expression.[173] Global Burden of Diseases, Injuries, and Risk Factors investigation provides a systemic evaluation of incidence, prevalence and mortality data related to several diseases, taking into consideration population characteristics, age, life-style, correlating disease severity and healthcare organization.[174] An American Heart Association document on cardiovascular social risk determinants points out the need of a focus on non-biological factors, such as economic status, social context, cultural level, ethnicity difference, access to the cure easiness, environment, urban development, residential setting, with the aim of determining an appropriate prevention in all life stages.[175] In 2024, World Health Organization confirmed that mortality and morbility rates correlate with the social gradient.[176] The social determinants model is used in public healthcare as a useful tool to assess the discrepancies of the different countries.[177] The healthcare management in some countries in economic distress shows how such difficulty leads also to a significant reduction in the provided services, particularly afflicting the female gender, therefore entering the gender equality topic.[178] Unfortunately, nowadays phlebology and lymphology studies are still widely lacking gender medicine sub-analysis, despite physiological, biochemical and physical features related to the gender can significantly influence the venous and lymphatic drainage. Preliminary data in chronic venous disease have sowed how female patients present more symptoms in all age groups compared to men. Moreover, the probability of developing varicose veins has been found higher for the women in a dedicated study.[179] Yet, many confounding factors exist in this analysis, including the different life-style conditions for which a dedicated real world data large investigation on the topic is highly awaited. The concern is not only for the quality of life impacting condition of venous insufficiency, rather also for the related thrombo-embolic complication, more prone to be present in case of oral contraceptive use, hormonal therapy and pregnancy.[180] Such gender-related difference has been recently highlighted in critically ill intensive care unit patients affected by venous thrombo-embolism: evident differences were reported in the general case characteristics, clinical conditions, medical history and examination items.[181] A specific gender related thrombo-embolic topic not to be underestimated in terms of incidence is the transgender hormonal therapy associated risk. In the largest cohort study investigating 2800 transgender women and 2100 transgender men the odds ratio at 2-year for venous thrombo-embolism was 3.2 (95% CI: 1.5-6.2). A careful evaluation of the co-existing thrombotic risk factors should always be performed before initiating transgender hormonal therapy.[182] Gender medicine awareness should also be enhanced in the pelvic venous field. While everybody knows about male varicocele, a general lack of awareness of the analogous condition in the woman exists, so much that pelvic venous disorder has been defined as the "forgotten disease".[84] Venous incompetence in the pelvic district represents one of the main causes of pelvic pain, potentially accounting for more than 30% of cases. Educational and scientific campaigns should be promptly developed to guarantee an appropriate management of this condition, still silently affecting a significant part of the female population.[183] Regarding venous ulceration, one of the major complications of chronic venous disease, a dedicate meta-analysis pointed out no significant differences in lesion healing related to gender (OR 1.055; 95% CI 0.955-1.165; Z = 1.05, p = 0.292), yet several confounding factors such as life-style, BMI and ethnicity have to be considered in future real world data investigations.[184] On the lymphatic side of the circulation, the gender compo-

nent is clearly evident, with an average ratio of one male for three females, pointing out the hormonal role. Yet, the same hormonal action on the lymphatic vessels requires further investigation to properly understand the physiopathology and the possible therapeutic action related to it.[185] The same consideration applies to lipedema: an adipose tissue disorder, mainly affecting women and just few men usually presenting a hormonal dysfunction. Still too many women are considered also by their physicians as obese, while a lipedema condition is actually the cause of their fat tissue appearance.[186] In conclusion, gender and ethnicity biases are still contaminating appropriate care, showcasing the need of real world data generation and of properly designed trial, taking into consideration of both genders in equal terms.[187, 188] This is particularly true in Phlebology and Lymphology, where the hormonal part and the gender related physical and biochemical features can play a major role in the development of the disease. For the abovementioned reasons, the panel suggests a maximum effort in gender medicine inclusion inside the vein-lymphatic scientific research projects as well as in the daily practice diagnostic and therapeutic actions.

APPENDIX 3

Telemedicine in vein-lymphatic care

In the traditional perspective and within a reductionist framework, telemedicine has been defined as the delivery of clinical services via video or phone calls, while telehealth is the use of electronic data and telecommunications devices for delivering healthcare services and education.[189] Nevertheless, in line with the approach endorsed by the European Union Health Ministers in 2003, it seems appropriate to provide a more comprehensive definition of telemedicine: "Telemedicine is that part of the medical sciences using the most advanced Information and Communication Technologies, among others, systematically applied in real time and real life, to accomplish the real and perceived needs of patients, healthcare personnel, and citizens. It also aims to advance research to enhance the utility and effectiveness of medicine in preventive, predictive, therapeutic, and rehabilitative fields, both from a clinical perspective at the individual level and in terms of public health for the community. Telemedicine offers the mean to overcome distance-related challenges, while optimizing care appropriateness and effectiveness."[190] Telemedicine potentials have become obvious during the COVID-19 pandemic, together also with the need of its appropriate use. Telemedicine and Information and Communication Technologies can save travel time and costs to the patients. Furthermore, during the pandemic, they allowed the development of models for public health, such as those based on Geographic Information Systems Spatial Analysis and big data advanced computing, optimizing the public healthcare resources and waiting list. This aspect is of extreme relevance for chronic conditions management, such as the vein-lymphatic ones.[191] At the same time, the technological advancement facilitating the delicate health data sharing has brought a high need of cybersecurity and privacy management, together with reliability, accessibility and insurance coverage concerns.[192, 193] As in general for the guidelines coming from the different parts of the world, also and in particular telemedicine has showed discrepancies requiring a proper lining up among the different nations stakeholders and key opinion leaders.[194] Among the significant benefits brought by the digital reach-out, there is the possibility of implementing the precision medicine component of the history taking, including aspects such as life-style and patient environment, eventually incorporated in real world data digital registries.[195] This aspect is of great importance in the vascular field, where genetics and environmental factors play a significant role together. Furthermore, advanced telemedicine systems together with suitable software (with or without Machine Learning or Deep Learning) can greatly facilitate the ability of medical specialists to formulate "precision" diagnoses or therapies, which is otherwise very difficult if not impossible.[196, 197] Indeed, data show a possible improvement in vascular medical visit completion, yet with apparent sociodemographic disparities.[198] Detailed analysis on telemedicine use in chronic venous disease patients have been already published, reporting up to 93.5% of patient preference in digital post-operative consultation, compared to in person settings. Both studies were conducted in the USA, for which further investigations in different countries and socioeconomic conditions are strongly encouraged to assess the feasibility of this practice.[199, 200] This is of paramount importance in a vein field that does not deal just with the aesthetic concern of the impaired venous drainage, yet with the more than significant patient population productivity loss and with the leading cause of preventable death linked to the same venous impairment, such as the thrombo-embolic complication. Also in this context, telemedicine proved its potentials, showcasing how patients followed up in remotely connected coagulation centers presented lower rates of adverse events, hospitalization and mortality.[201] A preliminary proposal has

been published also for the triage and evaluation of patients affected by possible deep venous thrombosis, combining telemedicine, Wells score and d-dimer assessment. Nevertheless, further clinical validation is required before introducing the protocol into daily practice.[202] Along the years telemedicine demonstrated its feasibility also in the other significant complication of venous disease: the skin ulceration. The sharing of clinical pictures and related inspection and clinical data in general can potentially improve significantly the wound care management, yet the reliability of the current state of the art requires further medical validation in the specific venous sector before its full incorporation in the good practice recommendations.[203] Last but not least, great expectations are present for the development of telemedicine also in the field of lymphedema and lipedema management, particularly after the significant experience developed during COVID-19 lock-down, but also in this case, dedicated investigations are encouraged to properly define the limits and effectiveness in the specific patient population.[204] In conclusion, telemedicine post-COVID "spring" is here to stay not only for emergency scenarios but as a significant potential asset also in vein-lymphatic care quality improvement. At the same time, rigorous scientific research must be developed to guarantee the appropriate use in acute and chronic disorders of the lower limb drainage, considering in particular the many modifiable and not modifiable factors involved in the related development, so to avoid the so called "boomerang effect", also in terms of ethics and legal aspects.[205] For all the above-mentioned aspects, this panel of experts suggest to explore the telemedicine enhancement in vein-lymphatic care, but only as adjunct to the in person clinical practice, until dedicated studies will assess in depth the related appropriateness. At the same time, the expert panel expresses the deepest hope for a prompt production of dedicated good practice/guidelines documents, at least at the European coverage level, for the appropriate use of the so potentially useful, if properly engaged, Telemedicine tool, in the context of widely diffused conditions, such as the vein-lymphatic disorders.

APPENDIX 4

Statements

A) Statement of compliance

The proposers of this document declare that all recommendations presented are in accordance with current Italian laws, regulations, and guidelines issued by Italian agencies and the Ministry of Health, including provisions related to the Essential Levels of Care.

B) Statement of commitment to presentation and publication

The proposers of this document commit not to present or publish the Clinical Practice Recommendations included herein, in whole or in part, before the completion of the evaluation process.

C) Statement of conflicts of interest

All professionals involved in this document have appropriately completed the conflict of interest declaration (available at the link: https://www.iss.it/documents/20126/10220964/COI+RBPCA-00046.pdf/36c0eaf3-df68-384e-8076-a34fcfc9d9e9?t=1755611370746).

D) Statement of expansion and updating

It is proposed to expand these recommendations by formulating 15 PICO questions for each of the macro-themes described in the 15 recommendations presented here. Updates are planned every two years.

E) Statement of editorial independence

The production of this document was not associated with any funding and has not been influenced by any external parties outside the technical-scientific panel.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
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